In Vivo

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November 2019

MARKET ACCESS

Balancing benefit and value against health care sustainability

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DEPARTMENTS

EXCLUSIVE ONLINE CONTENT

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From The Editor

LUCIE ELLIS

Today, market access as a function is an intricate beast that requires drug and device developers to think creatively while acting within rigid systems. This challenge is intensified in Europe, where the fragmented environment adds further layers of complexity and involves a greater number of stakeholders. Success appears to be the same for all players: access for patients to the treatments they need, when they need them. But individual goals differ.

It was an interesting experience this month to sit in on a roundtable discussion with market access experts from mid and large pharma companies. There were some extreme ideas placed on the table about what the future of patient access should look like. A Netflix-like model was one suggestion, while government tenders, such as those used in the aerospace sector, was another. Huge change and disruption on this scale seems unlikely. Still, the systems in place today have gaps where efficiency can be improved for the betterment of companies and the people they serve, and technologies already exist that could be put to work for regulatory and reimbursement proceedings.

The willingness to improve access to medicines is there, but the ability to act and the tools for true disruption are not. It was a fitting experience to hear speakers on this topic while working on *In Vivo*'s Market Access issue.

This month Melanie Senior explores the impact of ICER in the US, a group that is having an unexpected impact on the sector and society's expectations of drug manufacturers.

With another view on access, Jo Shorthouse looks at how smaller US companies can launch in Europe without a partner. Small and medium biopharmas that are targeting the US first with their new or first products have historically linked up with larger or local players to launch in Europe. However, a trend is emerging that has put the spotlight on some biotechs that have chosen to go it alone with their drugs in the European market.

Exploring the topic of "access for all," in an exclusive interview, the CEO of the Gates Medical Research Institute (MRI), Penny Heaton, talks about the group's plan to have 20 product candidates in the pipeline by 2023. The Bill and Melinda Gates Foundation established the Gates MRI in 2018 to develop drugs and vaccines targeting major neglected diseases of poverty like tuberculosis and malaria.

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Up-Front

SNAPSHOTS FROM NOVEMBER'S CONTENT

In the last decade, the health sector has seen a substantial rise in the number of mHealth apps, many of which are designed to assist users in weight reduction and diabetes management. In 2016, there were 79,000 apps available in the Health & Fitness category in the Google and Apple stores. However, the implementation of mHealth in oncology is lagging.

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EVIDENCE-FREE US DRUG PRICE HIKES, 2017-2018

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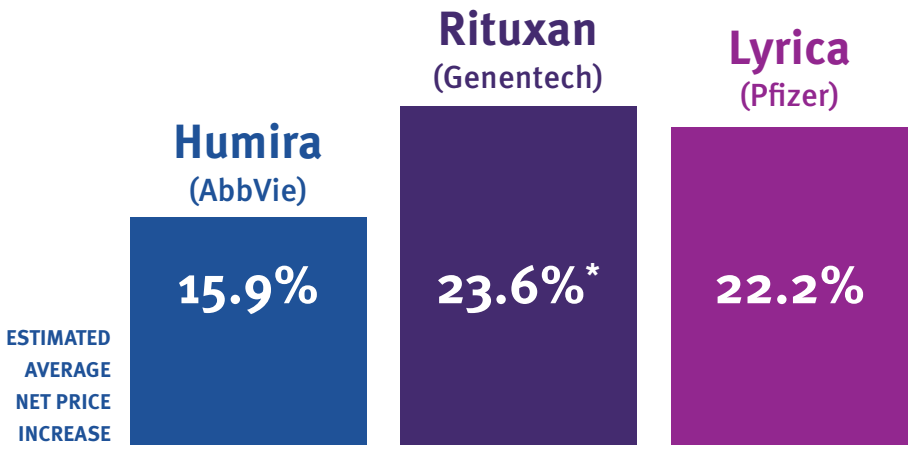

"3D is clinically proven to increase surgical speed and confidence and allows certain operations with a lot of intricate suturing to be completed far quicker. With the latest 4K resolution 3D imaging, Sony can provide the most advanced realistic pictures available for surgeons to utilize."

– **John Herman,**
PMM for Sony Europe Healthcare Solutions

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Stiff price competition is coming in all US therapeutic categories, including protected classes like cancer and rare diseases. For the industry to thrive in this environment, innovations in pricing will be as much, if not more, important than a product and the science itself.

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"We are at a special time in history, with new science that has enormous potential in saving and extending lives. The tools are within our grasp to confront the pathogenic and immunologic roots of infectious diseases that have plagued humankind since the dawn of civilization."
– Dr. Penny Heaton, CEO
Gates Medical Research Institute

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Around The Industry

MHealth And Research In Oncology

The World Health Organization defines mobile health (mHealth) as a "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices."

In the last decade, the health sector has seen a substantial rise in the number of mHealth apps, many of which are designed to assist users in weight reduction and diabetes management. In 2016, there were 79,000 apps available in the Health & Fitness category in the Google and Apple stores. However, the implementation of mHealth in oncology is lagging.

There is a need for the development of more mHealth apps in oncology settings, considering the increasing disease burden and potential clinical benefit. According to Cancer Research UK, there were 17 million cases of cancer and 9.6 million deaths globally in 2018. This is estimated to increase substantially to 27.5 million incident cases by 2040.

HOW ARE APPS HELPING RESEARCHERS?

In recent years health care delivery has moved back to the community and away from traditional care organizations such as hospitals. There are now several prevention initiatives, including mHealth, that are working with the community (users) to increase health care access, inform behavioral change and facilitate data collection. MHealth apps from pharmaceutical companies are providing personalized health care by giving patients the ability to track and monitor their disease. MHealth initiatives along with app-accompanied randomized controlled trials (RCTs), called smart RCTs, and app-based studies are expected to drive future medical research.

Conducting traditional research has always been challenging for numerous reasons, including biased samples not representative of the population as a whole, skewed responses/self-reported data and a lack of standardization of methods. MHealth apps can counter these design flaws by tracking activity and other health-related data more accurately and efficiently. They also have the flexibility to experiment and determine how to effectively engage with users to help them achieve their goals. With the use of apps, users can quickly opt-in to research studies relating to their health conditions, saving time and money for researchers. There are also no geographical limitations, and apps can capture significantly more data to help understand a disease better. This also means patient data can be sent directly to researchers more easily and frequently than if patients were required to travel to give samples or perform tests.

> There is a need for app developers and organizations working with health data to build trust to encourage users to share their personal information.

HOW ARE APPS HELPING CANCER PATIENTS?

Cancer patients often experience a long, and frequently stressful, personal care journey. Cancer mHealth apps can help promote better patient-doctor communication and encourage shared decision-making during treatment. After treatment, apps can ease follow-up care and help patients deal with side effects or make behavioral changes to improve their quality of life.

There are several apps on the market and in development aimed at providing cancer patients with more personalized care by tracking symptoms, patient journeys, treatment side effects and successes. Select examples include:

RESEARCH ON USER BEHAVIOR AND USEFULNESS OF APPS

A US-based consumer survey, conducted by Deloitte and published in 2018, reported findings on attitudes and behaviors across a patient journey; that is, searching for health care, accessing new care, and sharing personal health information. The report observed that about one-third of users were interested in using apps for identifying symptoms, advice on nutrition, exercise, sleep, and stress management, as well as directing them to a physician or nurse. It was interesting to note that users who considered themselves to be in excellent or very good health and those in poor health were more likely to use these apps when compared with those in moderate health. In all, 60% of surveyed users said that they were willing to share personal health data with their doctor to improve their health, with chronically ill users more likely to share tracked information. Overall, the use of tools for measuring fitness and other health improvement goals increased from 17% in 2013 to 42% in 2018.

A patient survey from JMIR mHealth and uHealth analyzed cancer patients' acceptance regarding app use and investigated the functions of cancer care health apps that are most required, and the main reasons to refuse app-assisted cancer care. Of all patients, almost half (48.5%) were willing to send data to their treating clinic

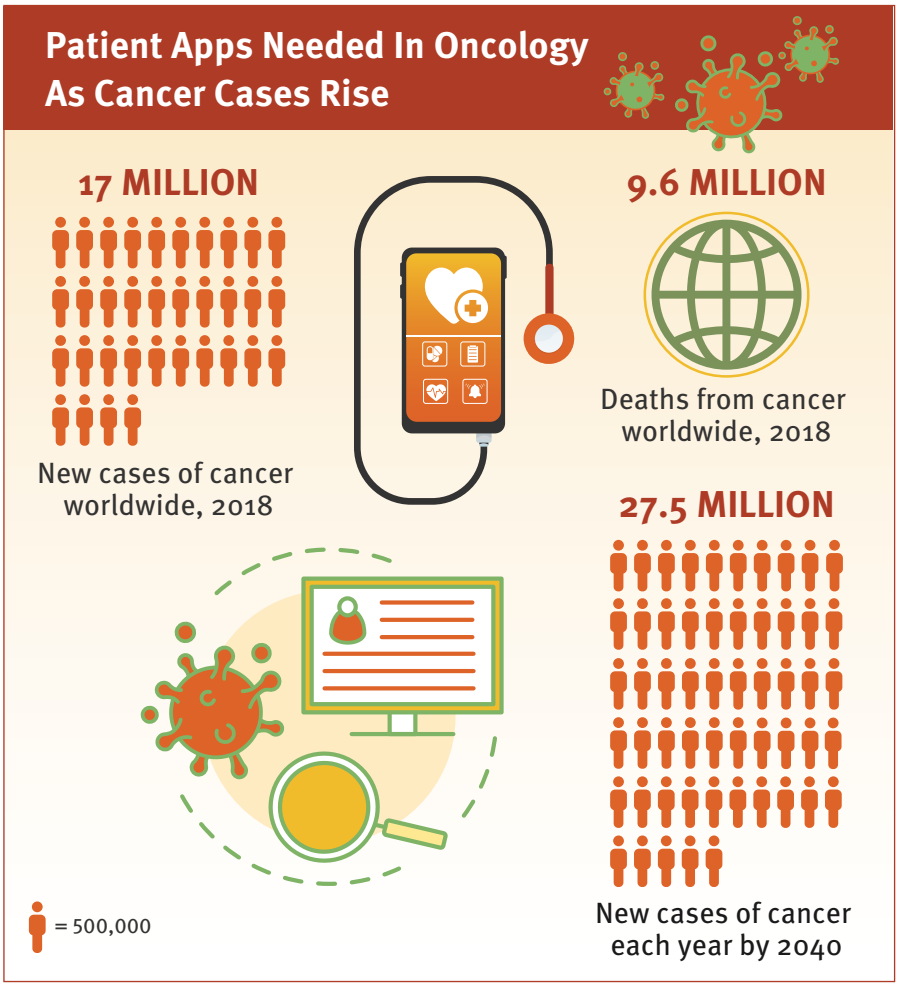
from their app, and among them about two-thirds believed that additional and regularly sent data are helpful.

Moreover, the vast majority (86.8%) wanted to be contacted when user-entered data showed irregularities. The main reasons for those who indicated they would refuse app use (43%) were: lack of skills, concerns about the use of data, lack of capable devices, and personal contact with the treating physician. The survey also reported that there was a significant relationship between patient demographic and app use, favoring males and patients aged 18-39 years. Also, it was interesting to note that those using cancer health apps were also using other mHealth apps such as running apps or tracking apps for blood sugar, heart rate or weight reduction.

In terms of the usefulness of mHealth in cancer prevention and care, apps have provided effective methods to conduct clinical trials by improving recruitment of patients, in addition to examples demonstrating improved quality of life and even better survival rates. The Metastatic Breast Cancer Project, for example, was able to recruit more than 2,000 patients in every US state in a span of seven months by using social media and a website, which otherwise would not have been possible. The project was aimed at examining factors that trigger breast cancer metastasis at a genomic level using patient tissue.

Another example is the Moovcare app that is used to detect cancer relapse or complications in Stage III/IV lung cancer patients during follow-up assigned through a web or app interface. A research study presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting reported that Moovcare improved patients' quality of life considerably. One of the most important findings of this report was that after one year of follow-up, 75% of app users were still alive, compared to 49% of non-users.

A review in 2019 by JMIR mHealth and uHealth that analyzed mHealth apps specific to breast cancer also revealed broad positive benefits. It was shown that breast cancer patients who participated in mHealth-based interventions had greater effects of weight loss, improved quality of life and less stress. However, the study noted that there is a need for stricter regulation, and apps need to be extensively research-tested for their utility, effectiveness and safety before making them available to the public. A separate study that assessed the quality of mHealth apps observed huge heterogeneity in assessment criteria for the apps in different studies, either due to the various assessment approaches used by researchers or different definitions for each criterion. Therefore, it seems necessary to reach a consensus among experts on definitions and assessment criteria. Addressing these points will lead to the improvement of existing mHealth tools and the development of more comprehensive apps.



THE FUTURE OF MHEALTH APPS

There is a need for app developers and organizations working with health data to build trust to encourage users to share their personal information. The 2019 JMIR mHealth and uHealth report pointed out that one way to do this is to let users own their health records. Data often reside in multiple places across different providers, which makes valuable pieces of information and a complete picture of one's health unavailable to doctors, researchers and the users themselves. This makes it difficult for health care systems to target care when most needed. Organizations are working towards this goal, including Apple, which released the Health feature on its smartphones that collates and centralizes the medical history and data of its users.

On similar lines, the mHealth start-up Ciitizen is providing cancer patients access to their own records, such as lab results, images and genetic information, that can be shared digitally. Such efforts to improve the accessibility of health data will be essential for the clinical potential of mHealth to be realized, both in the treatment of cancer and general health care.

IV124361

NIHARIKA DANDAMUDI

Sony's AV Tech Propels Medical Unit

Audiovisual media solutions provider Sony Corp. plays a largely unseen role in the success of end-user-facing capital equipment that manufacturers serve to the medtech sector. Product marketing manager for Sony Europe Healthcare Solutions, John Herman, explains Sony's role in the industry, and how it is stepping up its focus on 4K imaging.

The drive for digitizing hospital operating rooms (ORs) began several years ago with individual solutions, but this only solved part of the need. One of the main themes for hospitals now is digitizing workflows, in the OR and beyond. Sony has developed a brand and a platform to enable just that, as the group's product marketing manager for Europe Healthcare Solutions John Herman explained at the annual Medica conference and exhibition in Düsseldorf, Germany.

Speaking to *In Vivo*, Herman stressed that Sony Corp. is not a medical device company, but an AV media solutions and imaging technology provider. The group has a full business division in Japan focused on the medical industry, from operating theatre solutions to imaging technology. It also has divisions for image analysis, cell sorting equipment, biotechnology and artificial intelligence. But it is often an unseen part of the chain of health care delivery. "Where we fit in the medical device industry is as a strategic technology partner to modality manufacturers," said Herman during an exclusive interview.

In Vivo: Who are the types of client that Sony Corp. works with in the medical arena?

John Herman: We are a key imaging technology provider to leading medical imaging modality manufacturers delivering systems from ultrasound, CT, radiology, endoscopic imaging and surgical microscopes. You don't often see our products in the OR as Sony-labeled products, but a lot of our imaging technology is inside, embedded in these modalities. Almost like the concept of 'Sony Inside.'

Is this imaging in all its types?

It is everything from what we call "light to display" – i.e. from capturing the image, right through to processing, analysis, displaying, recording, documenting and being able to network, store and share. It means all of that clinical imaging workflow. That includes real-time imaging coming from endoscopic camera systems and microscope camera systems.

It is not a consumer or end-user facing business.

The end user is the hospital, and that's the ultimate target we try to reach. But we don't produce our own endoscopes or scanners, for instance. The larger ultrasound players use Sony's OLED technology for their imaging, and that's where we are the market leader in terms of the best imaging quality you can get. We have a multi-faceted offering for the market, not just offering products as part of a chain, but rather a complete imaging solution providing the full imaging chain that hospitals are looking for. It's our Video Over IP platform, which we call Nucleus. It brings all of a hospital's imaging together, and allows the efficient distribution and sharing of video, captured still images, patient metadata and related documents. For hospitals, using such a power system provides unrivalled training and education opportunities.

Does it allow interoperability of systems?

We can bring in images from any type of imaging device in the hospital and provide hospitals with storage and sharing solutions. We can share live surgery images with another OR for consultation and allow surgeons to interact in real time, as well as enabling the right images to get the right people. We have very smart intelligence in our imaging platform to do this. We also ensure everything is future-oriented, including 4K-3D, smart in-house technologies that none of the rival companies provide, such as telestration (a smart app that allows a remote surgeon to annotate on a live image stream to guide the surgeon performing a procedure), and an anti-rotation app (to stabilize an image from an endoscope as it rotates by keeping the horizon view horizontal) running on top of the platform. More and more we are seeing that hospitals' workflows need a platform to work from.

So, this is problem solving in a market that's changing?

The market has changed over the past couple of years, and is now oriented more around hospitals' operational efficiency, i.e. money: it's a business for them. Countries and regions are targeting savings, reducing bed hours per patient; and procedures need to be conducted in a more efficient way to save time. Downtime in an OR costs hospitals extraordinary amounts of money. Another change is in the technology, for example in 4K-3D.

How does Sony work with the client-facing technology providers?

Where we engage with hospitals directly is around the OR, imaging for laparoscopic surgery, robotic surgery and endoscopic surgery. We aim to improve efficiency in the OR – the engine room of the hospital. What's changed over the past few years is that hospitals increasingly try to do solve their image storage problems by themselves as there is no real equivalent in surgical imaging like DICOM for radiology. And you have this massive amount of information, increasingly in 4K resolution, that represents a huge problem: how do they store, secure and share it?

Is this a unique offering that Sony has brought to the market?

What we can offer is a vendor neutral Video-Over-IP platform; we can bring imaging from any device and integrate hospital information systems whether they use traditional copper CAT5 or fiberoptic cabling infrastructure. Sony has individual competitors, but it is unique in the way it can utilize its vast amount of technologies across corporate divisions to provide best-of-class products and solutions fit for the medical industry. We can pick the best bits of technologies developed in other areas and re-purpose them for leading medical applications.

Regarding the data that is produced, how can Sony use it in product development?

Any imaging that gets produced and stored is not our property – it's the hospital's property – and we don't use any of the data from AI or imaging analysis. But it's an area that's growing. In the future, there may be artificial intelligence (AI) or machine learning applied to cancer surgery: for example, to identify tumors or to speed up the diagnosis of cancerous areas. It also allows you to spot trends or images with similar features. So the bigger the data set a hospital can collect the more accurate AI can be applied to improve analysis or even diagnosis. I think it's a natural progression that more and more AI will be provided to images that are required by hospitals.

What is the level of clinician input in your R&D?

Our presence in the market is another reason for profiling Sony Corp., and we have a lot of hospital groups visiting us. Sony is fighting on different fronts. We very much value insight from key opinion leaders, and we engage very actively with certain high-profile surgical leads for different types of procedures. Ten years ago, we were very product focused. Now, while that's still a huge area of our business, for us it is more how products are used together, and how we share information. We are very much a complete solutions provider. We have to understand what is required before providing solutions into medical workflows. And we need input from the market to understand how we need to move forward.

How is Sony's R&D activity structured?

We have a complete business division within our digital imaging corporation which is purely focused on the medical business. Most of our R&D is in Japan, but for certain types of imaging technology, such as video over IP technology, this is done in Europe. As a professional group, we have a lot of presence additionally in the AV broadcast media market.

What does Sony hope to achieve at events like Medica?

We meet key customer accounts, modality manufacturers and hospital groups, and this is a opportunity to engage and show them what we can do now and in the future. We can show our road map of imaging technology for the future, looking two to five years in advance. We can share our R&D roadmap to see how we can solve some of their future problems. In general terms, the technology road map is pointing to 4K imaging, which is becoming increasingly mainstream. A lot of modality manufacturers have by now launched first-generation 4K camera systems. We are focusing very heavily on the whole market shifting to 4K, and in the future we see the merging of 3D and 4K. At the moment, they are two separate imaging workflows often with two sets of equipment needed. Typical hospital systems will have a 3D and a 4K camera system, which are used for different procedures and applications, with 3D more beneficial in urology and certain other procedures, and 4K used more for typical laparoscopic procedures. To acquire video images in true 4K resolution using a 3-chip camera requires a huge amount of data and image processing technology. We have developed from scratch a whole new image processing platform to do this, and in real time, because latency is no good for surgical imaging. All our customers have had to adjust too; their current cameras do not have the processing capability for 3-chip 4K imaging in real time. We can provide the core image processing technology for their systems to allow them to provide the next generation 4K systems.

THE 4K-3D COMBINATION

3D is clinically proven to increase surgical speed and confidence and allows certain operations with a lot of intricate suturing to be completed far quicker. With the latest 4K resolution 3D imaging, Sony can provide the most advanced realistic pictures available for surgeons to utilize.

How is Sony truly differentiated in the medical market?

We are not only a medical solutions company – we're an imaging company and our core business comes from AV. As a group, we are divided into different pillars, including medical. We can always link back to our other business groups to see what support we can get from them to improve workflows on our side. We are in a unique position; as a corporation, we can pick and choose technologies from other areas of the business to solve a medical imaging application.

IV124365

ASHLEY YEO

Accessing CAR-T Therapies

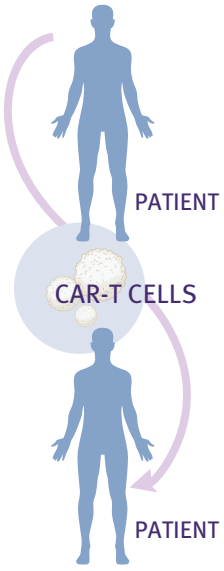
There are two CAR-T therapies on the market, both of which secured their first approvals in 2017. The pipeline of autologous and allogeneic CAR-T options is busy with several candidates in clinical studies. However, getting approval is only one part of getting these breakthrough therapies to patients.

2017

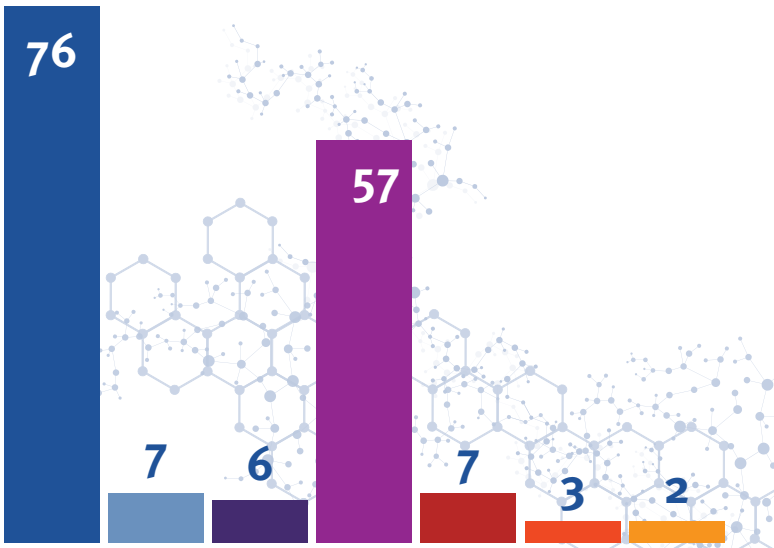
Novartis's **Kymriah** was first approved in the US for the treatment of diffuse large B-cell lymphoma in **AUGUST 2017**

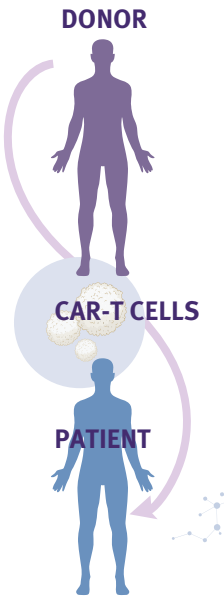
Gilead Sciences' **Yescarta** was first approved in the US for DLBCL in **OCTOBER 2017**

CAR-T CELL THERAPIES are part of a larger category of cell therapies termed adoptive cell transfer (ACT) in which immune cells are modified *ex vivo* in an attempt to target the immune system against tumor cells.

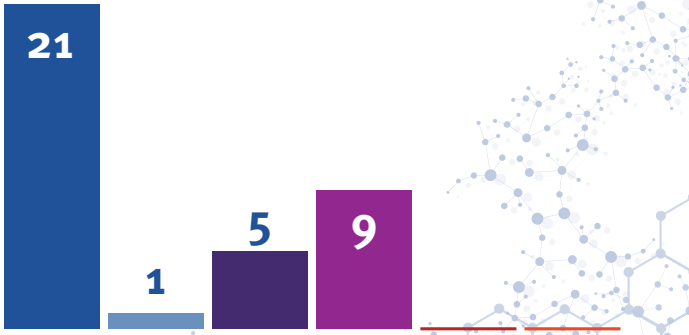


OVERVIEW OF AUTOLOGOUS CAR-T PIPELINE





OVERVIEW OF ALLOGENEIC CAR-T PIPELINE



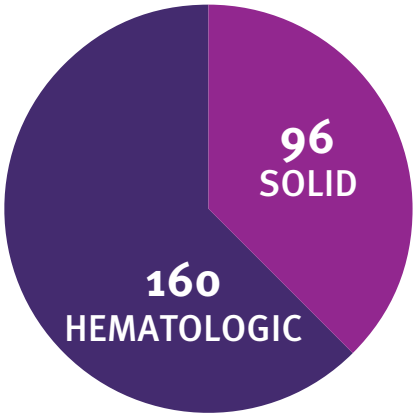
Overviews do not include programs outside of the US, where development phase is unknown

Sources: In Vivo, Pharmaprojects | Design: Gayle Rembold Furbert | Design | Pharma Intelligence

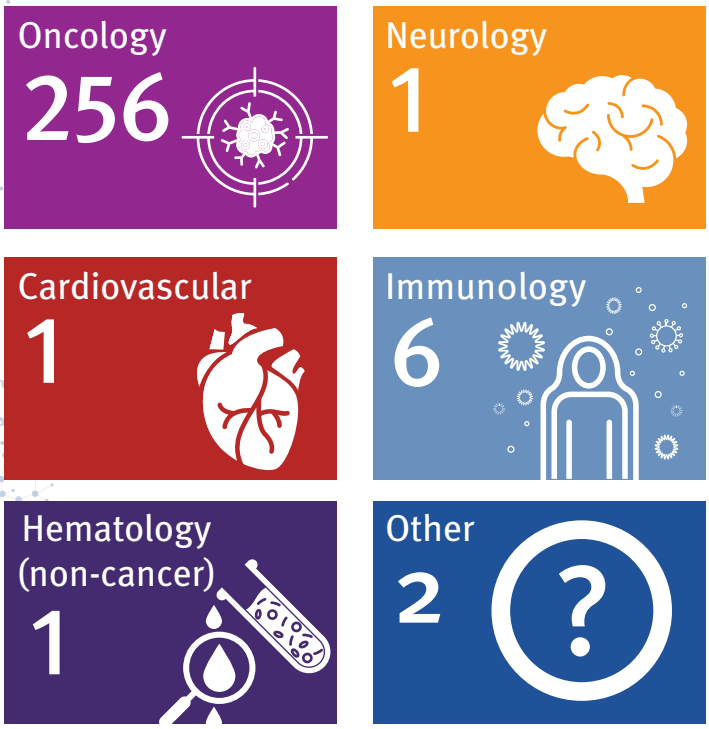
CAR-T DEVELOPMENT AREAS

CAR-T oncology development candidates (both allogeneic and autologous) are being explored for solid tumor and hematological indications.

NUMBER OF PROGRAMS IN PIPELINE BY CANCER TYPE



NUMBER OF PROGRAMS IN PIPELINE BY DISEASE AREA



CAR-T THERAPIES: APPROVALS VERSUS ACCESS

■ YES ■ NO	Yescarta		Kymriah	
Country	Approved	Reimbursed	Approved	Reimbursed
Australia				
Austria				
Belgium				
Bulgaria				
Canada				
Croatia				
Cyprus				
Czech Republic				
Denmark				
England & Wales				
Estonia				
Finland				
France				
Germany				
Greece				
Hungary				
Ireland				
Israel				
Italy				
Japan				
Latvia				
Lithuania				
Luxembourg				
Malta				
Netherlands				
Norway				
Poland				
Portugal				
Romania				
Slovakia				
Slovenia				
Spain				
Sweden				
Scotland				
Switzerland				
United States*				

*In 2019 it was confirmed that Medicare and Medicaid would cover CAR-T cell therapies nationally, reimbursing part of the costs.

In US Drug Pricing Debate, ICER's Voice Gets Louder

ICER's influence on drug pricing, and policy, is growing. Spotlighting the worst drug price rises is one recent example.

BY MELANIE SENIOR

The Institute for Clinical and Economic Review has steadily expanded its influence among healthcare stakeholders.

"ICER prices" – the benchmark value-based net price range ICER provides for some new drugs – now feature in many pharma-payer pricing negotiations.

A recent report highlighting 'unsupported price increases' got lots of attention – and some criticism. Calculating net prices in the US is fiendishly complex. Yet this opacity is part of the problem. Meanwhile, ICER is seeking to shape more than just drug prices.

Meanwhile, ICER is seeking to shape more than just drug prices. It is weighing in on biosimilars and real-world evidence, too.

Ten years ago, it would have seemed unthinkable that an independent, non-profit organization with no statutory power whatsoever could influence the pricing behavior of the multi-billion-dollar US pharmaceutical sector. Yet that is what the Institute for Clinical and Economic Review has achieved. Since its foundation in 2006, the organization has steadily expanded its authority and credibility among health care stakeholders. And now that it has industry's ear, it is seeking to shape more than just drug prices.

"Absolutely, we want to influence policy" around drug pricing and access, said Steven Pearson, ICER's founder and president and the driving force behind the organization's rising profile. One particularly effective attention-grabber appeared on October 8, 2019. ICER published a list of the top seven prescription drugs whose net price increases over 2017 and 2018 – as calculated by ICER – had the greatest impact on US drug spending, and which were, according to ICER's analysis, entirely unsupported by additional evidence. Top of the list: AbbVie's Humira (adalimumab). Humira is already the world's top-selling drug, with 2018 sales of nearly $20bn. Its estimated average net price increase of almost 16% over the period cost US payers a cool $1.8bn. The largest percentage price rise – over 32% – was for Eli Lilly's erectile dysfunction drug Cialis (tadalafil; *see Exhibit 1*).

The "unsupported price increases" (UPI) report made a splash among many health care stakeholders and the media. Few payers learnt anything new. "I have already felt the pain of Humira price increases," said one, who manages $3bn worth of drugs. But they nevertheless welcomed what they perceived as a systematic, objective analysis from an independent third party. "It puts the spotlight on issues that we are trying to bring forward," said Chronis Manolis, chief pharmacy officer at UPMC Health Plan in Pittsburgh, PA. "They are raising awareness."

Exhibit 1

The Worst Offenders: Evidence-Free US Drug Price Hikes, 2017-2018

DRUG (MAKER)	ESTIMATED AVERAGE NET PRICE INCREASE	SPENDING IMPACT ($M)	YEAR FIRST APPROVED
Humira (AbbVie)	15.9%	1,857	2002
Rituxan (Genentech)*	23.6%	806	1997
Lyrica (Pfizer)	22.2%	688	2004
Truvada (Gilead)	23.1%	550	2004
Neulasta (Amgen)	13.4%	489	2002
Cialis (Lilly)	32.5%	403	2003
Tecfidera (Biogen)	9.8%	313	2013

*Rituxan data updated 11.6 to 14% and $549m following input from Genentech.

SOURCE: ICER; drugs.com

Price-hikes are perfectly legal. Drug firms can raise the prices of their products anytime they like (payers do not have similar freedom around insurance premiums). Many of the top seven alleged product price increases in ICER's report are easily explained – if not justified – by the arrival of generic or biosimilar competition.

Yet only Eli Lilly acknowledged that dynamic in their written response to the UPI report. Several companies listed studies – including real-world trials – that, in their eyes, supported the inflation. ICER did not agree: at best, the studies backed up evidence that was already available, it said.

Worst-offender AbbVie said the "pricing data was inaccurate," ICER's methodology is questionable, and the agency "failed to consider the totality of the evidence." Amgen claimed the net price of Neulasta in fact grew in line with inflation over the period, and that it is committed to responsible pricing.

They may have a point. Calculating net prices in the US is fiendishly complex. After the report appeared, Roche's Genentech provided ICER with net price and volume data that reduced the estimated price increase for Rituxan to 14% and the spending impact to $549m. ICER updated the report on November 6, adding that "there remains uncertainty in all other net price changes."

This blunts the knife somewhat. Yet opacity around pricing what ICER is seeking to highlight. The idea is to hold up a mirror to industry, not to denigrate it, said Pearson. But the effect was more or less the same. And the timing is not entirely coincidental: policy-making around drug pricing in the US has been especially creative in the run-up to an election. Many politicians – including President Trump – are hell-bent on reducing drug prices. There are multiple bills swirling around Congress, from the bipartisan Senate Finance Committee bill, Prescription Drug Reduction Pricing Act of 2019, to Speaker Pelosi's "Lower Drug Costs Now" Act of 2019. Some are particularly radical: Democratic candidate Elisabeth Warren's "Medicare For All" plan would abolish private insurance entirely and require trillions of dollars' of tax rises.

Few if any of these bills are expected to see the light of day before the next election, experts say. Most will be heavily amended anyway. But the President may not need Congressional approval for his idea of an international pricing index which ties the price Medicare pays for hospital-administered drugs to a benchmark of prices in other developed countries. "Even if Congress fails to strike a big drug deal, Trump is likely to proceed with his international reference pricing proposal; we are expecting a final version next year," said Kim Monk, managing director at Capital Alpha Partners, LLC. Meanwhile, state legislators continue to reach out to ICER, "trying to figure out how to apply the UPI report," said Pearson.

The direction of travel is clear – clearer still as the UPI report lands on policymakers' desks. That is why pharma is worried, according to Michael Sherman, chief medical officer at Harvard Pilgrim Health Care, an East Coast payer (which has provided funding to ICER). "If they appear to be pushing unreasonable prices, the concern is that it is more likely something bad will happen." Conversely, by taking action to show that they are good corporate citizens, "they can perhaps forestall more invasive legislation," he said.

Not everyone agrees that the link is direct. "ICER is reputable, but is not considered as an alternative" to what may come out of Washington, opined Kim Caldwell, previously VP, pharmacy professional affairs at Humana, now principal at Texas Star Healthcare Consulting. But he does agree that the UPI report will help fuel some of the debate. Plus, the report was not a one-off. It is the first of a planned annual naming-and-shaming around prescription drug price hikes.

ICER's Influence On Pricing Was Growing Before UPI Report

ICER has already become a household name among some US payers. "They are the go-to organization when people talk about drug evaluation, heath technology assessment (HTA) or cost effectiveness," said Edmund Pezalla, who served as VP and national medical director at Aetna until 2016 and is now a consultant. The

CHANGING MINDS: ABBVIE'S HUMIRA FOLLOW-ON IS COST-EFFECTIVE AFTER ALL

An initial draft ICER report of next-generation RA drugs, published in early October, condemned three new janus kinase (JAK) inhibitors, AbbVie's Rinvoq, Pfizer's Xeljanz and Lilly'/Incyte's Olumiant as offering only marginal or uncertain clinical benefits. It hinted that pricing higher than existing RA mainstay Humira (facing biosimilar competition) would not be cost-effective.

Days later, that report was pulled and replaced, the following week, with a version that was much friendlier to Rinvoq. The revised draft report brought the drug's estimated added cost per QALY versus Humira below the $150,000 threshold. There was insufficient data – in particular head-to-head data – to assess the other two drugs, the report said.

ICER changed core assumptions about the RA treatment pathway, treatment timelines and the drug's net price. Patients failing first-line treatment were assumed to transition to a basket of targeted immune modulators, not palliative care – more accurately reflecting what happens in the real world.

Cost effectiveness was calculated over a year, not over a lifetime – the longer the time-horizon used, the more the beneficial effects of the expensive drug get washed out. "We weren't happy with the perspective that we felt [the initial report] would leave policy-makers," said ICER president Steven Pearson. The earlier model implied that a better, potentially more expensive drug was less cost-effective because its use delayed transition to much cheaper (and less effective) alternatives.

"It is important that we remain transparent, and humble. If we change our minds, or make a mistake, we are not going to push that under the rug," said Pearson.

organization's main output is reports analysing the effectiveness and value of new or existing drugs that have, or are likely to have, a significant budget impact. The final versions of these reports include a "value-based" benchmark price range that would allow the drug to reach commonly-cited cost-effectiveness threshold (usually between $100,000 and $150,000 per quality-adjusted life-year [QALY] gained).

Some groups, like CVS Health (which owns health insurance firm Aetna and the pharmacy benefit manager [PBM] CVS Caremark) have allowed employer groups to use ICER reports as a basis for formulary and benefit design – in other words, to exclude drugs priced outside ICER's threshold range. (CVS' program faces fierce resistance from pharma and pharma-funded patient groups though.)

Meanwhile, even payers that can afford in-house research teams to determine what drugs to cover, find ICER reports offer a "welcome second opinion" on the value or otherwise of new drugs at their given prices, said UPMC's Manolis. For many of the smaller payers that lack in-house expertise or resources to perform cost-effectiveness analyses, ICER reports are all they have to keep check on "whether the PBMs that they contract with to provide medicines are making wise decisions, or seeking to line their own pockets," said one experienced payer.

So-called "ICER prices" – the benchmark net price range provided in ICER's reports – now feature regularly in pricing negotiations between pharma and payers. More than a third of the US payers recently surveyed by ICON, a consulting firm, indicated that they were likely to request a rebate to match the net ICER cost-effective price or range.

Manufacturers have been forced to get on board. Most have entire teams devoted to dealing with ICER; consultants are churning out white papers and pitching ICER-focused project teams. Analysts comb through ICER decisions and factors likely to influence them, as they do for other European HTA bodies. Those drug firms that do reach – or come close to – the ICER price are noticed and rewarded. Several payers referred to Sanofi/Regeneron's responsible pricing for Dupixent (dupilumab) used to treat eczema and other allergic diseases. "Even though the drug was expensive in dollar terms, we concluded from reading the ICER report that it was dollars well spent" and made it available without unnecessary hurdles, said Harvard Pilgrim's Sherman. Other payers point to the PCSK9 cholesterol lowering drugs, whose priced were tied to the ICER review.

"The biggest mistake [for pharma] is failing to engage" with ICER, advised Pezalla. "It precludes the opportunity to give and take."

ICER Changes Its Mind To Be Policy-Relevant

ICER does change its mind. Not often: researchers at the Tufts Medical Center found that in fewer than 5% of cases, between 2017-2019, did public comments following a draft report lead to a change in conclusions in the final report. In October 2019, though, ICER performed a significant about-turn in an analysis of next-generation treatments for rheumatoid arthritis, in particular three new JAK inhibitors, AbbVie's Rinvoq (upadacitinib), Pfizer's Xeljanz (tofacitinib) and Lilly/Incyte's Olumiant (baricitinib).

The U-turn happened because the conclusion from the first analysis "was counter-intuitive and not helpful for policy-making," Pearson said. It concluded that the new drugs offered only marginal benefits, and were unlikely to be cost-effective if priced above Humira. But the newer products are being used in the real-world; US formulary designers cannot refuse to cover them (as can occur in some European markets if a drug is deemed too expensive). So, saying that they should not is not helpful. ICER re-evaluated its models to generate a slightly different – more positive – result. The situation showcases the sometimes uncomfortable transition between cost-effectiveness theory and practical policy.

Cost-effectiveness, as the word suggests, is influenced by both price and

effectiveness. A new drug may be more effective than an existing (cheaper) therapy, but if the price difference is found to outweigh the incremental effectiveness, then the cheaper – and perhaps only slightly less effective – drug wins. Hence the choice of comparator is key.

Novo Nordisk is feeling this tension right now. Its recently approved Rybelsus (semaglutide) is the first oral GLP-1 agonist available for diabetes. It allows patients to benefit from the well-proven effects of the GLP-1 class without enduring injections. But at an estimated annual net price of $6,103, ICER concluded in a November 1, 2019 report that Rybelsus was probably less cost-effective than another, much cheaper kind of oral diabetes drug, Merck's Jardiance (empagliflozin). Payers have taken note (see *Choosing The Comparator).*

ICER Speaks Out On Other Areas

While everyone is paying attention, ICER has seized the opportunity to talk about other meaty policy areas, too. Among them: biosimilar interchangeability and the use of real-world evidence (RWE) to support drug efficacy and differentiation. "ICER has worked hard to gain prominence, so why not use the platform to delve into other areas. It just increases their value proposition," opined UPMC's Manolis.

ICER's recent (revised) draft evidence report on rheumatoid arthritis therapies highlights the low penetration of biosimilars in the US, despite the FDA having approved over 20 such products. It is a thinly-veiled dig at payer, regulator and pharma behaviour within a system that does little to encourage the use of cheaper biologics.

In Europe, the arrival of biosimilar copies of drugs like Remicade (infliximab) and Humira, priced 30-40% (and sometimes more) below the originators, have generated significant savings, albeit after a slow start. Yet in the US, four of the country's top insurers – Anthem, Cigna, Humana and United Healthcare – "designate infliximab [the originator drug] as the preferred product compared to [Inflectra] infliximab-dyyb [Pfizer/Celltrion's biosimilar, approved in 2016]," states the report. In other words, they continue to prioritize the reference drug over the cheaper equivalents; patients must fail on branded Remicade before they are allowed to receive the biosimilar.

ICER is well aware of the main reasons for this. Originator drug manufacturers offer juicy rebates on their products to dissuade payers from moving to alternatives whose list-price may be lower, but which also come with lower rebates (and a much smaller market share and track record). The result is that the originator drug may

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>
> *Chronis Manolis, Chief Pharmacy Officer, UPMC Health Plan*

CHOOSING THE COMPARATOR

The challenge for Novo Nordisk is that ICER is comparing Rybelsus (oral semaglutide) not only to injectable equivalents, like Novo's own once-daily Victoza (liraglutide), but also with cheaper oral therapies (Merck's Januvia (sitagliptin) and Jardiance, added to metformin). Jardiance's estimated annual net price is just a third of Rybelsus', based on a wholesale acquisition discounted by 35%, similar to discounts for Novo's Ozempic (injectable semaglutide).

Indeed, ICER also concluded that oral semaglutide enables better blood sugar control than all the comparators, and better weight loss than Januvia or Victoza. And even though it does not quite stack up against Jardiance, Rybelsus was considered cost-effective compared to Victoza (annual net cost: $8,000); versus Januvia there remains "substantial uncertainty" as to the relative cost-effectiveness, the report concluded.

It is not a clear-cut picture and it rarely is. But that actually works in Novo's favor. In over two-thirds of cases, ICER has point-blank undermined the prices of drugs under review, according to Bernstein analysts. That did not happen here. ICER also acknowledged data showing Rybelsus is better at preventing cardiovascular complications than its comparators.

Hence at least some payers are bracing themselves for higher GLP-1 costs – already a high-spend category. "Our concern is that oral GLP-1 will lead to more GLP-1 use when other [oral] drugs may be more appropriate," and cheaper, said Harvard Pilgrim's Sherman. There are constraints on when Rybelsus can be taken, but an oral drug is still likely to lead to greater adherence among some patients. As such, "we're certainly going to cover it, likely as an alternative to [injectable] GLP-1s," he said. "We are just not sure on the tiering," (which determines how easily patients can access it). Some analysts are predicting blockbuster sales despite a frantically competitive market.

come in cheaper. (As is clear from the UPI report, the price of many biologics has increased considerably, giving sponsors plenty of room to rebate aggressively.)

More importantly, the FDA has ruled that biosimilars are not interchangeable with the originator drug – patients cannot just be switched from one to another. If they were interchangeable, payers could decide to only cover the biosimilar, igniting more price competition. But without interchangeability, payers must still cover the originator drug, removing the incentive for price-lowering.

ICER's report implicitly critiques the FDA's decision on interchangeability, which is controversial within the payer community and seen by some as evidence of pharma's undue influence on the agency. (Pharma funds the FDA via user fees.) The report also takes the trouble to showcase payers, including Aetna, which do not prefer originator brands. Divisions of Kaiser Permanente have surveyed patients switching to biosimilar infliximab, and found the vast majority to be satisfied, it said. Kaiser Permanente Northwest "uses the biosimilar for about 97% of infliximab infusions," the ICER report states.

Policing Real-World Evidence

As well as cheering for biosimilars and the payers that encourage them, ICER also wants to lead the debate around the use of RWE. This is a huge area, attracting growing investment – but lacking clear standards and guidelines. The FDA has declared its interest, but so far provided little concrete guidance to manufacturers on how and when RWE might be considered in approval decisions.

Post-approval, mountains of RWE are being generated by patients, payers, providers and manufacturers. Such evidence is particularly important in capturing patient-relevant outcomes, including, for instance, around quality-of-life. As such "we want to contribute to methodological discussions and [ultimately] to actively generate RWE in our own reports," said Pearson.

ICER's support for RWE did not come across clearly in the UPI report, despite its being "happy to consider" this evidence category. Many studies submitted by the seven black-listed companies in defence of their price hikes were RWE; they included observational studies, patient-report-

> *"We want to contribute to methodological discussions and [ultimately] to actively generate real-world evidence in our own reports."*
>
> *Steven Pearson, ICER founder and president*

outcome trials or studies of drugs' impact on quality of life. Yet none of them justified a price hike, according to ICER. Most provided "no new clinical evidence," and some of the observational trials were considered insufficiently robust. What were ICER's evidence criteria? "ICER applies the same evidentiary standards to RWE that it applies to all other forms of evidence," it said in response to manufacturers' frustrated comments.

That may not be appropriate. RWE is different to the controlled, randomized clinical trials that comprise the bulk of pre-approval trials. Standards are not yet agreed. The National Pharmaceutical Council (which represents research-based biopharma companies) was quick to declare that the "troubling" and "one-sided, biased" UPI report set an "unreasonably high bar for the types of evidence it would consider, and a low bar for the pricing data utilized."

Pearson said he did not want to convey the message that ICER was anti-RWE, or that companies should not bother investing. "We are not saying RWE is inferior to RCT evidence just by being RWE," he said. It is about study quality, and about the questions they are set up to answer. Many submitted studies simply confirmed drugs' already-known benefits, albeit sometimes over a longer time-frame.

Yet perhaps evidence that a drug's benefits are maintained over the longer term is worth something. "We will wrestle with that question," acknowledged Pearson. "It is not unreasonable to suggest that the health system benefits by knowing that short-term advantages [of particular therapies] are sustained."

How such longevity may be measured and, potentially, rewarded is another thorny issue. ICER promises to learn from the feedback to this inaugural report; one of its core principles is multi-stakeholder engagement.

Meanwhile, the organization continues to broaden the range of tools it is offering, ultimately to help support a fairer, more transparent and more value-focused system. It is launching a digital evidence compendium of all its value-assessment work, to make it easier to access and use. It is also creating an interactive modeller program, on the cloud, that allows manufacturers and payers to plug their own assumptions into ICERs' models – for a fee.

And, in part to avoid being seen as picking on pharma, ICER may launch an '*Unsupportable Barriers to Access*' report in 2020, said Pearson, that instead would put the spotlight on payers. The report would highlight fairly-priced drugs that are not deemed to be appropriately covered by health plans. "The goal [of both kinds of report] is to ensure there is affordable access," said Pearson.

These additional projects will require ICER to increase its headcount by 50% over the next 18 months. Most of ICER's funding comes from non-profit foundations, including the Laura and John Arnold Foundation. Billionaire John Arnold has been vocal in his support for lower drug prices.

Whatever happens in Washington, ICER has taken on the job of drug pricing and access referee. It is not perfect. But there are not any better candidates. And ICER has shown it is not afraid to blow the whistle – on either side.

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Email the editor: *Lucie.Ellis@Informa.com*

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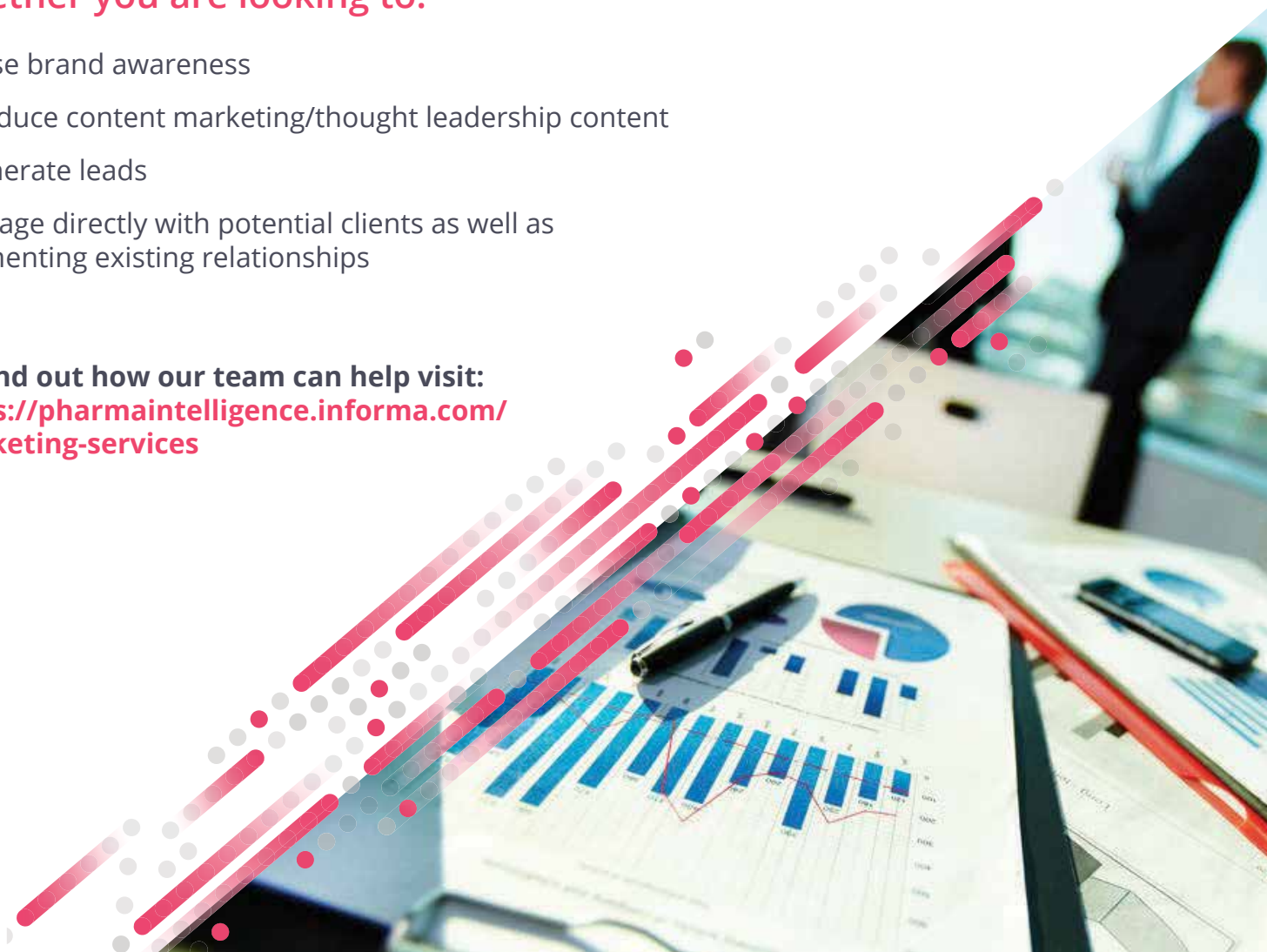

Market Access 2020: Understanding US Payer Expectations

Big pharma is facing a difficult US competitive landscape as its traditional customers realign to build their own redoubts of size, scale and reach.

BY WILLIAM LOONEY

Consolidation on the payer side is changing the dynamics of success in health care.

Pharmacy benefit management groups (PBMS), far from being marginalized, are now positioned within insurers to realize with verifiable metrics what big pharma has so far only promised – lower costs and better outcomes.

So what? Big pharma moves at a slow pace, and payers face their own internal divisions, but the embrace of risk-sharing will grow as the price of many new therapies soar to seven figures – some drug-makers will surprise with market disrupting price strategies designed to win first-mover advantage even in crowded therapeutic segments like cancer.

Last month, *In Vivo* convened a roundtable of principals at one of our partner editorial advisers, Real Endpoints Inc., to examine the impact of US market structural changes on the industry's growth prospects in a world where it seems everyone else now speaks a different language: of insurance design, not drug design, of coding text, not clinical trials, and of service apps, not science.

Government pressure on big pharma is not a major factor going forward, with the industry's fate depending more on the private-sector realignments taking place in health care overall. With three major insurance players delivering medicines reliably to more than 80% of the US population, it is hard to envision a scenario where politicians agree to displace it with something untested – and, in an era of annual trillion-dollar budget deficits, absurdly expensive.

Stiff price competition is coming in all US therapeutic categories, including protected classes like cancer and rare diseases. For the industry to thrive in this environment, innovations in pricing will be as much, if not more, important than a product and the science itself. Examples of risk-sharing and other industry contracted pricing arrangements are emerging, but the pace has to pick up. Just as drug makers are exposed to huge potential losses on the R&D pipeline every year, so they must accept more risk in their commercial investments through value-based agreements.

The following are key excerpts from the roundtable discussion:

In Vivo: What is your take on the key developments driving market access over the past 12 months?

Jeff Berkowitz: There's now disruption at every turn, on both ends of the pharma supply chain, and for three reasons. The first is the acceleration of vertical and

horizontal integration in key segments of the business outside pharma – namely its customer base. The second is the pressure for increased transparency on drug pricing and the explosion of information in health care overall. And the third is a side effect of the first two, posing questions for the long-term viability of the pharma business model: as the customer base consolidates and its command of the strategic asset of information grows, what should the pharma C-suite be doing to ensure its own future growth and profitability? I've been engaged on the commercial side of this industry for more than two decades, working at innovative drug manufacturers as well as payers in PBMs and retail distribution, yet these are the most drastic, fastest changes I've seen.

The most startling development is the pace of vertical integration outside the pharma space. At Real Endpoints we track developments across four segments: retail pharmacy, PBMs, drug distributors, and payers. Increasingly, we look at specialty pharmacy and the contracted patient services component too. All these businesses were once heavily siloed. But now three behemoths deliver health care services, including drugs, for over 80% of the US population. UnitedHealth Group is one, a major insurer with its own PBM, Optum; Express Scripts, the country's second largest PBM, now has its own insurer, Cigna; and finally CVS Health, the country's largest retail pharmacy chain, owns what was once the US's third largest health insurer, Aetna. Walgreens, the second largest US pharmacy retailer after CVS, is also involved in the distribution/wholesaler business due to its one-third stake in one of the largest drug distributors, AmerisourceBergen. But note that providers and patients do not figure prominently!

With this market reach comes an extraordinary level of negotiating power, especially as the pharma business remains not only vertically siloed but also highly fragmented within its own space: not one big pharma company controls more than 10% of industry sales. You have significant change and integration on one side of the coin while pharma continues to conduct business as usual.

Drug company executives say that PBMs are merely middlemen, adding little value to the system, and will eventually diminish in importance.

Berkowitz: They've been saying the same thing for the two and a half decades I've been in this business. Today, PBMs are more powerful than they've ever been. And their integration with insurers means they have no incentive to disrupt their own businesses – except that they now, integrated with payers, can try to deliver care seamlessly, toward a better outcome, hopefully at lower cost.

Silos Are Not A Strategy

What is the biggest structural challenge for big pharma faced with this consolidation in its customer base?

Berkowitz: One problem is the strangely persistent disconnect between the R&D organization and the commercial business leads responsible for securing acceptance of new products among payers. The commercial side is often still not trusted

ROUNDTABLE PARTICIPANTS FROM REAL ENDPOINTS

Roger Longman, Founder and Chairman

Jeffrey Berkowitz, CEO and Director

Susan Raiola, President

Jane Barlow, Executive Vice-President and Chief Clinical Officer (not pictured)

Ryan Walsh, Vice-President Client Services

– perhaps "valued" is a better term – by the R&D teams, whose instinct is to defend development projects that have been in the works for years. And the business side can be caustic about the scientists who lack that real-world perspective they encounter every day, outside the lab, with a changing roster of customers and stakeholders. This tension is often compounded in small biotechs, led by entrepreneurial founders convinced their science is so unique it will be embraced immediately, without question, by payers. Despite our efforts and those of other outsiders who work to help each side connect the dots and overcome the lip service biopharmas pay to cooperation, they always seem to be operating on completely separate tracks.

Roger Longman: That same disconnect appears between pharma and payers. Pharma's leaders have grown up with the physician as the principle customer. The new payer customers have very different goals and incentives – indeed they speak an entirely different language, the vocabulary of insurance design, reimbursement coding, formulary management. How many R&D executives understand it? And if they don't understand it, how can they know their customers? As elementary as it might sound, one important step forward for pharmaceutical companies would be a kind of payer boot camp – a deep dive into the structure, vocabulary, incentives and business practices of the payer and distribution world. I've seen this happen on an ad hoc basis – we just did such a program for the new president of a global pharma as well as a number of C-suite teams. But I'll also say there were no R&D execs in the room. I wish there had been.

Berkowitz: When I left Merck & Co. to join Walgreens, the

transition was – to put it mildly – challenging. I was used to a business that had an average 25% margin on marketing innovative medicines and I moved to a distribution and retail pharmacy business that was lucky to post 3%. It took me a while to understand how Walgreens made money; who was important to them and who was not. I realized that I was now working for an organization that dispensed 25% of the entire prescription volume of the US. That's huge. So why did drugmakers know so little about them? It may be that pharma is still paying lip service to a broader definition of customer centricity, beyond the provider physician. While the big pharma innovators are focused on gene therapies for those rare unmet needs, Walgreens, UnitedHealth and CVS/Caremark want solutions for cardiovascular disease, diabetes and obesity. So big pharma is on one end of the spectrum still looking inward, enamored with their own innovation, while the rest of the health care ecosystem is grappling with real-world issues, having a very different, integrated conversation. Even now, there is very little cross-sectoral dialogue taking place – at least not enough to make a difference.

Patients And Payers: Are You Leaving Money On The Table?

Aside from the disconnects between R&D and commercial are there additional areas within pharma acting at cross purposes?

Susan Raiola: Yes, there is a disconnect between what you might call the coverage side of reimbursement (getting payers to put a drug on formulary in a somewhat advantaged position) and the access side (helping patients adhere to, and afford, a new medicine). Both can be expensive, the former in terms of rebate dollars, the latter in terms, for example, of co-pay assistance or free drug provided. But both are tactics within a broader market access strategy. In the broadest sense, how hard should you push the pedal, how much should you spend, to maximize coverage and revenue through rebates – and how much should you pursue access through a free drug or co-pay? Most important, how should those two basic activities be coordinated? The problem is that the two categories of activity are often split. One group oversees patient support and service hubs, and another focuses on payers. There's no integrated strategy and certainly no integrated P&L.

Berkowitz: Exactly. It's quite common for the head of pharmaceuticals in a big US company to get a big bill for the rebates paid to the PBM in return for a place on the formulary, followed by another big expense for patient assistance and services. Yet you are still not getting much insight on whether you've optimized your investments on either side to get to a target market share at a target cost.

Raiola: I should also point out that patient assistance programs are rarely seen as strategic.But they are. They can have a significant impact in product take-up, particularly in crowded therapeutic classes where a strong patient support program is a source of competitive differentiation. Patient attitudes are also changing, in that many now want the same customer experience from pharma as they get from Amazon or Netflix, with service from one source, covering the full spectrum of needs, available at any time. We are now at the point when you can no longer refer to patient assistance as a "program." Instead it's a customized "service app" capable of serving the whole person, who just happens to be a patient too. Drug companies must adopt the mindset that the patient customer wants a different model than what he or she is currently being offered.

Innovative Contracting: A Driver Of Competitive Advantage

Step back for a moment: can we define pharma's pricing and revenue challenge?

Longman: The established brands on which pharma has depended are under extreme competitive pressure. Rebates for insulin are in the 75% range. New, highly innovative drugs in large categories are quickly seeing competition – and therefore high rebates. The anti-CGRPs for migraine are a good example. Or a great success like Regneron's Dupixent for atopic dermatitis: just a year or two after launch it will face, thanks in part to the same scientific wave of progress in immunology that enabled its creation, a group of oral JAK inhibitors with startlingly good efficacy. Meanwhile, society is less willing to tolerate the double-digit price increases which have fueled revenue growth more than they should in comparison to prescription growth and new drug introductions. And even these price increases are less valuable to pharmas thanks to clauses in virtually every major payer contract that limit price increases. A 10% nominal increase in wholesale acquisition cost (WAC) translates, in the real-world of Aetna or Optum, to maybe a 3% increase.

What is pharma doing about this?

Berkowitz: For one thing, companies are investing heavily in categories theoretically resistant to pricing restrictions: oncologics, drugs for rare diseases, and next-generation innovations like cell and gene therapy.

Jane Barlow: In the past two years, more than half of FDA approvals of novel drugs are for rare or orphan indications that impose a big cost on small populations of eligible patients. Now on top of that we have a pipeline of gene therapies promising outright cures to disease. The common theme is a high level of visibility to payers.

This also takes place against a backdrop of powerful emerging players like the Institute for Clinical and Economic Review (ICER), which stresses its independence and reliance on evidence to establish the true value of these novel treatments. Roger Longman and I were both speakers at the Alliance for Regenerative Medicine's recent summit in San Diego, a distinguishing feature of which was the near universal declaration by the attending companies that new gene therapies would be sold with performance guarantees for the payers. That's a dramatic change from the approach to pricing and reimbursement taken by the industry up to now. It demonstrates the pressure on gene therapy companies to reset the terms on how they go to market.

It is also changing the dynamics of pricing in the rare disease space, once seen as less prone to the restrictions that payers placed on chronic care medicines. Rare disease drugs faced scant competition and were intended for small target populations. But in the last three years we have seen biotech and big pharma rush into this segment, replicating many of the same conditions

we've seen in more common chronic diseases.

A good example is spinal muscular atrophy (SMA), a high-profile genetic disorder with a small cohort of several thousand patients in the US. The first effective gene-based treatment, Spinraza, was approved by the FDA in December 2016; since then, another possibly curative treatment, Zolgensma, has entered the market and three more similar products are now in pipeline. Payers may not be jumping to impose the same kind of blanket, race-to-the-bottom pricing regime as they've imposed on primary-care cardiovascular and diabetes drugs. However, payers will demand concessions from manufacturers to avoid significant restrictions. Biotechs recognize this, which is why you're seeing a proliferation of risk-sharing agreements.

Looking forward, innovation is no longer just about the science; innovation can drive the contracting structure as well. An innovative contract by itself can differentiate against a competing product in the same category, and preferred status will come precisely because the manufacturer has offered a better way to buy the product. What this means is more variety in types of contracts, not just one preferred approach. This is good for all parties.

Ryan Walsh: The embrace of integrated care models of financing and delivery creates a natural home for innovative contracting. But the situation must be placed in perspective.Although many big pharma CEOs have warmed to the idea of innovative tools like value-based contracting, there is "no one size fits all" approach. The circumstances that make these agreements feasible are often unique. Not everything is measurable. Not every outcome is achievable or meaningful within a time frame acceptable to payers and pharmas. That said, there is no question that innovative contracting is now an essential tool for pharmas and payers.

Case Study: There Is Reward In Risk

Barlow: The increasing power of payers, a consolidating marketplace, price pressures – these require companies to take a novel approach to pricing, particularly in very high-cost or competitive categories. If you think about the three basic elements of a drug's value – efficacy, safety, and cost – only cost is not an intrinsic property of the drug. And the higher the cost, the greater the need for its justification. Just as companies have to prove safety and efficacy to the FDA, they will more often have to prove value – which is what a risk-sharing agreement does. As Ryan Walsh notes, we can't minimize the complexities of these arrangements. But pharma is going to have to put its money where its mouth is. It does it all the time in R&D when spending millions on clinical trials. By the same token, it will more often have to risk its commercial investment with a value-based agreement.

Take the Illumina/Harvard Pilgrim risk-based contract for coverage of non-invasive prenatal testing (NIPT). NIPT is more expensive than traditional prenatal screens – but it's also more accurate. And, Illumina argued, using their NIPT technology would not increase costs: doctors would stop spending money ordering traditional screens and the more accurate NIPT would reduce the number of false positives and therefore the number of invasive tests, like amniocentesis. And the fewer the invasive tests, the fewer the adverse events. But payers balked at expanding coverage because of the price.

So, in a deal we helped arrange and monitor, Illlumina went at financial risk – if Harvard Pilgrim expanded coverage to average risk pregnancies, the plan's screening costs would not go up, and invasive testing would go down. And 18 months after the deal was signed in January 2018 the results are in – more NIPT tests were ordered, invasive testing and overall screening were reduced, and costs were flat. Illumina now has a trove of highly credible, real-world data it can use with other payers and Harvard Pilgrim members have access to high quality care. That's the power of risk-sharing.

Cancer Gets Competitive

When I first asked what pharma is doing about pricing, you lumped together oncology and rare diseases. But are there differences?

Longman: Absolutely. Oncology is still the most price-protected of all major therapeutic categories – which is why you see so little rebating in the category, or the kind of innovative contracting we have been describing. Payers have little ability, and less will, to force the kind of formulary or use preferences they're happy to require in other categories – and which they will use in even rare diseases when competition heats up.

For one thing, oncology has regulatory advantages. It's one of Medicare's six protected classes so it's very difficult for a plan to keep any new entity off a formulary. On the public side, oncology is THE scary disease – no payer wants a headline saying it denied "Sally Smith," mother of three, a life-saving cancer drug.Oncologists also make a significant share of their income from the buy-and-bill economics of cancer – they're still incentivized to use the more expensive therapies. Fighting motivated providers is tough. But the most important issue is payer habit. In most other specialty categories, payers can require "PA to label," that is, they'll only authorize reimbursement if the drug is being prescribed for a labeled indication. In oncology, payers will, in essence, "PA to guidelines" in the compendia, like the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, which are very liberally determined. If there is even modest evidence that a drug works in an indication, it's generally listed in the compendia – and a payer will most likely approve the reimbursement.

The question going forward: how long will this situation last? Our bet is that as competition heats up, as we see more head-to-head trials within categories – say the PD-1 inhibitors – the also-ran drugs, the ones that are fourth or fifth into the category, will create strategies in collaboration with payers and providers that focus on reducing patient cost. And those strategies will begin to change oncology reimbursement.

The Great Evidence Divide

Can new information tools like real-world evidence help raise the level of confidence in the assumptions that underpin innovative approaches to contracting between pharma and payers?

Barlow: Real-world evidence is often a prerequisite for clinical approval and adoption of a rare disease therapy. It's clearly part of the fabric in how such drugs are evaluated. The problem is the disconnect between the design of a pivotal trial and linking

measurements from that to an outcomes-based metric to assess the execution of an innovative contracting arrangement. An example is the "Six-Minute Walk test" introduced some years ago to evaluate a patient's aerobic capacity and endurance. While this measure is commonly used in the clinical trial setting, it is not a practical test for use in clinical practice and rarely used. That makes it much harder to obtain verifiable outcomes linked to the trial that can be trusted as relevant by both parties to a contract. Defining those outcomes has been a large part of our recent work: can we establish an endpoint in a clinical trial that that can also be used as an endpoint in a risk-sharing contract?

Looking Forward

Cumulatively, how will the forces you have outlined shape industry prospects for market access in the coming year?

Berkowitz: It appeared for much of this year that the Trump Administration would introduce a major change in the current business model for pharma through removal of the federal anti-kickback statute's safe harbor clause for rebates on medicines in the commercial sector. Then suddenly, over the summer, it was quietly withdrawn.

The lesson we draw is that the polarization of politics today effectively prevents Congress and the White House from agreeing on a coherent strategy toward the industry, good or bad. Government is actually less relevant if we consider how the vertical integration of the past two years has inoculated key private-sector players in health care against the disruption that removal of the safe harbor clause might have caused. In fact, the consolidation of roles formerly played separately by Insurers, PBMs, retail pharmacy and distributors remove the incentives for any one actor to blow up the system. The Medicare Part D benefit has been in place for more than a decade; it's one of the more successful federal programs in terms of public support. Now that a few massive, well-integrated private-sector companies are delivering medicines consistently and safely to more than 80% of the US population, it's hard to envision a world where government displaces that system with something new and untested.

What about the rise of health technology assessment influencers like ICER? Will it and other similar institutions emerge as the true arbiters of market access by defining what constitutes value in medicines?

Barlow: It is becoming important to consider in advance the reaction of groups like ICER in pricing a new drug. How will your entry fare as ICER lays out the value landscape in a therapeutic area? ICER is influential, no doubt. But there is a bigger strategic question for industry, which is the need to assess the impact of other players with a significant customer base of their own. Are you going to Aetna, UnitedHealth, or Cigna and asking them what's on their mind and the issues you should be solving for? In many ways, this is a conversation that is much more strategic than the kind of narrowly focused dialogue one has with ICER.There is more to business than pitching the value of a particular drug. It's better to start with a broad perspective on solving the customer's problems rather than simply trying to make that customer buy what you're trying to sell to him.

What's the best course for drug-makers to take in navigating successfully through this complex political environment in 2020?

Walsh: The industry has an opportunity to pursue and, importantly, promote more rational and defensible approaches to pricing. Although drug pricing, however tempered, will always be a lightning rod for criticism, this kind of self-regulation will go down well in an election year. Interestingly, it's already underway, but rarely publicized, and even more rarely credited to the manufacturers (often other channel partners will take credit for these very actions as a result of their marketplace pressure). Many companies have moderated their traditional price increases, in both size and frequency, and others have taken opportunities to make increases contingent on meeting a defensible benchmark, like the medical inflation ratio. On launch pricing, there has also been some more deliberate, rational pricing, especially in more competitive spaces where payers are looking closely at market dynamics like generic penetration, brand saturation and differentiating therapy characteristics. Overall, self-regulation will carry the greatest impact, certainly more than government can expect to achieve given the lack of alignment in politics at the federal level.

Overall, self-regulation will carry the greatest impact, certainly more than government can expect to achieve given the lack of alignment in politics at the federal level.

Longman: Companies will continue to surprise with actions that the investment community would have dismissed as improbable – even impossible. In 2017 I was a member of an advisory group looking at the competitive outlook for the PCSK9 inhibitor class of anti-cholesterol drugs. We were about 15 people from companies and payers and the big question was whether the two companies competing in the space would opt to cut list prices to grab more market share. The verdict was unanimous – no way, never. Yet Amgen late last year slashed its price for Repatha by 60%. Lilly did something similarly bold to shake up pricing for insulin. Right now, bluebird bio is suggesting it could price its beta-thalassemia drug, Zynteglo, in a way that meets payer concerns about the durability of this curative therapy, given its likely $2m plus price tag. It's an amortization arrangement where payers pay 20% up front, with the remaining 80% spread over five years and at risk if the therapy doesn't work. This is a risky strategy, but it certainly represents an effort to meet the market more than halfway.

Comments:
Email the editor: *Lucie.Ellis@Informa.com*

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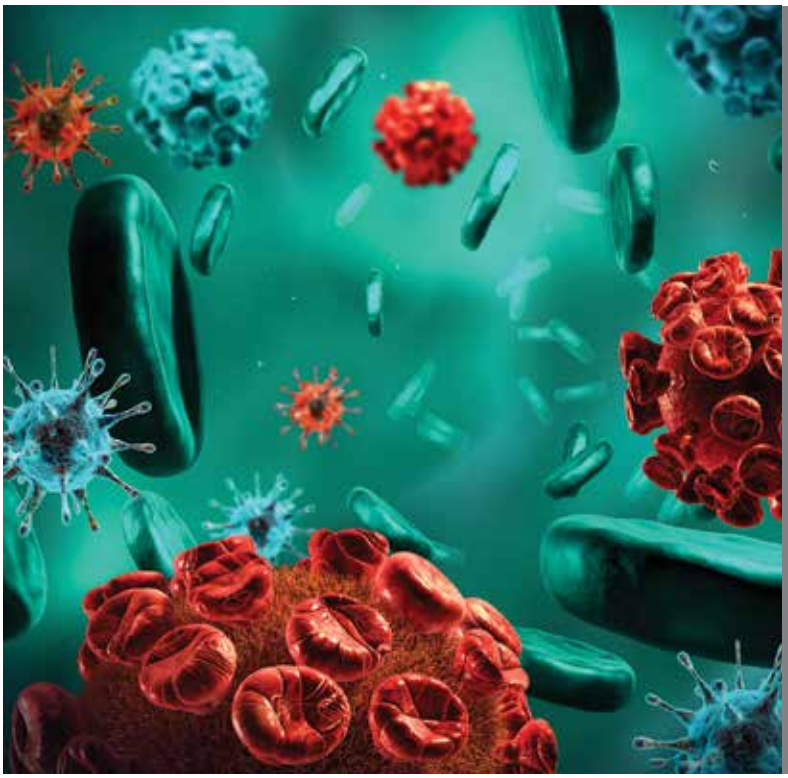
Gates Foundation Plots A Fresh Metric For Market Access: Lives Saved



In Vivo visits Gates Medical Research Institute CEO Dr. Penny Heaton to review its first pipeline of drugs and vaccines to attack four of the world's biggest killers: TB, malaria, enteric diseases and other conditions affecting maternal, newborn and child health.

BY WILLIAM LOONEY

As a drug developer, Gates Medical Research Institute will apply to the FDA for an IND just like any biotech. Last month, it launched its first clinical trial, in South Africa, for a booster vaccine against TB; it is also exploring novel options like applying monoclonal antibodies as a seasonal treatment for malaria when it is most virulent.

CEO Penny Heaton hopes to have 20 product candidates in the pipeline by 2023, with half of these in trials.

So what? The MRI is testing an unusual proposition: can generous, hassle-free financing be combined with a business mindset to treat life-threatening conditions whose persistence is historically associated with market failure? Watch and wait - its an early portent for global market access in the next decade.

What it means to be a drug company has begun to change in recent years, as societal expectations of performance extend beyond investor returns and NGOs and governments claim medicines as a universal public good, accessible to all. Adjacent industries are entering the drugs business while non-commercial actors like patient advocates and philanthropies fund their own R&D programs for medicines to address conditions with high unmet need. Perhaps the most prominent of these emerging players is the Bill and Melinda Gates Foundation, which last year established its own non-profit biotechnology enterprise, the Gates Medical Research Institute (MRI), to develop drugs and vaccines targeting major neglected diseases of poverty like tuberculosis (TB) and malaria.

The Gates MRI initiative is representative of a strategic shift among major private health donors from passive funding to hands-on doing. Interest is high in using the integrative, results-oriented practices of translational medicine to better manage disease etiology in vulnerable populations and increase the speed in which new treatments reach patients on the ground.

What is unique about the Gates MRI is its focus on learnings from the private-sector – including big pharma and biotechs – in moving drugs and vaccines from proof of principle to clinical proof of concept, followed by clinical trials, and ending with registration and uptake in the marketplace. Every Gates MRI project is evaluated on a simple, two-word metric of performance: lives saved. The charge looks simple – deceptively so. The fact is Gates MRI was launched out of the awareness that it is not enough to develop a new life-saving technology; you also have to create the expertise to execute around it, with the organization, logistics, information, policy and partnering skills to ensure that the drug or vaccine can be delivered safely to the market. And, most important, be widely used.

True to form, the Foundation has invested heavily in the money (more than $100 million annually over the next 15 years) and the talent (recruiting top experts in clinical operations and project management, as well as in new fields like quantitative science modeling and AI) to achieve this vision of moving new treatments seamlessly from bench to bedside. Leading the effort is Dr. Penny Heaton, a 55 year-old physician with one of the more distinctive backgrounds in medicine and public health, as an infectious disease expert in academia and the US government and more recently as a vaccine developer at Merck & Co., Novartis AG and the start-up biotech Novavax Inc. As the CEO of Gates MRI, Heaton is also intimately familiar with the working culture of the Seattle-based Foundation, where she helped develop the group's current strategy targeting major diseases with a disproportionate impact on vulnerable populations, especially women, infants and young children.

Heaton thus brings to her new assignment a diverse set of career experiences touching virtually every aspect of the health care landscape. It began with an early introduction to tuberculosis – the world's most deadly infectious disease – when her father, a minister in rural Kentucky, contracted it two years before Heaton was born. "I spent my first years in a household under siege, as my father's eventual recovery left him in constant fear the bacillus might return and infect us all. The one positive was it drew me into the mystery of how something so small could wreak such havoc on human civilization. Even before high school, I knew I wanted to devote my life to the study and treatment of infectious diseases."

Pathogens Pointed The Way

Indeed, Heaton's fascination with bugs led her to the University of Louisville Medical School, where she received an MD in pediatric medicine, followed by an additional research fellowship in infectious diseases funded by a local charity. But, coming as it did just as large-scale health maintenance organizations were depersonalizing the physician-patient relationship, Heaton began to question whether a license to practice medicine was enough to make a difference in people's lives. Looking for opportunities outside Kentucky after the death of her mother, Heaton obtained a position at the federal Centers for Disease Control and Prevention (CDC) in Atlanta where she was assigned to the Epidemic Intelligence Service, specializing in the investigation of foodborne and diarrheal disease outbreaks around the world.

Dr. Penny Heaton, CEO
Gates Medical
Research Institute

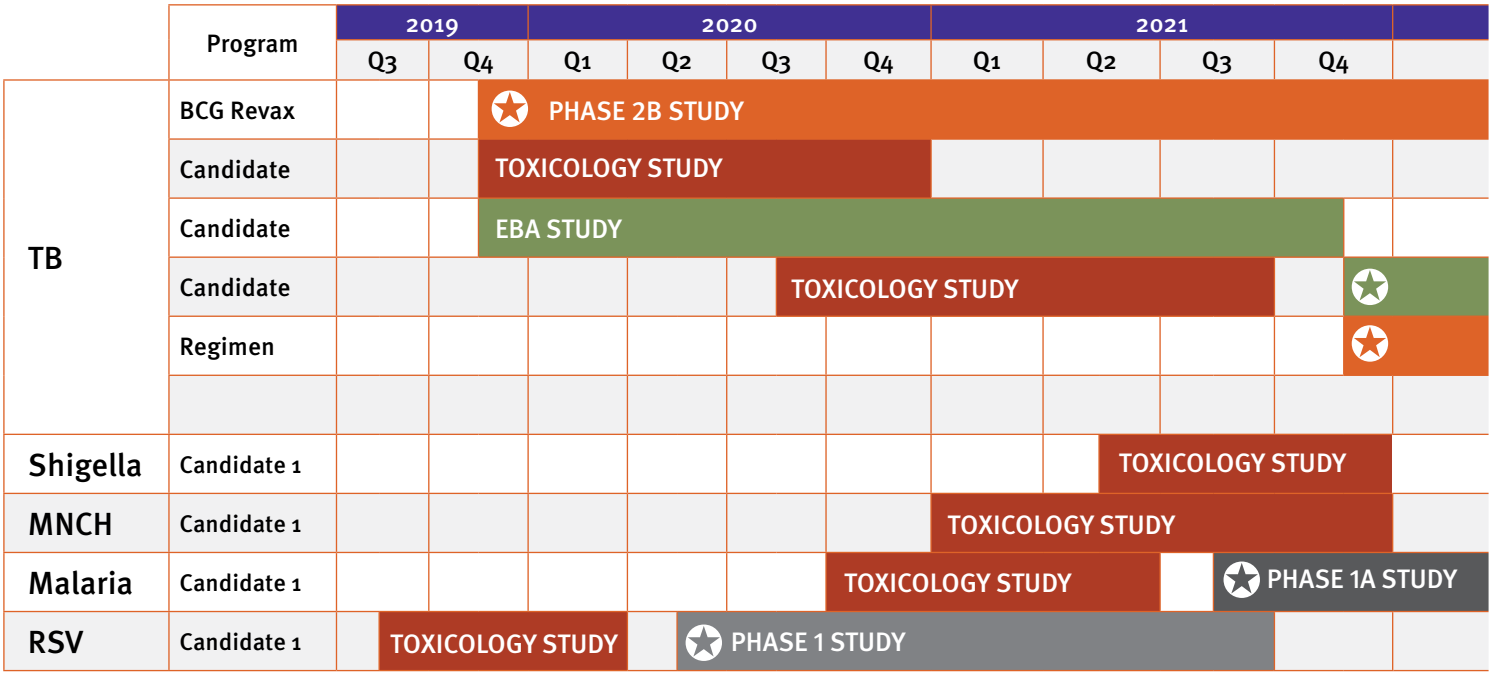
> *"The Gates Medical Research Institute was launched out of the awareness that it is not enough to develop a new life-saving technology; you also have to create the expertise to execute around it".*

"Working at the CDC gave me a first-hand look at how hard it is to control the spread of pathogens, even in countries with advanced health infrastructure like the US. The inequities in global health also became glaringly obvious, with the prime example being diarrheal disease, which kills more than 500,000 children a year and is almost entirely preventable. More important, it showed me that progress against endemic infectious diseases could benefit from the active involvement of stakeholders outside government, such as the private sector. At the CDC, we knew that simple, remedial measures like boiling water and hand washing could lower the incidence of disease. But I wanted so much more, such as the ability to introduce vaccines and other innovative technologies to prevent these conditions – a goal that publicly-funded efforts could never achieve on their own."

Industry's Calling Card: The Rotavirus Vaccine

It may have been serendipitous but recruiters for big pharmaceutical firms began contacting Heaton as the science advanced on new vaccines for major killers, including for her own specialty in pediatric diarrheal disease. Merck &

Exhibit 1
Gates MRI Drug/Vaccine Pipeline 2019-2023



First Subject In

Co. Inc.proved the most persistent, with a vaccine for the rotavirus in final stages of testing that reflected years of struggle to perfect a liquid formulation suitable for children. "I took the job as head of Merck's rotavirus vaccine development team, taking the candidate through late-state testing as well as dealing with the safety surveillance fallout due to some adverse side effects from a competitor's FDA-approved vaccine. It was a formidable but instructive learning experience – at the time, Merck researchers were best in the world in this field." Heaton followed her time at Merck with a stint at a small Maryland-based biotech, Novavax Inc., where she managed a broad portfolio covering vaccine strategy and early-stage development, and then migrated to the biggest of big pharma, Novartis AG, where she led clinical research for the company's vaccines portfolio.

Of her time in the private-sector, Heaton said it was the ultimate broadening experience. "I learned how to operate in complex, tightly-focused organizations, large and small, prioritizing among a portfolio of drug candidates and marching them through the pipeline to a discernable end – a product that works for patients. Combined with my earlier roles in academic medicine and government service, it put me in the best possible position to lead this new hybrid institution inspired by Bill Gate's vision combining public service and private know-how to generate great medicines for the greatest unmet medical needs."

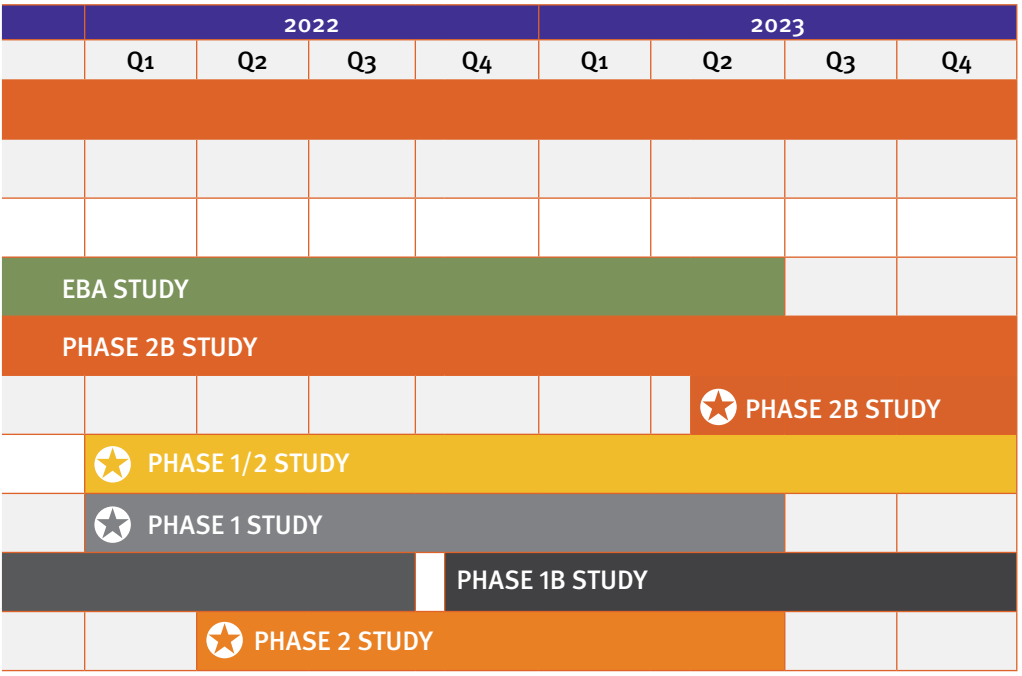
Heaton's attention turned to the Gates Foundation after she was approached in 2013 by Dr. Trevor Mundel, President of the Foundation's Global Health Division, to discuss a reorganization adding a specific product development component to the group's baseline strategies to fight disease.

Shortly after, Heaton joined the Foundation with the charge to apply her experience in industry to lay out an approach to vaccine development in resource-constrained settings. "A lot of what I did was introduce the processes used in private industry, starting with that living document called the target product profile, laying out all the upfront work necessary to conduct the clinical trials and everything thereafter, especially the regulatory protocols and manufacturing/distribution logistics that are critical to vaccines but weren't really part of the Foundation skill set at the time."

Opportunity Knocks: Origins Of Gates MRI

Thus, when Bill Gates decided in 2017 to create a new unit of the Foundation to develop new drugs and vaccines – just like big pharma, but with a broader access footprint – Heaton was the logical choice to run it. It would work in the manner of a nimble biotech start-up, focused on products to prevent, treat, and cure the diseases of the poor. It would open a new chapter in the Foundation's evolution from a grant-making philanthropy to a hands-on enterprise guided by a business plan relevant to conditions on the ground.

The Gates MRI was launched in January 2018 with a $270m grant from the Foundation, an office in the Cambridge MA biotech hub, and Heaton as CEO. Backed by a staff now totaling 65 professionals from diverse backgrounds in science, clinical practice and commercial operations, the group reports to a board chaired by the Foundation's global health lead Mundel, and which also includes the Foundation CEO, Dr. Sue Desmond-Hellmann, herself a drug industry veteran as the physician oncologist behind Genentech's breakthrough drug for breast cancer, Herceptin.



SOURCE: Gates Medical Research Institute

In addition to the Cambridge HQ, there is a satellite office in Seattle WA, at the University of Washington campus.

Running a non-profit that emulates the mindset of a for-profit enterprise has been a liberating experience for Heaton. "Six weeks in, I felt like a bird let out of the cage, fighting infectious disease while reaping the psychic benefits of giving something back to a world consumed by want. Moreover, I no longer had to worry about finding the financial resources to justify a business plan and the marketing logistics around it, activities that in the private-sector took three quarters of my time. We had the funding to do what we needed to do."

From the start, Gates MRI has observed this simple work rule: the Foundation sets the strategy; MRI executes it. The Foundation has written a broadly framed, 15-year business plan for the Gates MRI stipulating activities on two levels: the first to develop and then introduce to market with partners individual products like drugs and vaccines, geared to combatting pressing threats to patients and public health in low income settings; the second to focus on long-term investments in improving the clinical development process itself, resulting in a more rapid and efficient translation of gains in science to success in the field. Above and beyond the $270m received so far, the Foundation anticipates the Gates MRI will require an operating budget of at least $100 million a year going forward, depending on the pace of progress in the group's portfolio.

Focus On Four Diseases

The strategy is for Gates MRI to develop products to accelerate progress in ending four pervasive conditions that together pose the greatest threat to global health. These are:

- tuberculosis;
- malaria;
- enteric and diarrheal disease, particularly in children under age five; and
- other conditions that lead to adverse maternal, newborn and child health outcomes (MNCH).

Global health statistics bear this out. The TB bacillus is present in one quarter of the world's population, with 10 million new cases a year and 1.3 million deaths reported by the World Health Organization in 2018. It is a leading co-morbidity factor in deaths from HIV, with more than 250,000 deaths linked to TB in 2018. Malaria accounts for nearly 500,000 deaths annually, out of a case burden now totaling more than 200 million in 87 countries, mostly in Africa. The third priority, enteric diseases like shigella, one of the leading causes of diarrhea in infants and young children, kills more than 2,000 children under age five die every day. Added to this are other diseases affecting nursing mothers and young children. One, respiratory syncytial virus (RSV) is the current focus of Gates MRI activities for this vulnerable public health cohort. The big takeaway is all four of these disease areas are preventable – and the technology and expertise already exist to make their eradication feasible, with an equally big payoff in terms of fighting poverty and advancing the Foundation's operative premise that "all lives have equal value."

Shortening The Time From Idea To Impact

Getting organization and process in line with this objective dominated the Gates MRI's first year. "I had to build a group that could turn an abundance of ideas from many quarters into a few specific solutions, aiming to apply the Foundation strategy to projects showing a measurable outcome," Heaton tells *In Vivo*. "In practical terms, my charge is to invoke the principles of translational medicine, pursuing development of new drugs and vaccines with partners that we either contract with ourselves or leverage through the Foundation, progressing to clinical proof of concept and then working with others to pursue market access for the product, including manufacturing and distribution at scale."

The Gates MRI does not expect to do all the heavy lifting, all the time; in many cases, a partner will take the lead in conducting a clinical trial or other milestones required to move the asset into the market. There are plans to work with CROs on the conduct of clinical trials. In fact, one of Heaton's priorities is to find local companies in low-income countries that can manage commercialization, which has the added advantage of transferring know-how to stimulate the growth of a strong market for life sciences investment.

The vehicle to make all this happen

is the product development team (PDT), which Heaton introduced based on her experience in the private sector. The model is integrated and cross-functional; each PDT operates with a single end goal in mind, to deliver a product that is both clinically useful and accessible to low/middle income patients in resource-constrained settings. The process itself focuses on a product development plan that sets out, step by step, how a potential asset will move from pre-clinical review and testing to a completed proof of concept addressing the target population, at which point a joint Portfolio Steering Committee decides whether to move ahead on adaptive phase two or three trials that can be conducted through a partner or, in some cases, by MRI itself. "In doing so," said Heaton, "we are probably a bit more rigorous than a private enterprise might be on access issues like ensuring that the asset fits the needs of the relevant patient community and can be administered successfully in the context of conditions on the ground. We want to be sure it represents the safest and most efficient approach to getting the right therapy to the right patient."

Every PDT is co-led by a physician or PhD scientist with experience in clinical development and a project manager able to coordinate the mix of talent, resources and logistics required by the Gates MRI's translational approach to medicine. Team members include MRI staff grouped into eight zones of expertise: clinical development, project and portfolio management; clinical operations; translational discovery; biomarkers and assay development; regulatory affairs; quantitative sciences; quality assurance; and chemistry, manufacturing and controls. There is also a group that manages business development through partnering.

Importantly, Gates MRI's translational discovery group strives to put all this expertise together, working with the Foundation's extensive list of partners to provide a steady flow of clinical-stage development candidates for the PDTs. "The Foundation funds upstream partner work in the MRI's four priority disease areas, so our discovery team works with these partners to keep tabs on how their projects are progressing and suggest ways to accelerate them into clinical trials and eventually to commercialization," Heaton said.

We Do Drugs ... And Vaccines Too

The bottom line is, yes, the Gates MRI will apply for an IND from the FDA or equivalent agency just like a big pharma or biotech. "We interface with the regulatory agencies, we draft the protocols, we conduct the studies with investigators at each site, using contract research organizations (CROs) to monitor and collect the data which we then report back to the FDA – our business model positions Gates MRI to act as a full-service enterprise."

To guide its work, the Gates MRI adheres to a few principles of public policy developed by the Foundation. Promoting access to products through donations is not part of the MRI agenda – the belief is something that is free is not necessarily the best way to ensure full uptake of a product. Incentives are present, even in a resource-constrained setting. To Heaton and her team, access involves commitments on making products available to low-income countries at an affordable price, which in turn involves negotiations on volumes and timing as well as price.

It follows that a company involved in producing drugs or vaccines is entitled to earn a profit from their investment, although how much profit is always an appropriate topic for discussion. Heaton said, "Over the years, the Foundation has formed a consistent position on how we approach access to health and medicines, and transparency is a key part of our thinking." Thus, Gates MRI supports open sharing of data, clinical studies and other active learnings as well as relevant price information. While the Gates MRI has no plans to consult cost-effectiveness evaluation bodies like the Boston-based Institute for Clinical Evaluation and Research (ICER), evidence is an important tool of its access agenda. What is distinctive is Gates MRI applies different measures of acceptability than the private-sector. "We are willing to fund development of drugs or vaccines that are 'market failures' but they must be affordable and have a significant impact on metrics like disability adjusted life years (DALY)."

Heaton continued, "When we negotiate access for our products, we look at the target population and the potential demand based on need. With that, we establish prices that are affordable to that target within a given time frame. The cost of goods, including manufacturing costs, is part of every consideration. Overall, affordability depends on circumstances that are unique to each product, so we don't think about maximizing profit margin in the same way as a commercial business might. What's important to remember is that, evidence and profits aside, the bottom-line metric for us consists of two simple words: lives saved."

Power From Partnering: MRI's Force Multiplier

The practical expression of MRI's commitment to translational medicine is the desire to work with partners – this is not just a "do it yourself" operation. The net is broad, including, in addition to partners already involved in Foundation-level initiatives, representatives from academia; industry, from big pharma to biotech start-ups; non-profits and NGOs; and CROs and manufacturers. Many are based in low- and middle -income countries, where MRI's disease areas of interest are most prevalent.

The model MRI intends to build on is the Foundation's 2012 launch of the TB Drug Accelerator project, working with the biopharma industry to address a longstanding drought in new drugs to attack the world's biggest infectious disease. The impetus was the arrival that same year of J&J's bedaquiline (Sirturo), the first new treatment for TB in 50 years. To help jump start more R&D, the Foundation organized the Accelerator, which in seven years has morphed to 18 organizations committed to obtaining market approval for a new generation of drugs and vaccines to fight TB. Eight, including J&J, are from big pharma and biotech; the other 10 are leading academic and research institutions. Among other things, members pledged to open their compound libraries to screen for candidates that could activate against the TB bacillus, work that has now produced a large pipeline of possible drugs.

The plan is for Gates MRI to assume the task of neutral broker in taking this bounty forward. "We intend to prove

researchers' estimation that a shorter, safer and simpler TB drug regimen is going to require two or three separate drugs used in combination," Heaton noted. "Chances of something as novel as that coming out of the labs of one company is very low. So we are excited about being selected to manage this next phase, in which the Gates MRI will coordinate with four company members of the Accelerator plus the Foundation to identify the first new investigational TB drug regimens for TB, taking forward the most promising regimens regardless of which company they come from. It offers us a great opportunity to notch some new gains against TB, which despite its prevalence remains a truly neglected disease."

In June, MRI announced its first outside partnership, a drug development collaboration with Spero Therapeutics Inc., a Cambridge MA-based biotech active in treatments for multi-drug resistant bacterial infections and rare diseases. Spero has granted Gates MRI a license to develop and commercialize one of the company's candidate antimicrobial drugs, SPR720, for treatment of lung infections caused by the *mycobacterium tuberculosis*, the principal causative agent of TB. The Gates MRI will fund and conduct preclinical and clinical studies on SPR720 to advance it to FDA approval for use in low- and middle-income countries where the disease is endemic. A phase one trial on safety and tolerability of SPR720 has already been conducted by Spero, with a report on top-line data from the trial due out before the end of this year. The candidate has also been designated by the FDA as a Qualified Infectious Disease Product (QIDP), giving it rights to accelerated review time and a longer period of market exclusivity.

"Spero was focusing on SPR720 because of its effect on rare microbial conditions outside TB, but we saw synergies because the drug works by a different mechanism than existing products for TB, where the drug armamentarium has really not changed for decades," Heaton told *In Vivo*. "It was a logical choice for them to be our first partner from private industry and it fits nicely within the remit of the Accelerator initiative."

Heaton expects a significant number of partnerships to be contracted in 2020,

GATES MRI CEO PENNY HEATON SPEAKS...

ON PROGRESS IN GLOBAL HEALTH ...

"When I look back and think about what things were like in 2000, the big multilateral donor institutions we take for granted today did not exist. There was no GAVI for vaccines; no Global Fund for AIDS, TB and malaria; no PEPFAR to prevent the spread of HIV in Africa; the Bill and Melinda Gates Foundation was in its infancy. This concerted institutional response has cut child mortality from infectious disease by more than half, from 10 million deaths annually to less than six million.Deaths from malaria have also been cut by half, new cases of TB are declining by an average of 3% a year, and 80% of sub-Saharan Africans diagnosed with HIV are now on life-saving anti-retroviral drugs."

... AND THE CHALLENGES THAT REMAIN

"Too many people – especially women, infants and children – continue to die of diseases that are largely preventable. I worry about maintaining our progress in improving health status, for two reasons. One is that, from a technological and logistical perspective, what we have left to do is really hard. Having clocked so many "wins," the complexities involved in delivering health solutions on the ground – that "last mile" to the patient – are daunting. The second is basic public health interventions still need more support from private-sector players like big pharma and biotech. They have the product development know-how to help us succeed. But, as investor pressure on the bottom line intensifies, keeping them involved has become tougher than ever."

WHY SHE'S AN OPTIMIST AT HEART ...

We are at a special time in history, with new science that has enormous potential in saving and extending lives. The tools are within our grasp to confront the pathogenic and immunologic roots of infectious diseases that have plagued humankind since the dawn of civilization. Insights derived from the oncology and rare disease space are capable of being translated into interventions with even broader impact on the neglected diseases of poverty that kill millions – *if* we get the access and affordability issues right.

WITH A CLEAR VISION ON THE FUTURE ...

I can envision a time when the potential of every woman, man and child is unleashed by good evidence and unbiased information. Can we use the cloud and the cell phone to overcome the absence of a traditional health data collection and retrieval infrastructure in low income communities? I think we can – and it's a logical step from there to introduce, without the barriers imposed by legacy systems, the latest real world evidence (RWE) technologies to inform our clinical trials and support development of a new generation of vaccines to improve health standards in communities where the unmet medical need is greatest.

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divided between 1:1 deals and collective arrangements involving multiple organizations, with the TB Accelerator being the obvious precedent. All are geared to fighting the four diseases identified by the Foundation as strategic priorities. It's unconfirmed, but GSK, Otsuka, J&J/Janssen, Evotec, the TB Alliance and Institut Pasteur are said to be in active negotiations with the Gates MRI.

Culture: Five Mantras To Motivate

Scoping the disease landscape, building a drug pipeline and cementing external opportunities demand a responsive and disciplined internal culture geared to the Bill and Melinda Gates philosophy of constantly extending the boundaries of what's possible in the pursuit of saving lives. Heaton has put her stamp on the work environment through the delineation of five mantras: (1) innovation; (2) collaboration; (3) courage; (4) rigor; and (5) urgency. "We had some situations where we had to rely on these workplace principles very soon after MRI was established, confided Heaton. "There was one drug we were asked to take into clinical trials in our first six months as an organization, and we were excited about it. But as we were conducting due diligence on the drug we noted a few toxicity issues; ultimately, we had to inform the Foundation board not to proceed unless there was further evaluation."

"It wasn't the best message – the desire to quickly demonstrate our *bona fides* and get something out to patients was strong.But reviewing the evidence against our mantras on courage, rigor and urgency helped us clarify, come together as a team and render the right decision to ask for the delay."

Gates MRI achieved its most important strategic milestone earlier in the summer, when it agreed on a pipeline of candidate drugs and vaccines in the four priority diseases areas (*see Exhibit 1*). On malaria, where the overall goal is to find products that contribute to its ultimate eradication, work is commencing with the Foundation and other partners to develop a vaccine with greater efficacy and durability than the RTS,S vaccine, which is now being introduced for pediatric use in three countries in Africa – Ghana, Kenya and Malawi.

> *"We are a window on emerging country markets of the future, with their enormous untapped demand for better health and well-being, including access to good medicines and vaccines. I wish biopharma CEOs had a better appreciation of that latent desire for a better tomorrow. It's universal among todays poor."*

The Potential Of Monoclonal Antibodies In Malaria

Gates MRI is coordinating an active learning program based on the clinical history of RTS,S. According to Heaton, "We've already learned a lot from RTS,S about the immune response to malaria. What's really exciting us now is how monoclonal antibodies – a treatment platform first identified 30 years ago – could work as an effective and powerful bridge in treatment until a more durable vaccine with longer efficacy in patients can be brought forward. So rather than administer a long-acting but less efficacious vaccine to induce that antibody response, we could focus on a more impactful seasonal approach, giving the antibody before the rainy season when carrier mosquitos proliferate and prevent malaria until the dry season when the threat of infection diminishes. Right now, we know the antibody approach works in animal tests, so the goal is to do human studies, including children, the most vulnerable victims of the disease."

The plan calls for toxicology studies to begin on a selected candidate in late 2020, followed by a phase 1(a) study in third quarter 2021 and a Phase Ib to commence in late 2022, continuing to the end of 2023. At that point, a decision will be made to proceed with human trials leading to full development and eventual commercialization. Another payoff from this effort could involve finding ways to reduce the cost of manufacturing monoclonals so they become more affordable to low income countries. On its own, the Foundation has been considering this for some time.

A Wider Template For TB Vaccines

The pipeline is also primed for new therapeutic options – both drugs and vaccines – to help fight TB. The most important is last month's start of Gates MRI's first sponsored clinical trial on the Bacillus Calmette-Guerin (BCG) vaccine, which was first tested in humans in 1921 and has long been vetted as a potential prophylactic against TB when given to infants. The trial, funded by the Foundation, will see if a booster dose of BCG given when those infants become adolescents and young adults can confer lifetime immunity against TB. The trial

will be conducted in South Africa. Heaton said, "This trial is big for us, as it provides the opportunity to demonstrate that the MRI partnering model is as proficient as industry or government in driving so many moving parts to a successful, timely conclusion. We've worked with investigators in designing the study, sites have been selected, recruitment is on schedule, and the necessary regulatory submissions are complete. Training for investigators and nurses has been conducted at each trial site and a final investigator group meeting was held in September – so we are good to go."

The collaboration with Spero Therapeutics, MRI's first in-licensing deal with a non-Foundation partner, is moving forward as well. A research plan for drug candidate SPR720 has been agreed, beginning with conducting the toxicology study that will enable the asset to commence with human clinical trials. Spero will manage the toxicity work and then MRI and Spero will work together to conduct a phase II trial focused on identifying how SPR720 influences bacterial activity and to show it has efficacy in humans.

Focus On Shigella

The third priority, enteric and diarrheal diseases, is perhaps the closest to Heaton's heart. She was instrumental in putting top of this list a vaccine against shigella. "I saw shigella's impact up front when I worked in Kenya for the CDC." The gastrointestinal disease is resistant to conventional antibiotics and kills about 100,000 people a year, mostly infants and young children. The vaccine program is being conducted in collaboration with the Institute Pasteur in Paris. "Our target is a very interesting conjugate vaccine with a unique chemistry that we anticipate will be highly efficacious compared to the vaccines developed in the 1990s. These were fairly effective in adults but were useless in treating children under age three. Hence the goal of our work with the Institute is a vaccine that will be proactive with this very vulnerable patient cohort."

To start, the MRI is working on a manufacturing blueprint for the vaccine, chiefly in building out the chemistry to make a conjugate vaccine against the four strains of shigella that represent the majority of cases among infants and young children. The Pasteur Institute has perfected the chemistry on two; Gates MRI has the assignment for the two others. The MRI expects it will take about two years to initiate the human trial phase, which requires the four strains to be incorporated into a quadrivalent or tetravalent prototype vaccine suitable for testing.

On a broader front, MRI is interested in learning more about the immunology behind shigella, where there is currently no reference point for evaluating an antibody that might counter the strains of bacteria that induce disease. "I am convinced we need to evaluate immunologic factors as a potential avenue in curing enteric conditions, using the same tools and approaches that researchers have applied in fighting cancer," Heaton told *In Vivo*.

A Better And Faster Head Start

Finally, the MRI is beginning to act on a fourth overarching priority driven by the Foundation's research agenda – maternal, newborn and child health (MNCH). In February 2018, the Foundation authorized a funding stream to support work in this high-profile demographic. In response, Gates MRI has decided to focus on treatments for respiratory distress, in particular the respiratory syncytial virus (RSV) which is a key factor behind the deaths of approximately one million premature infants annually, mostly in low income countries. While rich countries have access to the lung intubation tubes and ventilators that help babies with RSV struggle for every breath, these are absent in many parts of the world – a better intervention against RSV is needed.

In response, Gates MRI is supporting a partnership that is working on a drug composed of a dry powder surfactant to be given to infants born prematurely i.e. before they can develop the disease. Much of the work so far is centered on the right particle size to dispense the alveolar surfactant powder in the right amount to the right part of a premature infant's tiny lungs. Preclinical data based on studies involving sheep have been positive; Gates MRI and partners are hopeful a human trial can commence by early 2021.

How Heaton Measures Success

Putting all this together, how does the MRI intend to mark its progress over the normal four year planning cycle? Heaton responded immediately in stressing that hers is an assignment that is going to take many years to reach fruition. Despite that, Heaton is confident about really moving the needle in four years – and in four areas.

First is advancing the pipeline portfolio with solid, well-executed clinical trials that largely meet their intended end points. To put a number on it, Heaton hopes by 2023 to have 20 product candidates in various stages of the pipeline. And at least half of these will be at the clinical trial phase.

Second is establishing an internal culture that will attract – and retain – the best talent, in all parts of the organization. MRI will only succeed if it has the right mix of people who are curious and embrace diversity of opinion and cross-functional thinking as the driver of innovation.

Third, and related to these other two, is getting the process right in the pursuit of our disease priorities. "Process can be boring, but if we are to meet the many objectives set forth by the Foundation we must be very efficient about executing. I intend to spend time ensuring our quality controls are working as intended and that all our partners have the shared data they need to help us succeed as a team. Process is vital in coping with an environment of maximum uncertainty – what's ever been predictable about public health, or science itself?"

Heaton's fourth, and final, goal is certifying MRI as a good partner – the partner of choice. "I'd like to convince *In Vivo* readers in big pharma that working with us is a reputation enhancer, particularly among millennials, soon to be the biggest demographic in employment. And we are a window on emerging country markets of the future, with their enormous untapped demand for better health and well-being, including access to good medicines and vaccines. I personally wish biopharma CEOs had a better appreciation of that latent desire for a healthier tomorrow. It's universal among today's poor."

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We Need To Talk: When To Get Early Scientific Advice

Hearing direct from HTA agencies on what evidence they want to see is now an option through early dialogue. With many options for early dialogue available, it is hard for companies to know whether to get advice, from which agency and how to get the most out of the dialogue.

BY LEELA BARHAM

Getting a 'yes' from a Health Technology Assessment (HTA) agency is the goal for any company who submits. Achieving a positive recommendation can be difficult for a host of reasons, including an evidence package that does not meet the needs of the agency.

Hearing direct from HTA agencies on what evidence they want to see is now an option through early dialogue (also known as early scientific advice, early engagement or scientific consultations). The challenge for companies is deciding whether to get advice, which agency to go to, and how to get the most from early dialogue.

So what? Successful early dialogue can put companies in a better position when it comes to appraisal of their drugs by HTA agencies, ultimately affecting market access.

There are some common elements to many early dialogue services available: registering interest, submission of a briefing book, sometimes scope for clarification questions, followed by some form of dialogue – often a face-to-face meeting – with outputs varying from the company taking their own notes to a formal report from the agency. The advice companies are given is confidential and non-binding.

Core to early dialogue are the questions that the company wants the agency (or agencies) to answer; that's the focus of the conversation. Questions can cover the comparator(s), patient population in pivotal studies, outcomes and cut across design for the pivotal trial to complementary sources of real-world data. With agencies like the UK's National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH), early advice discussions are likely to include health economic modelling too.

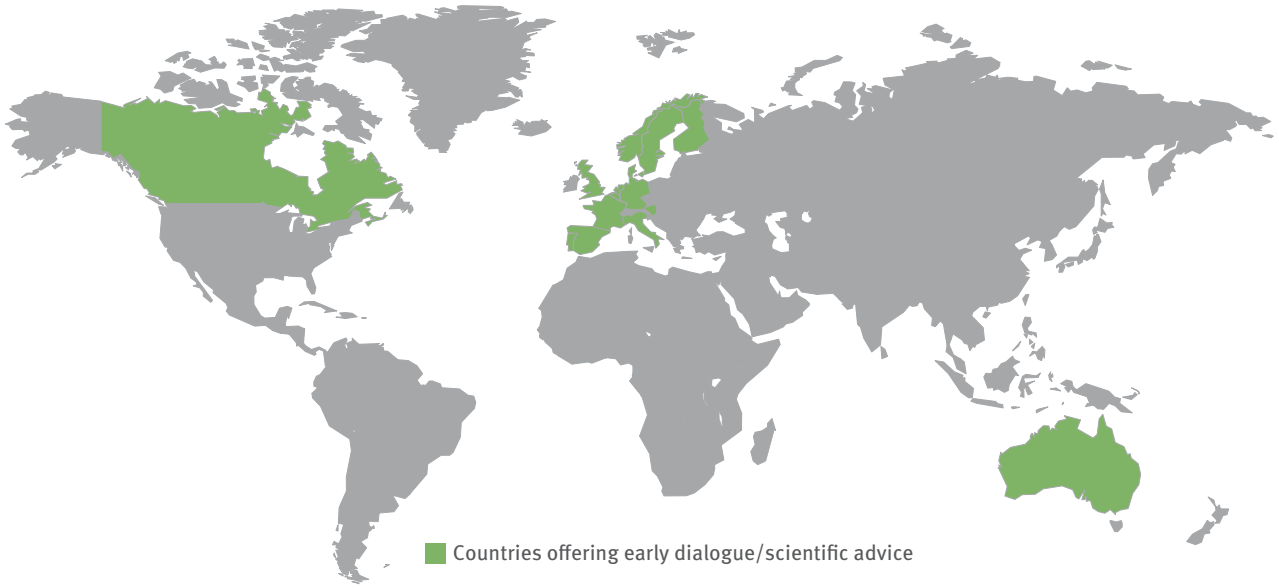
Getting Advice Is A Major Piece Of Work

Seeking advice from a HTA agency is a major undertaking. Sangeeta Budhia, global HTA strategy lead at Parexel International – a global contract research organisation and biopharmaceutical services company – has supported companies on 10 early dialogues. Budhia highlighted the company workload associated with early dialogue, "It can take a lot of time, five to six months. Plus, I usually recommend two to three months preparation before that."

Ross Selby, head of global patient value and access at Takeda Oncology, said Takeda had received advice from NICE, CADTH and Germany's Gemeinsamer Bundescausschuss (G-BA) or Federal Joint Committee amongst others. Selby described how "the

Exhibit 1

Countries Whose HTA Agencies Offer Early Dialogue/Scientific Advice



SOURCE: Data From European Commission And Agency Websites

briefing book can be 150 to 200 pages long." That is not always the case; NICE notes that a briefing book is typically around 50 pages. Selby added, "From the company perspective, getting advice is a massive piece of work."

It costs £30,000 ($38,900) to £75,000 to get advice from NICE, depending on the size of the company, and the speed and scale of the project. The fees for CADTH advice range from CAN$65,000 ($49,400) to CAN$100,000. In Slovenia, the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) told *In Vivo* that the agency charges on the basis of working hours required at EUR50 per hour. Not all agencies have a cost for this service: getting advice from France's Haute Autorité de Santé (HAS) is free of charge.

Achieving reimbursement can only be helped – but not guaranteed – by understanding what HTA agencies are looking for in an evidence package. Budhia explained how advice can mitigate risk, "Getting advice can minimize the risk that companies have not understood payers' needs, that they haven't tailored their evidence package to minimize risk and uncertainty from the payer perspective."

Jeanette Kusel, director, NICE scientific advice, explained that "scientific advice can help companies to optimize their evidence generation plans." Kusel said it was a help to companies because "it should make their lives easier when it comes to getting through the NICE process."

Michelle Mujoomdar, director, scientific affairs, CADTH, put early dialogue into the broader context of the pathway to reach patients. She said, "It's about helping to smooth the pathway to reimbursement and ultimately improving timely access to innovative drugs for Canadians."

The value of advice is in the help it can give a company in reaching that all important HTA 'yes.' "When it comes to the appraisal later, we're in a better position to demonstrate value and get a positive recommendation," Selby said.

More Choice Of Agencies To Talk To

Ten years ago, NICE was the first HTA agency to formally offer scientific advice to companies. Australia offered a pilot process for meeting with both the regulator, the Therapeutic Goods Administration (TGA), and the HTA agency, the Pharmaceutical Benefits Advisory Committee (PBAC) in 2009. In Sweden, the Tandvårds- och läkemedelsförmånsverket (TLV) or Dental and Pharmaceuticals Benefits Agency and the regulator, the Medical Products Agency (MPA), also opened their service in 2009.

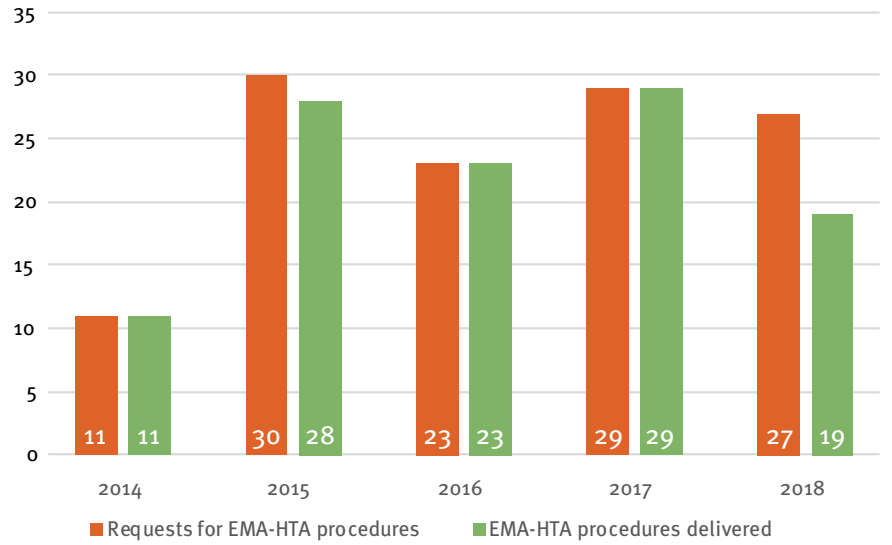
According to a mapping of HTA organizations published in May 2017 by the European Commission, 12 EU Member States, and Norway, offer early dialogue services (*see Exhibit 1*).

By July 2017, companies were offered the opportunity to get advice in parallel with the European Medicines Agency (EMA) and multiple HTA agencies via the European Network for Health Technology Assessment (EUnetHTA).

The landscape for early dialogue continues to evolve. In December 2017, NICE added the Preliminary Independent Model Advice (PRIMA) service to specifically quality assure health economic models. There is also the NICE Office for Market Access that enables confidential conversations not just with NICE, but with key decision makers in the National Health Service (NHS) too. NICE has also added in a patient participant in recent years, whereas CADTH included a patient from the outset when they set up their service in 2015. In February 2019, NICE and CADTH announced a parallel service.

Not all agencies have websites that

Exhibit 2
Number Of EMA-HTA Procedures Requested And Delivered



Note: Procedures delivered up to October 2018. ATMP = Advanced Therapy Medicinal Products.

SOURCES: Data from Tavridou, A. (2018). EMA experience on joint scientific advice EMA/HTA with ATMPs. And EMA. (2019). Annual report 2018.

detail what they offer or at least, they cannot be easily found. Companies need to go agency by agency to find out just what is available and how it works.

Interest and uptake of early dialogue programs has been rising. Nineteen EMA-HTA scientific advice procedures were delivered in 2018 between January and October, compared with just 11 back in 2014 (*see Exhibit 2*).

Choosing An Early Dialogue Service

With many different agencies offering early dialogue and different models – alone, with other HTA agencies and/or with the regulator – companies face a choice about what option to take up. It is not easy or straightforward for companies to know which to choose. Budhia has some tips: "It is quite complex to decide which ones to go to. I take it back to the company's objective, what it is that they want to get out of it. It might be to achieve internal alignment, and in that case, it makes sense to go to the EMA-EUnetHTA service which includes multiple HTA agencies." It is also about the product too. Budhia added, "If it's a new and novel treatment where there is no precedent, then it makes sense to go to a few select agencies on their own."

The nature of the evidence that the company wants to discuss can shape the choice of early dialogue. If a company has a clear – and well supported by precedent – plan for their pivotal trial and are focusing on supplemental evidence to support their value proposition, then there is no need to involve the regulator. "If the company wants to supplement their core trial with real world data then they just need to go to a HTA agency without the regulator. They can see how their plans resonate with HTA bodies," explained Budhia.

Selby approaches choosing the agency in a different way. Getting advice from NICE, G-BA and CADTH means that Takeda has "covered the three main archetypes of payers," Selby said. That puts the company in a good position for countries that are similar to those archetypes. Being able to learn lessons that apply beyond the national borders of the agencies makes sense.

Don Husereau, from the University of Ottawa – whose work has included surveying the views of companies who have sought advice from CADTH – said that companies could gain efficiencies by going to multiple HTA agencies at the same time. He noted, "Getting advice from multiple HTA agencies doesn't multiply the cost [to the company], so it's an efficient way to get more input."

Amy Sood, manager of scientific affairs, CADTH, echoed the potential for a more efficient approach by engaging with both CADTH and NICE at the same time. "A joint face to face meeting is more efficient for the company. There can be challenges in scheduling meetings with HTA bodies. We can offer the company the choice of a face to face meeting in either London or Toronto," explained Sood. Kusel concurred: "We have similar ways of working. The level of discussion is the same as doing it separately, but companies can also understand where NICE and CADTH have similar views, and where they differ. There are efficiency gains for the company: one briefing book, one meeting, and less flying people across the globe for meetings," she said.

Kusel highlighted how the depth of discussion differed according to the service used. Going only to NICE meant, "an in-depth discussion with NICE and experts. Companies can ask those experts and NICE a lot of questions in the meeting." She added, "At the EMA – EUnetHTA meetings – there may be less opportunity for an in-depth discussion with NICE, but there are certainly advantages to this multi-agency approach. Companies really do get a broader perspective from a conversation with lots of agencies together."

Graham Foxon, managing director at Remap Consulting – a UK-based specialist pricing, market access and health economic consultancy that has supported companies in getting advice from HTA agencies across Europe both alone and together with the regulator – stressed that the right choice was also informed by practicalities. "The answer to what service to go for is what is the objective that the company wants to address but also how much time, resource and effort the company can put in," Foxon explained.

Acting on valuable advice

When Kusel took on her role in leading the NICE scientific advice service she took the time to speak with 11 companies who had used the service. They told her, "There was real value in talking to NICE early," she said.

Some companies keep going back; the

CADTH service – still young with only four full years of experience – has seen repeat business with five companies using the service twice up to the end of 2018. Mujoomdar said that, in part, the interest in CADTH's services was a reflection of the quality of service that CADTH offers. She said, "We're able to provide relevant, quality advice. I believe that we have the expertise in spades." JAZMP has also seen companies back for advice too.

Companies have made changes to their evidence generation plans on the basis of the advice that they have received. "We do change clinical trial designs," Selby said. Mujoomdar added that, "We have had companies come back to CADTH and we can see that their development plan reflects our advice."

Husereu was more circumspect about the real difference made to evidence generation plans by companies. "Let's be clear that the model in companies is that the market access department is basically doing the best they can with evidence that was largely developed for regulatory programs. Progressive companies are trying to get away from that. But there's only so much that can be changed."

Pang noted that companies do not always follow all the advice, "sometimes it might be difficult to implement, and it's at the company's discretion to have alternative approaches for mitigating that element of reimbursement risk." He gave a practical example to illustrate this point. "For example, the advice may recommend the implementation of EQ-5D in trials, although the company may decide to use other approaches for generating utilities, such as a mapping technique or vignette approaches."

Listening to advice is not just about adding to the evidence generation plan, but also removing evidence that just will not cut it with the agencies. Budhia explained, "Where it becomes clear that a piece of evidence won't be a decision driver for the agency, then companies will reevaluate that investment."

If the company has gotten advice from multiple HTA agencies, where they agree, companies are much more likely to make a change to their evidence generation plan. There is a less convincing case to make changes if only one agency asks for a particular change or study, but at least the company knows there's an issue. Selby described how "if you get three or four advice reports, it's marvellous when you get common advice. When everyone says you have to change this, then of course, we're just going to do it. When only one body is asking for something, even if you don't do it, you at least know it's a weak point. You can maybe do something outside of the trial."

"Where it becomes clear that a piece of evidence won't be a decision driver for the agency, then companies will reevaluate that investment."

It is not just a one-way conversation, agencies gain valuable knowledge too. CADTH points out that scientific advice also "provides an opportunity for CADTH to gain early knowledge of new technologies and approaches on the horizon. This knowledge can be used to better prepare CADTH review teams for the challenges of future drug assessments."

Top Tips

There are some lessons to learn from experience. "Prepare, prepare, prepare!" said Foxon. While Budhia added, "Companies who are new to getting advice should do their homework. Companies need to understand the decision process of each agency that they want to get advice from." Timing is part of good preparation too. Pang said, "It's important to book a slot early as they tend to go quickly."

Selby was able to reflect on the Takeda experience and echoed the importance of being prepared. "The biggest job is to get the clinical development team on board. They need to buy into this constructive critique that the early dialogue will deliver. You've got to start with education internally," he said. Pang added that companies needed to "make sure to allow enough time for preparation of the briefing book and [internal] international review."

Husereau noted that companies needed to think carefully about the questions

to pose to agencies. He recommended that companies went in with succinct questions. "You can't just go in as the company and say, 'What do you think?'"

On this topic, Sood noted that "as the company, you must be specific in the questions you want to ask. The broader the question, the more likely you'll get broad answers." Pang picked up on this also, "Questions need to be close-ended, and hence, significant work and thinking needs to have been done upfront before seeking advice to obtain the most value," he said. "There is real skill in how to ask the questions to obtain valuable and implementable feedback."

Getting the most from the meeting needs some thought too. "Companies should try to have the key people from global head office and local affiliates, that's decision-makers from clinical and outcomes research all the way to market access at the meeting," Sood said. Kusel highlighted the need for companies to be open, as then "they will get more out of the meeting."

The discussion at the early dialogue meeting should be a real conversation and for that to happen, company representatives need to play their part. Foxon said that company staff needed to "be prepared to defend their corner and challenge the agency on their responses. Don't necessarily take what they say at face value. They're going to say that they want to see a head to head trial with overall survival as the endpoint. If that isn't feasible, be ready to explain why it isn't, and what you're proposing instead."

The discussion at the early dialogue meeting should be a real conversation and for that to happen, company representatives need to play their part.

Challenges Remain

According to Alicia Granados, head of global HTA scientific strategy for **Sanofi**, in a 2018 report that outlines learnings from EUnetHTA early dialogues, not all HTA agencies are fully doing their bit. Patients are involved too late and reports are not always clear and specific, so they cannot be used to drive plans for evidence generation. Last but not least is the gripe that advice with HTA agencies is a one-off, and as everyone knows, things can change over time.

Pang also highlighted that in his experience sometimes the advice is not new. He explained, "There is often a tendency for reports to recite official positions from methodological guidelines/processes rather than give specific advice."

Selby added that the agencies needed to keep delivering value or companies simply would not go back. "It's a paid for service, so you're only going to pay if you get value. There's an expectation that you're going to get high quality feedback, which is supportive and that you can do something with it."

Impact On HTA Recommendations

The biggest question: what difference does getting advice – assuming it is acted upon –make to the recommendations made by HTA agencies?

Under the EMA scientific advice service, companies can keep coming back and many do. It is clearly set out in the European Product Assessment Report (EPAR) that the company has sought advice and how many times. There is also evidence that not only getting advice, but going back for more, makes a different to getting marketing authorization. Such evidence is not – yet – available for early dialogue with HTA agencies.

NICE has the longest running service and Kusel has reviewed the NICE recommendations made for the 25 drugs where advice was sought earlier on. Of these cases, for those that have gone through the full NICE process, they have all been successful. "They have all been recommended in some way: recommended in full, in line with their marketing authorization or recommended via the Cancer Drugs Fund." The Cancer Drugs Fund is an interim fund, providing access typically for around two years, before NICE looks again at an oncology treatment to determine if the drug can go into routine funding or should not be funded at all. It is too early for CADTH to do analysis on the recommendations made; no drugs have gotten all the way through the appraisal process given that they started their service in 2015.

No HTA agency includes in their reports on specific drugs whether a company sought advice, but that could change. Mujoomdar said, "Transparency around early dialogue is an interesting topic. It's something that will likely evolve." That evolution could follow the model used by EMA, preserving the confidentiality of the conversation and advice given, but allowing everyone to see if advice was sought and when. Kusel also said that transparency was on the minds of senior staff at NICE. "We're discussing transparency around early dialogue internally and we're cognizant of the EMA's stance on it."

In time, as these services mature, showing that there is a link between seeking advice and a positive HTA recommendation could be just the thing to sell the methods to companies – and ultimately improve patient access.

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Email the editor: *Lucie.Ellis@Informa.com*

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From US To EU: Young Biotechs Going It Alone

Europe's patchwork of reimbursement agencies makes it a daunting place for a small US biotech to do business. Traditionally large pharma partners or CMSOs have provided an experienced hand to hold, but as a new wave of gene therapies and orphan drugs gets the EMA green light, smaller drug developers are applying innovation to commercialization and choosing to go solo.

BY JOANNE SHORTHOUSE

The traditional route to European commercialization for a young US company is to partner up with a large pharma partner that will effectively become that company's eyes and ears for a share of the profits.

But with a wave of rare disease and gene therapy companies hitting their stride, there have been some high profile biotechs choosing to take the path less trodden and go it alone.

So what? There are several barriers for a US biotech to overcome for a successful launch in Europe. *In Vivo* explores some of the lessons learned so far by come of those companies that have departed from tradition.

The call of Europe for US biotech is certainly enticing. More than 500 million people live in the EU, while the continent has a combined annual health expenditure of $145bn per year according to KMPG's 2018 *Site Selection Report for Life Sciences Companies in Europe*. However, the barriers to entry – such as the different languages, many different reimbursement systems and time zone challenges – mean the path to Europe is not without the odd ditch to fall into.

A biotech that specializes in cardiovascular therapeutics, for example, may struggle to roll out a commercialization and market access strategy in the primary care markets alone. Alex Grosvenor, a consultant with the market access organization Precision Xtract, told *In Vivo* that companies working in this space do need a commercial partner in Europe to put weight behind sales and promotional aspects. "The in-market knowledge and contacts are the biggest factors to making that a success. Primary care markets are very competitive. You need a big infrastructure, particularly with sales and marketing [operations], in place to make that launch a success," he said.

Investor sentiment for a small US biotech to commercialize alone in the EU would be "'For the love of God don't do it,'" said David Nierengarten, managing director and head of Healthcare Equity Research at Wedbush Healthcare told *In Vivo*. "I talk to plenty of investors and plenty of companies, and its nearly universal that a biotech investor would prefer to see a biotech company partner or license out," he explained. Europe, in particular, is seen to be time consuming and distracting with expensive regulatory approval roll outs and pricing negotiations in each territory. "You've got to talk to 10 different people in each country and the general investor sentiment is that it is not a productive use of time in the lower reimbursed environment," he said.

Investors do not want the distraction. "European commercialization for a young

biotech company that doesn't have a presence there is seen by investors as a high risk, high cost and low reward proposition," he said. Adding that the view from investors was often, "'Don't do it, especially not with my money. Do it with a pharma company's money.'"

The health care industry is moving away from the "dying" primary care model, Grosvenor said. Around 50% of approvals are now for products with orphan designations, as such industry is seeing a new wave of targeted and personalized medicines that impose a new way of thinking about commercialization.

Grosvenor is working with many gene therapy companies which, by the nature of their products, do not need the kind of scale and infrastructure a traditional marketing roll out would require. "They just have a handful of people in Europe, you probably need a representative in each country, someone that will handle the pricing and reimbursement negotiations and maybe two or three people that will handle the regulatory and sales side of things. It's on a much smaller scale," he said.

As a general rule, its easier for these kinds of organizations to commercialize on their own but by extension it means these very specialized biotechs need to have market access expertise in-house. "We have observed gene therapy companies hiring market access experts in the different European countries, people for instance with orphan drug backgrounds who have that very specialized knowledge and they're now applying it to the next wave of innovation," said Grosvenor.

Nierengarten agreed that rare disease and cell and gene therapy companies may be the exception that proves the rule. He mentioned Amicus Therapeutics as a "different prospect" for investors. "The differences are even stronger between the US and EU for oncology reimbursement, whereas rare disease therapies are priced roughly the same. There's more willingness in Europe to reimburse for some rare diseases, and gene therapy might be another example of that going forward," he told *In Vivo*.

Innovation In Commercialization

Some US-based biotechs that have proved to be exceptions include Vertex Pharmaceuticals Inc., Intercept Pharmaceuticals Inc. and Alnylam Pharmaceuticals Inc. And a recent example of this independent route to market is the strategy taken by the specialist gene therapy company bluebird bio Inc., headquartered in Cambridge, MA.

Bluebird bio was granted conditional marketing approval in May 2019 by the European Medicines Agency for Zynteglo (autologous CD34+ cells encoding ßA-T87Q-globin gene) its first gene therapy, for a subset of patients with transfusion dependent thalassaemia.

In an exclusive interview with *In Vivo*, Andrew Obenshain, head of Europe for bluebird bio, said that the decision to enter Europe alone was "not only about our first product but the entire portfolio. We see ourselves as a long-term player in gene therapy and want to establish ourselves from the beginning and this requires unique capabilities."

He continued: "We are developing a market access model for one-time treatment, looking for payment over time based on outcome, which has not been done before. At the same time, our treatment network is also unique." The therapy will only be provided in a limited number of centers per country. In this unprecedented model the supply chain is integrated, while it is not usually visible as part of the overall model.

"While a partner should bring capital and knowledge, we are conscious that there are some aspects that a partner cannot bring, hence we would rather invest in these areas ourselves," Obenshain said.

Bluebird bio is currently filing its pricing and reimbursement dossiers, and expects to launch first in Germany, followed by France, Italy, the Nordics and the UK. Obenshain said the company's investors were "supportive" of the company's strategy to date, particularly the value-based payment model, but they are still "waiting to see the outcome."

Making The Decision

Nazira Amra, founder of the consultancy Bee-Spoke Strategy, was Intercept's vice president of global commercial strategy at the time it launched liver disease drug Ocaliva (obeticholic acid) for primary biliary cholangitis in the EU without a partner. She highlighted the three main considerations a biotech should weigh up before deciding on the solo route:

- speed to cash;
- cost of entry; and
- tax implications

"A company needs to decide what its appetite is for all of those things," advised Amra. "What is the cash position of the company at the point in time that they're making the decision to enter Europe? Does it think that its revenue/profit potential is going to be large enough, and the payback fast enough, for them to be able to fructify cost of entry investments?"

Companies in gene therapy or orphan disease were more likely to successfully roll out a European go-it-alone strategy purely because of patient numbers, said Amra. "You can do it in a very targeted way, and you don't necessarily have to have a massive presence in every major market. By making strategic choices about which markets to enter, placing only key competencies such as market access and sales in country, you can achieve cost-effective solutions for market entry which will be profitable in a shorter time frame," she said.

The heady enthusiasm of rare disease and gene therapy companies, buoyed by the significance of bringing life changing therapies, possibly cures, to a new market of patients is intoxicating. But realistic challenges are very apparent.

"It has been a challenge to launch a product and build a company at the same time. And a challenge in realizing that no-one had successfully launched a large-scale gene therapy in Europe before," admitted bluebird bio's Obenshain. "With this comes the managing of many steps involved in the technique and payment procedures, since gene therapy is a one-time treatment it does not fit with the current funding methods for medicines. Hence, we are working to recode the system and change the way in which governments think about delivering and reimbursing their therapies. We're trying to create a new business model for gene therapy."

In general, "the benefits do outweigh the challenges," said Amra. "But for them to outweigh the challenges it is about the management of expectations. You get regulatory approval in the US and your product is on the market two days

later. It's a fast turnaround. The uptake curve is slower in Europe due to varying market access timelines. The benefits do outweigh the challenges if you are conservative with ramp up of personnel and manage the size of the organization in Europe from the get-go."

For bluebird bio the advantages massively outweigh the challenges. The company is realistic about the long road ahead but believes its inroads into the reimbursement system in Europe will blaze a trail for future gene therapies. "Gene therapies are disruptive to a system that is set up primarily to manage chronic diseases. We are at the beginning of this process but believe that this is the right model in order to provide access to gene therapies to those who need new treatment options," Obenshain said. "Our mission is to lay down a set of tracks on which future gene therapies can travel. We want to create a model now that we can recreate."

Options And Alternatives

Of course, there are alternatives to solo commercialization for gene therapy companies and biotech. One method is co-promotion using a local distributor or using a large contract manufacturing and sales organization (CMSO) such as Syneos Health. This is an attractive proposition to a young biotech because of the cost structure. It does not carry the cost of the extra headcount needed for a market entry project, with personnel contracts able to be swiftly terminated if regulatory approval is not successful.

However, the barriers to many younger biotech companies of using this strategy are twofold. Firstly, the initial cost outlay to sign the contract is very high. Second, the large multinational organizations find it very difficult to provide their services to small clients when they are set up to deal primarily with large pharma.

One company proposing an alternative solution is Bridgehead Group, a syndicate of 12 specialist service providers including preclinical strategic advisory, regulatory, market access and pricing, and investor relations firms.

Bridgehead manages and co-ordinates the project for its young biotech clients while also promoting that syndicate and its capability to a US audience. Bridgehead is a young company itself, only officially launched at JP Morgan in January and already providing consulting and advisory services for several US clients, many arising from the the BIO convention this year in Philadelphia. The group is the brainchild of Laurence Callow, an experienced pharma and consumer health care industry executive.

> *"It has been a challenge to launch a product and build a company at the same time ... No one had successfully launched a large-scale gene therapy in Europe before."*
>
> *– Andrew Obenshain*

"It's such an unusual thing, where you get such well qualified people who are so brilliant with all that they do and how they do it, and yet coupled with this extraordinary naivety of Europe," Callow told *In Vivo*. "Maybe it's not that surprising; Europe can be complex even when viewed from the UK, as we are experiencing right now! To look at it from San Francisco or Boston is really daunting."

The Bridgehead Group provides an alternative route to market for young US companies. "Don't give away your asset, don't just partner up with a big pharma and take licenced revenues, keep your asset value but don't try to do it yourself because it is extremely challenging," he advised.

There is a real need for co-ordinated services, said Callow. Young US firms realize the international potential of their assets but are too busy readying for FDA approval, often with limited funding. "This was the consistent message," explained Callow. "We asked 'If we could co-ordinate the planning for Europe, in parallel and on a pay-as-you-go basis, would that be of interest?' And of course it was hugely interesting to that community."

Bridgehead's *modus operandi* is to engage with smaller clients at an early stage and build a lasting relationship. Callow said this "makes good sense because your advice is most potent" earlier on. Also, this strategy avoids competition at the later stages with large CROs and big pharma. "We aim to be in at the beginning and help with the total planning."

Callow said his was a unique business model for this community. An operational assessment is provided to the biotech which includes information on clinical planning, the regulatory landscape, patient numbers, competitors and a likely price point for the drug. This gives the company a five-year revenue projection and costs, a profit line and a valuation. "A fledgling company can have a European valuation which is really helpful for them when discussing investment with a VC firm, a private equity firm, or even a big pharma venture fund," said Callow.

"What people don't want is big capital investment up front," said Callow, "particularly when it's something that's new. This solution is solving some of the problems that keep CEOs awake at night."

As companies such as Bridgehead build services and innovators such as bluebird bio apply a no holds barred attitude to the tapestry of European market access, the impossible may start to seem possible. The game is definitely changing for US biotech innovators getting into Europe.

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The SMA Market: Assessing The Unknowns

The introductions of Spinraza and Zolgensma in SMA offer new insights into how to address neurodegenerative diseases. But more real-world evidence is needed.

BY ALESSIA DEGLINCERTI, FRANK BOROWSKY AND MARK RATNER

With the approval of two disease modifying agents, some patients with SMA are becoming healthier and their medical needs are shifting.

A new natural course of the disease is emerging, with a larger population of individuals having stabilized disease. But the extent of residual issues is not yet known – a picture that will only come into focus over time.

So what? This evolution is influencing the clinical development and implementation of new treatments, leading to greater opportunity for franchises that include supportive therapies. SMA could become a blueprint for development and market access for other neurological diseases.

The landmark FDA approval of Novartis AG's Zolgensma (onasemnogene abeparvovec-xioi) in May 2019 shook the biopharma world in several ways including its price ($2.1m per dose) and as important, the very small data set on which the FDA primarily based its decision – an ongoing open-label single arm trial of 21 infantile-onset patients with spinal muscular atrophy (SMA) under two years old. Biogen Inc.'s Spinraza (nusinersen) had already been approved in SMA in December 2016.

As disease-modifying therapies, these compounds are a rarity in the field of neuromuscular diseases of genetic origin. They are also at the core of a fascinating, ongoing real-world case study in how the natural course of a disease can change rapidly. How companies' SMA drug development and market access strategies evolve, both in terms of new disease-modifying agents and supportive therapies that address residual symptoms, could become a blueprint for other neuromuscular diseases like Duchenne's Muscular Dystrophy (DMD) or Huntington's Disease.

Changing The Natural Course Of SMA

SMA is a genetic disease caused by an absence of or defect in the SMN1 gene, which encodes the survival motor neuron (SMN) protein. A back-up gene, SMN2, also produces SMN, although at lower levels (approximately 10-20% of what SMN1 makes) due to alternative splicing. Zolgensma is an adeno-associated virus vector-based gene therapy that delivers a fully functional copy of human SMN gene into the target motor neuron cells. Spinraza and also Roche's risdiplam, a small molecule in late-stage clinical trials licensed from PTC Therapeutics Inc., modulate splicing of SMN2 so that it produces levels of full-length SMN protein similar to that of SMN1.

Exhibit 1

Disease-Modifying Therapies Are Favorably Shifting The Natural Course of SMA

	TYPE 1	TYPE 2	TYPE 3	TYPE 4
Symptoms	Severe muscle weakness; does not achieve milestones, including sitting Trouble breathing, coughing and swallowing	Delays in achieving milestones; some can sit up without assistance whereas others need support General weakness, difficulty coughing, joint contractures	Can stand and walk but develops increasingly limited mobility Difficulty running, climbing steps, or rising from a chair	Similar symptoms to type 3 (progressive muscle weakness), but with later onset
Prognosis	Onset between 0 and 6 months with a lifespan of 2 years Mortality often associated with pulmonary complications	Onset between 6 and 18 months Life expectancy is ~30 years old, with mortality often due to respiratory impairment	Onset between 2 and 17 years old Normal or near-normal life span but ~50% become wheelchair dependent	Onset during adulthood –typically after 20 years old Normal life span

SOURCE: Bionest Partners

SMA falls into four categories based on a combination of age and severity (see *Exhibit 1*). The hope is that disease-modifying therapies can lessen the severity of the disease: type 1s may become more like type 2s, and similarly up the chain to 3s and 4s.

Before Spinraza, and now Zolgensma, infants with SMA were often unable to move by the time they were six months old, needing ventilation and by the time they were two, a feeding tube. They often did not live past two years old – or with rigorous intervention, maybe to five years old. "Now, we have kids that are walking sometimes, and certainly not ending up on ventilators, who are speaking and able to feed themselves," said David Rind, chief medical officer of the the Institute for Clinical and Economic Review (ICER), whose amended *Final Evidence Report* from May 2019 found that Zolgensma can be reasonably considered cost-effective even at its $2.1m price. "That's an enormous change."

What happened with Zolgensma was also unusual, Rind said – to have Phase I trial results results so dramatic that it was obvious the drug worked. The only other treatments Rind could recall having that level of dramatic effect were protease inhibitors in HIV (the triple therapy) and, to some extent, Novartis's Gleevec (imatinib) in chronic myelogenous leukemia. "We don't have many events like that in medicine where suddenly a treatment comes along and the degree of change is so large that it's obvious, even with a small number of patients, that it is something patients should be getting," he said.

"We are inevitably seeing a dramatic change in the time course of new cases of the disease," added John Day, director of the neuromuscular disorders program at the Stanford Neuroscience Health Center. But for prevalent cases already in existence, it is more of a leveling out of the disease course so that individuals with SMA are no longer progressing.

"These are amazingly effective treatments but they can't significantly reverse profound disability," Day said. "We are increasing life span but in a sense increasing the morbidity associated with the disease because very few of these children will be actually physically normal or typical." After treatment, already-symptomatic patients will have some residual degree of motor neuron loss and attendant weakness and fatigue. The earliest onset features are proximal weakness in the lower extremities. "That will continue to be a fairly common element, depending on the age and stage of development," he said. The degree of change will also depend on the level of severity of the disease and the degree to which the patient had been affected before starting treatment.

The Future Treatment Journey

In the discussions leading to the ICER report, there was back-and-forth between Biogen and Novartis over which therapy was getting to all the necessary places to alter production of SMN, as the drugs target different loci in the body. The question points to unknowns around how these drugs will change the natural course of the disease: over what period of time are the effects sustainable, and for which patients? (With Gleevec, for example, its effects ultimately proved not to be as durable as originally hoped.) "We don't really know what the long term looks like for these kids with either therapy," Rind said.

New morbidities may also emerge, although presently there is no concrete evidence of this. That is because even with a static disease process, as a child matures, the growth in body weight, height and bone length increase the strain on muscles. "As you get taller there may very well be a functional decline even though there is no ongoing disease process," Day said, not unlike a post-polio syndrome.

"The challenge we and others will face

in this field is what is the new natural history of the disease," offered Scott Jordan, senior vice president, new product planning and commercial development, at Cytokinetics Inc. "With these new SMN-directed therapies, I think we are looking at a change from an approach of characterizing patients based on their genotype to one centered based on their phenotype," he said, perhaps measured by meeting milestones over time instead of looking at the number of functional copies of SMN2, age of disease onset, or assessments based on the ability to sit without support, stand or walk.

"It remains to be seen what the new disease is," added C. Frank Bennett, senior vice president, research, at Ionis Pharmaceuticals Inc., which discovered Spinraza and licensed the asset to Biogen as part of the companies' broad strategic partnership around the use of antisense oligonucleotides to treat neurological diseases.

The ability to upregulate SMN production to stop disease progression, and delineating this new natural course of disease, opens the door for development of novel supportive treatments, today focused on therapies that address the decline in muscle function that SMA causes. Targeting muscle function is "a very appropriate approach now that we believe the underlying disease process is under control," Day said. He is also optimistic there might be ways to increase energy utilization through addressing the metabolic side of muscle function, although that work is still early. These strategies are aimed at improving the health, function and longevity of the depleted pool of motor neurons in patients with SMA, as even with disease stabilization, that pool of motor neurons remains reduced. Muscle regeneration could also address the deficit, but again, research in this area is early-stage.

Cytokinetics has been developing reldesemtiv, a next-generation skeletal muscle compound, in SMA in partnership with Astellas Pharma Inc. It is intended to slow the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers to improve muscle function and physical performance. In 2018, Cytokinetics announced results from a Phase II study of the compound in SMA that showed increases in the Six Minute Walk as well as a measure of respiratory muscle strength, but failed to demonstrate differences as compared with placebo across several other assessments commonly used in SMA. "We are evaluating the best way to move forward with reldesemtiv," Jordan said.

According to Day, if reldesemtiv increases muscle efficiency or force production by 20% or 25%, it could be a very valuable addition to any of the SMN upregulating treatments. Increasing the efficiency of muscle force production means it would take less effort and energy utilization to generate the required force, which should improve stamina.

Cytokinetics's approach is based on modulating the biology of muscle contraction. Alternatively, several companies are developing myostatin inhibitors, which could allow muscle to generate more force per action potential, allowing individuals to do more work without having to increase neuronal activity, which is depleted in SMA.

The most advanced myostatin inhibitor is SRK-015 from Scholar Rock Holding Corp. Myostatin is a preferential regulator of fast twitch muscle fibers (type II muscle, which fatigues easily following exertion). In SMA, there is a prominent atrophy and deficit in fast twitch fiber mass and function. "In our view, the logical hypothesis is that in SMA there is prominent atrophy of fast twitch fibers and so the idea is to block myostatin to address the motor deficit," said Yung Chyung, Scholar Rock's CMO.

Myostatin inhibitors may work best in individuals with growth capable muscle, like younger people in SMA. Notably, in SMA the skeletal muscle does not appear to have any intrinsic structural defects, at least in later onset SMA. "That's important because we think if you build fiber mass in an impaired muscle, it is not clear it will translate into meaningful motor functional gains," Chyung said.

Scholar Rock's Phase II trial of SRK-015 is focused on patients with type 2 and 3 disease. Most will have already been receiving Spinraza. "It is our belief that a muscle-directed therapy would complement any SMN directed therapy irrespective of the way they achieved restoration of SMN," Chyung said, whether through gene therapy or a small molecule or antisense drug.

Taken together, the availability of disease-modifying agents with different mechanisms that target different cell populations, the expectation of residual disease for patients already showing symptoms and the promise of muscle-directed supportive therapy suggest that sequencing of treatments and establishing the benefit of combination therapies for different sub-populations will be important future considerations. "One drug for one patient is probably not the wave of the future," said Susan Begelman, vice president, rare disease and neuroscience medical unit, US medical affairs at the Genentech Inc. unit of Roche.

Roche plans to submit risdiplam for approval before the end of the year: On November 11, it announced that the compound met its primary endpoint – change from baseline in an assessment of motor function at year one versus placebo – in a pivotal Phase II/III study. An oral formulation that could be administered on an outpatient basis, it is being tested in pivotal studies enrolling a broad range of SMA patients from presymptomatic up to the age of 60. Roche also has an ongoing study looking at individuals on previous treatments, which include the approved disease modifiers and also olesoxime, a neuroprotectant via the acquisition of Trophos SA, on which Roche stopped development in June 2018.

"The way we think about our entry with risdiplam is that there are still quite a few patients who do not have any treatment options or access to any treatment options," Begelman said. An oral drug could be advantageous for older patients. It also could help Roche compete with Spinraza, which is an intrathecal therapy and can be challenging to administer in individuals with scoliosis or spine fusion resulting from SMA.

Similarly, Biogen is testing more convenient dosing schedules for Spinraza: delivering higher doses administered less frequently could be a benefit for older patients. It also has access to a small molecule program aimed at modulating SMN splicing via a 2019 discovery collaboration with Skyhawk Therapeutics Inc.

Understanding which patients should get which treatments and when they

should receive them is critical. Assuring that the best subpopulation is enrolled to be better able to demonstrate benefit will also be a priority. Real-world evidence (RWE) will show longitudinally how patients change over time. But in SMA, those data are limited. That's a challenge, Jordan said, when it comes to doing clinical trials. "What are the appropriate endpoints for ambulatory patients and non-ambulatory patients when we don't know the natural history," he posed, in particular if patients have been treated with the new SMN-directed therapies. "That will complicate clinical trial design."

Assessing outcomes becomes complicated when layering in a therapy where you don't know when a patient is stabilized according to a short-term endpoint measure like the Six Minute Walk, especially as children grow. "The questions are: When does a patient become stable following treatment with these new SMN-directed therapies? And what is the new natural history of the disease?" Jordan said.

Engaging with patients, advocates, regulators and health technology assessment groups can help to direct clinical trial strategy and study design given this evolving natural history – identifying the best outcomes measures important to patients regardless of the natural history, then conducting a study that allows you to look at a patient and make sure you are seeing the benefit associated with a supportive therapy rather than another therapy they may be on or have been treated with historically.

Market Access Considerations

Optimizing clinical design will help determine the range of access to patient populations for both disease-modifying and supportive treatments. Establishing the duration of response of a disease-modifying treatment and the benefit of sustained treatment will also help define the extent of access to certain SMA populations. Eventually, guidelines will emerge.

It is likely that a large number of SMA patients are untreated today. Those with less severe forms of the disease may not have enrolled in clinical trials or may go undiagnosed for some time because of a delayed manifestation. "SMA is not top of mind for a local treating physician, as opposed to say type 1 babies who immediately start to have problems," Begelman said.

Disease stabilization should lead to an increase in the number of people living with what becomes a chronic disorder, who will have to deal with the consequences of adjusting to and managing their various symptoms. Increased awareness could mean more older individuals living with milder forms of SMA will seek (or return to) treatment. Conversely, in some cases, older adults given a clinical diagnosis of SMA without genetic testing are now getting tested and found not to have SMA, Day said.

Indeed, assessing SMA in adults without a genetic diagnosis can be tricky. In studies done at key medical schools evaluating the effect of Spinraza in adults, patients reported a perceived benefit in stamina and more ability to do things, said Bennett, but the clinical measures being used did not capture those. "The challenge is to develop new metrics for adult patients," he said.

It is unclear whether the evolution in SMA care will signal a move away from Centers of Excellence into secondary and tertiary medical practices as the disease stabilizes. "We are a little bit anxious about that," Day said: Especially for the newly diagnosed patients, the concern is that they will likely still need other services such as physical therapy, pulmonology, respiratory therapy or occupational therapy, because of some degree of physical disability. "We want to make sure those are being addressed and attended to, and consequently we are working hard to coordinate with the local providers and pediatricians, at least for the pediatric side of the equation, to make sure all of the chronic care needs are being attended to."

Newborn screening for SMA is gradually spreading throughout the US, with the promise that all newborns will have it in a few years. So, access for presymptomatic and infantile-onset SMA patients is virtually assured. Reimbursement is also a given for these patients. ICER found both Spinraza and Zolgensma clinically effective, and in the case of Zolgensma, cost-effective as well. (The group thought Spinraza was overpriced: "It's very hard for a drug that costs as much as Spinraza year after year to be cost effective," Rind said.)

Still, the high price of these drugs has prompted discussion of new payment models, especially with scant RWE. In the case of Zolgensma, payers have embraced an outcomes-based model, but have shown little interest in the installment plan model proffered at the time of approval.

"In many cases, ICER feels outcomes-based contracts don't accomplish very much," Rind said. "If you have a PCSK9 inhibitor, for example, and you say if somebody has a myocardial infarction or a stroke within the given timeframe, we'll give back money, it's basically like a discount," based on the likelihood the event will occur, he explained. "You might as well just give that discount to people." However, with a $2.1 million one-shot therapy where you are basing the value of that price on the expectation of sustained benefit over decades, an outcomes-based contract potentially makes more sense, he said. "If you've paid with the expectation of long-term benefit and over time it's shown that's not true, you've way overpaid."

The thornier question is what to do when new therapies come along. To date, no studies have been done using two SMN splicing modifiers, leaving open questions of the overall value to a patient of combining them, and how that would be looked at by a payer in terms of cost. "That is one of the challenges today," Begelman said.

If a new disease-modifying drug like risdiplam comes along that's intended to be used in place of or on top of another one, it would have to be used before loss of function occurs, Rind suggested. For add-ons like muscle-directed therapies, in principle there is no reason why they could not be started in tandem with a disease-modifying treatment. But payers may require proof of disease stabilization first.

Building a Neurodegenerative Disease Franchise

Three large biopharmas – Novartis, Biogen and Roche – are aiming to establish disease-modifying SMA franchises (*see Exhibit 2*). Biogen and Roche are also developing therapies to address muscle

Exhibit 2
Overview Of The SMA Pipeline

COMPANY	PRODUCT/PROGRAM	STATUS
Biogen	Spinraza (IV infusion SMN2 upregulator)	Approved 2016
Novartis (AveXix)	Zolgensma (SMN gene therapy)	Approved 2019
Roche/Chugai/PTC Therapeutics	Risdiplam (oral SMN2 upregulator)	Phase III, filing expected 2019
Scholar Rock	SRK-015 (myostatin inhibitor monoclonal antibody)	Phase II
Astellas/Cytokinetics	Reldesemtiv (oral fast skeletal troponin activator)	Phase II
Catalyst/Jazz Pharmaceuticals	Firdapse (oral potassium channel blocker)	Phase II
Novartis	Branaplam (oral SMN2 upregulator)	Phase I/II
Biogen/AliveGen	BIIB110 (Activin receptor IIA/B antagonist protein)	Phase I

SOURCE: Biomedtracker

atrophy, suggesting a portfolio strategy. Roche is planning a Phase III study of the anti-myostatin adnectin candidate RG6206 (BMS-986089) in a different indication, DMD, while Biogen has licensed recombinant proteins from AliveGen USA Inc. that inhibit myostatin by interfering with the activin receptor.

To compete, companies developing novel SMA drug candidates must address the key questions around how to design efficient trials to optimize treatment timing and effect and whether alternative routes of administration offer advantages.

In the hundreds of ultra-rare neurodegenerative diseases, being able to show a large effect size in a small patient population is a necessity. With Spinraza, for example, after 20 patients, Ionis knew the drug was working. "We are counting on a large effect size to make our strategy work for rare diseases where it is difficult to find homogeneous patients for clinical trials," Bennett said. And to be able to demonstrate efficacy in a relatively short amount of time, as was also the case with Spinraza.

The evolution of SMA treatment could become the blueprint for developing disease-modifying and supportive therapies in other neuromuscular and neurodegenerative diseases and in the case of the latter, potentially applying them across indications. Fatigue, for example, is common across many disorders including multiple sclerosis, Alzheimer's Disease, and DMD. A myostatin inhibitor or reldesemtiv might have a beneficial effect in several.

The fact that Spinraza and Zolgensma are significant revenue-generating drugs with obtainable reimbursement also provides a benchmark for future clinical and cost-effectiveness assessments in other diseases, and with Spinraza, shows that companies should also have a broad-based plan for evidence development – an even more important consideration in other neuromuscular diseases, with multi-factorial causes and symptomology compared to SMA.

Had the Spinraza data been only pretty good rather than great, Biogen's research plan for it, where they did multiple randomized trials looking at different groups, might have been a saving grace. "I think it should be a model for looking at diseases and new treatments for diseases," Rind said. Contrast that with the studies of Sarepta Therapeutics Inc.'s Exondys51 (eteplirsen) in DMD, another neuromuscular disease in children. ICER panned that drug in a recent review of DMD drugs. "I can't tell from the data we have now if Exondys51 works or doesn't work," Rind said. "They didn't do a trial that looked like what Biogen did. If Sarepta had done what Biogen did, we would certainly know by now whether it is helping patients."

The nature of SMA made it a good starting point for drug development, which the Neurogenetics Branch of the National Institute of Neurological Disorders and Stroke recognized in the 1990s when it identified SMA as an appropriate target to develop novel treatments because of the disease's almost idealized clinical features. SMA affects motor neurons but not a lot else. It does not alter cerebral function: as opposed to most infants with weakness, children with SMA are alert and awake and fully interactive – they have a fairly isolated muscle weakness due to the motor neuron loss. Plus, it is a recessive disorder with a back-up gene that makes the identical same protein, providing two ideal targets to try to correct genetically.

Technologies altering genes have matured and companies now have multiple gene-targeting platforms to choose from. "I think the thought all along was SMA would allow us to move this methodology into other neurodegenerative and neuromuscular diseases," said Day.

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About The Authors

Alessia Deglincerti (adeglincerti@bionest.com) is a senior consultant and Frank Borowsky (fborowsky@bionest.com) a consultant with Bionest Partners based in New York. Mark Ratner (mlratner@verizon.net) is a contributing editor to In Vivo.

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COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Beverley Carr	Achilles Therapeutics	Chief Business Officer	GlaxoSmithKline	Vice President, Business Development, Immuno-inflammation Therapy	4-Nov-19
Tanisha Carino	Alexion Pharmaceuticals Inc	Chief Corporate Affairs Officer and Executive Vice President	Milken Institute	Executive Director, FasterCures	4-Nov-19
Kevin Norrett	Angion Biomedica Corp	Chief Commercial Officer and Senior Vice President	Aimmune Therapeutics	Vice President, Marketing, Market Access and Commercial Operations	14-Oct-19
James Sapirstein	AzurRx BioPharma Inc	Chief Executive Officer and President	Hepion Pharmaceuticals	Chief Executive Officer and President	10-Oct-19
Merav Bassan	BiomX Ltd	Chief Development Officer	Teva Pharmaceutical Industries	Vice President, and Head, Translational Sciences	10-Oct-19
Kevin Buchi	BioSpecifics Technologies Corp	Chief Executive Officer and Director	Dicerna Pharmaceuticals	Chairman	10-Oct-19
Christopher Kenney	Cadent Therapeutics	Chief Medical Officer	Acorda Therapeutics	Senior Vice President, Medical Affairs	17-Oct-19
James Wooldridge	Checkmate Pharmaceuticals	Chief Medical Officer	Aeglea BioTherapeutics	Chief Medical Officer	15-Oct-19
Amy C. Peterson	CytomX Therapeutics Inc	Chief Development Officer and Executive Vice President	BeiGene	Chief Medical Officer	14-Oct-19
Matthew L. Sherman	Deciphera Pharmaceuticals Inc	Chief Medical Officer and Executive Vice President	Acceleron Pharma Inc	Chief Medical Officer	2-Oct-19
Christopher Degnan	Galera Therapeutics Inc	Chief Financial Officer	Verrica Pharmaceuticals Inc	Chief Financial Officer	21-Oct-19
Merdad Parsey	Gilead Sciences Inc	Chief Medical Officer	Genentech Inc	Senior Vice President, Early Childhood Development	1-Nov-19
Marcus Irsfeld	IOmx Therapeutics AG	Chief Financial Officer	Venock Inc	Chief Financial Officer and Co-Founder	9-Oct-19

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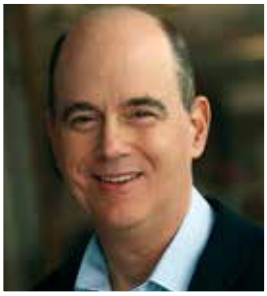
KEVIN NORRETT

ERIC ROWINSKY



MATTHEW SHERMAN

ROBIN WALKER

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Sreeji Gopinathan	Lupin Ltd	Chief Information Officer	Reckitt Benckiser	Director IS, AMESA	3-Oct-19
Stephane Durant des Aulnois	Lysogene	Chief Financial Officer	Ipsen	Chief Financial Officer, Ipsen Iberia	17-Oct-19
David Panzarella	Magnetic Insight Inc	Chief Commercial Officer	Quanterix	Vice President, Global Sales and Technical Applications	14-Oct-19
Steve Ferguson	Medix BioChemica	Chief Executive Officer	Thermo Fisher Scientific	Vice President, European Commercial Operations, ImmunoDiagnostics	1-Jan-20
Mark H. Pollack	Myriad Genetics Inc	Chief Medical Officer, Myriad Neuroscience	Rush University Medical Center	Professor and Chair, Department of Psychiatry	15-Jan-20
Steffen Heeger	NBE Therapeutics	Chief Medical Officer	Selvita Poland	Chief Medical Officer	8-Oct-19
John McCabe	Oncorus Inc	Chief Financial Officer	Salarius Pharmaceuticals Inc	Chief Financial Officer	22-Oct-19
Marella Thorell	Palladio Biosciences	Chief Financial Officer	Realm Therapeutics	Chief Financial Officer and Chief Operating Officer	11-Oct-19
Kerry Ingalls	Poseida Therapeutics Inc	Chief Operating Officer	Amgen Inc	Vice President, Site Operations	10-Oct-19
Colin Broom	Pulmotect Inc	Chief Executive Officer	Nabriva Therapeutics plc	Chief Executive Officer	17-Oct-19
Peter Heerma	Retrophin Inc	Chief Commercial Officer	Amgen Inc	Global Product Manager, Oncology and Cardiovascular	1-Oct-19
Barbara S. Fox	Rheos Medicines	Chief Executive Officer	Tilos Therapeutics Inc	Chief Executive Officer, Founder and Director	21-Oct-19
Wolfgang Dummer	Rigel Pharmaceuticals Inc	Chief Medical Officer	Aridis Pharmaceuticals Inc	Chief Medical Officer	23-Oct-19

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Joan Wood	Stoke Therapeutics	Head, Human Resources	Karyopharm Therapeutics	Chief Human Resources Officer and Senior Vice President	16-Oct-19
Robin A. Walker	Stoke Therapeutics	Chief Legal Officer and Senior Vice President	Casebia Therapeutics	Head, Legal and Senior Vice President	16-Oct-19
Angela Justice	TCR2 Therapeutics	Chief People Officer	Surgery Partners Inc	Chief Human Resources Officer and Executive Vice President	9-Oct-19
Stephen Brady	Tempest Therapeutics	Chief Operating Officer and President	Immune Design	Executive Vice President, Strategy and Finance	7-Oct-19
Sadik Kassim	Vor Biopharma Inc	Chief Technology Officer	Kite Pharma	Executive Director	1-Oct-19
Kathryn O'Driscoll	Zymeworks Inc	Chief People Officer	Snowflake	Vice President, People	16-Oct-19

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Regina Marek	Aerpio Pharmaceuticals	Principal Financial Officer and Principal Accounting Officer	Vice President, Finance	23-Oct-19
Kyle Jenne	Akcea Therapeutics	Chief Commercial Officer	Commercial Head	23-Oct-19
Guillaume Laverdure	AMD Medicom Inc	President, North America and Chief Operating Officer	Chief Operation Officer	17-Oct-19
Peter H. Griffith	Amgen Inc	Chief Financial Officer	Executive Vice President, Finance	1-Jan-20
Vesa Kemppainen	ArcDia International Oy Ltd	Chief Executive Officer	Director	7-Oct-19
Lon Cardon	BioMarin Pharmaceutical Inc	Chief Scientific Strategy Officer	Chief Scientific Officer	7-Oct-19
William Martin	BlackThorn Therapeutics	Chief Executive Officer and Director	President and Chief Operating Officer and Chief Scientific Officer	21-Oct-19
Vered Gigi	CURE Pharmaceutical Inc	Chief Scientific Officer	Vice President, Strategy and Business Development	1-Oct-19
Magali Taiel	GenSight Biologics	Chief Medical Officer	Vice President, Clinical Development	8-Oct-19
Andrew Dickenson	Gilead Sciences	Chief Financial Officer	Executive Vice President, Corporate Development and Strategy	1-Nov-19
Xiangyang Chen	InnoCare	Chief Technology Officer	Vice President, Medicinal Chemistry	1-Oct-19
Apollon Papadimitriou	IOmx Therapeutics AG	Chief Executive Officer	Chief Development Officer	9-Oct-19
Gisela Mautner	Noxopharm Ltd	Chief Medical Officer	Global Medical Director	16-Oct-19
Sami Shihabi	Progenity Inc	Chief Commercial Officer	Senior Vice President, Marketing and Portfolio Strategy	22-Oct-19
Mark Foley	Revance Therapeutics	Chief Executive Officer and President	Director	14-Oct-19
Kevin R. Smith	Sirtex Medical Ltd	Chief Executive Officer	Interim Chief Executive Officer	16-Oct-19

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
John Dal Poggetto	Sonoma Pharmaceuticals	Chief Financial Officer	Executive Vice President, Finance	1-Oct-19
Karl Lamprecht	ZEISS Group	Chief Executive Officer and President	Head, Semiconductor Manufacturing Technology and Executive Board Member	1-Apr-20

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Ertharin Cousin	Bayer AG	Supervisory Board Member	1-Oct-19
Martina Molsbergen	Bio-Path Holdings Inc	Director	11-Oct-19
Aaron Fletcher	Cue Biopharma	Director	9-Oct-19
Eric K. Rowinsky	Kitov Pharmaceuticals	Chairman	2-Oct-19
Kumar Srinivasan	Pulmotect Inc	Director	16-Oct-19
Jami Rubin	Relay Therapeutics	Director	1-Oct-19
Peter Hongaard	Scandion Oncology AS	Chairman	1-Oct-19
Mark Thierer	Xeris Pharmaceuticals Inc	Director and Member, Audit Committee	1-Oct-19
Chris Bowden	ZIOPHARM Oncology Inc	Director	15-Oct-19

ADVISOR

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Catherine Sears	bioAffinity Technologies Inc	Scientific and Medical Advisory Board Member	2-Oct-19
Gerard Silvestri	bioAffinity Technologies Inc	Scientific and Medical Advisory Board Member	2-Oct-19
Martin Tammemagi	bioAffinity Technologies Inc	Scientific and Medical Advisory Board Member	2-Oct-19
Neil Alexis	bioAffinity Technologies Inc	Scientific and Medical Advisory Board Member	2-Oct-19
Pierre Massion	bioAffinity Technologies Inc	Scientific and Medical Advisory Board Member	2-Oct-19
Steven Gygi	Casma Therapeutics Inc	Scientific Advisory Board Member	16-Oct-19
Brian Leyland-Jones	NED Biosystems	Chairman, Scientific Advisory Board	17-Oct-19

OTHER

EXECUTIVE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE	MOVE TYPE
David W. Meline	Amgen Inc	Chief Financial Officer and Executive Vice President	31-Dec-19	Retirement
Jeffrey T. Walsh	bluebird bio	Chief Strategy Officer	6-Jan-20	Resignation
Paul Weiner	Conformis Inc	Chief Financial Officer	18-Oct-19	Resignation
Barrett Katz	GenSight Biologics	Chief Medical Officer	8-Oct-19	Resignation
Peder Holk Nielsen	Novozymes AS	Chief Executive Officer	31-Mar-20	Resignation
Peer M. Schatz	Qiagen NV	Chief Executive Officer	7-Oct-19	Resignation
L. Daniel Browne	Revance Therapeutics	Chief Executive Officer, Co-Founder, President and Director	14-Oct-19	Resignation
Joseph P. Slattery	TransEnterix Inc	Chief Financial Officer	31-Dec-19	Retirement

Deal-Making

Covering deals made October 2019

Derived from Strategic Transactions, Informa's premium source for tracking life sciences deal activity, the Deal-Making column is a survey of recent health care transactions listed by relevant industry segment – In Vitro Diagnostics, Medical Devices, Pharmaceuticals, and Research, Analytical Equipment and Supplies – and then categorized by type – Acquisition, Alliance, or Financing.

Strategic Transactions is updated daily with in-depth deal analysis, structural and financial terms, and links to SEC-filed contracts.

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MEDICAL DEVICES

Mergers & Acquisitions

AngioDynamics pays $46m up front for **Eximo Medical**

Klox acquires full ownership of **FB Dermatology** JV

Alliances

LeMaitre buys **Admedus'** *CardioCel* and *VascuCel* patches

Bryn licenses exclusive global rights to **Aptar**'s bidose nasal delivery device

Stryker gets IP from **Conformis**

Teijin gains Japanese rights to **NeuroSigma**'s *Monarch* eTNS device for ADHD

PHARMACEUTICALS

Mergers & Acquisitions

Alexion buys **Achillion** for $930m in cash

PE consortium buys **Nestle Skin Health** for CHF10.2bn; re-brands as **Galderma**

Sonnet BioTherapeutics reverse merges with Chanticleer Holdings

UCB to strengthen myasthenia gravis offerings through $2.1bn acquisition of **Ra Pharmaceuticals**

Zealand Pharma acquires fellow GI drug developer **Encycle Therapeutics**

Alliances

Takeda divests non-core assets to **Acino** in deal worth over $200m

EPI Health acquires **Aclaris'** *Rhofade* topical rosacea treatment

Emerge Health to sell *Symjepi* in Australia and New Zealand for **Adamis**

Alexion gets exclusive option to **Stealth**'s elamipretide

Bausch & Lomb gets US and Canadian rights to **Clearside**'s *Xipere*

GSK divests two travel vaccines to **Bavarian Nordic**

Ipsen licenses exclusive global rights to **Blueprint**'s FOP candidate BLU782

Brii Bio gets rights to various **Qpex** infectious disease programs in Greater China

RedHill gets US rights to **Cosmo**'s *Aemcolo* GI drug

DongKoo gains Korean rights to **Moberg**'s MOB015

Entos signs $109m autoimmune/inflammation deal with unnamed partner

Eyevance gains global license to Novartis' ophthalmic suspensions

Insilico and **CTFH** enter $200m AI-centered drug discovery deal

Pfizer gains global rights to **Akcea**'s Phase II cardiometabolic therapy

Neumentum gets rights to **J&J**'s non-opioid pain therapy

Mayne gains US rights to **Mithra**'s *Estelle* combo oral contraceptive

Mitsubishi Tanabe licenses rights to **Viela**'s inebilizumab

Novartis applies AI to pharma discovery/development efforts in collaboration with Microsoft

Novartis licenses global rights to **Pliant**'s PLN147 for NASH

Specialised Therapeutics to market *Yondelis* for **PharmaMar**

Takeda and **Prometheus Biosciences** enter IBD partnership

Financings

Initial public offering nets $91m for **Aprea**

Public offering nets $23.4m for **BeyondSpring**

BioNTech nets $141m through initial public offering

Cabaletta Bio nets $69.6m via initial public offering

Private placement grosses $65m for **Constellation**

DBV Technologies completes $134m global ADS offering

Frequency Therapeutics nets $78.1m in IPO

Heron Therapeutics nets $141.3m via FOPO

Innate Pharma nets $73.5m in initial public offering

Innovent Biologics nets $300m via PIPE

Ovid Therapeutics nets $30.6m in concurrent public offerings

Oyster Point Pharma files for IPO

Phathom goes public netting $194.3m

Principia nets $197.4m through public offering

ProQR nets $54m via FOPO

Rhythm Pharma nets $162m via FOPO

Registered direct offering nets $23.5m for **Sorrento Therapeutics**

TherapeuticsMD nets $77m through FOPO

Viela Bio goes public, nets $160.5m

Vir Biotech nets $132.9m via IPO

Y-mAbs nets $117.5m through public stock sale

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MEDICAL DEVICES

MERGERS & ACQUISITIONS

BAXTER INTERNATIONAL INC.
CHEETAH MEDICAL INC.

Baxter International Inc. will acquire privately held monitoring device firm **Cheetah Medical** for $190m in cash plus up to $40m in earn-outs based on clinical and commercial achievements. (Sep.)

Cheetah was founded in 2000 and designs and markets specialized noninvasive hemodynamic monitoring systems. Through the acquisition, Baxter gains the company's *Starling* SV system, which provides a dynamic assessment of fluid responsiveness for accurate maintenance of organ and tissue perfusion. The technology is based on Cheetah's *Bioreactance* technology which uses the application of electrical current (AC current) through external sensors applied at the thorax to help measure time delay and phase shifts, parameters which are tightly correlated with cardiac stroke volume. Baxter notes that the Cheetah platform will be integrated with its own IV infusion pumps, IV fluid offerings, and medications to provide a more integrated patient monitoring and treatment experience.

INTEGRA LIFESCIENCES HOLDINGS CORP.
REBOUND THERAPEUTICS CORP.

Integra LifeSciences Holdings Corp. acquired privately held minimally invasive surgery (MIS) technologies start-up **Rebound Therapeutics Corp.** (Sep.)

Rebound makes single-use medical devices that enable imaging during minimally invasive neurosurgeries and other MIS procedures, providing access and using integrated optics and illumination for visualization. Rebound's *Aurora* surgiscope system and evacuator were both FDA cleared earlier this year. The *Aurora* surgiscope consists of a disposable neurosurgical endoscope and a reusable control unit that enables the user to control a high-definition video image of the neuro anatomy. The *Aurora* evacuator is an electrosurgical device that includes a power instrument and a single-use handpiece for soft tissue aspiration or removal in neuro, spinal, pelvic, ENT, and other MIS procedures, enabling direct visualization of surgical sites with limited access.

STRYKER CORP.
CARDAN ROBOTICS
MOBIUS IMAGING LLC

Stryker Corp. agreed to acquire privately held device companies **Mobius Imaging LLC** (point-of-care imaging) and its sister spinal robotics company, **Cardan Robotics** (aka GYS Tech LLC; navigation), in an all cash transaction. (Sep.)

Stryker will pay $370m up front and could provide up to $130m in earn-outs associated with the achievement of development and commercial milestones. Founded in 2008, Mobius creates tools that fit into and assist the imaging workflow. Its 510(k)-cleared *Airo TruCT* scanner is a mobile, real-time x-ray computed tomography (CT) imaging system for use in emergency departments as well as numerous applications in spine, orthopedic, and neuro surgeries, thoracic procedures, and radiation oncology. Cardan, founded in 2015, offers the *Orion* line of robotic arms and guidance systems, image-guided navigation systems (and related hardware and software) used in surgical and interventional radiology procedures.

ALLIANCES

BAYER AG
ONE DROP

One Drop partnered its digital health platform with **Bayer AG**, which will use the technology to provide bio-digital solutions in the areas of oncology, cardiovascular disease, and women's health. The deal is worth $10m. (Sep.)

While Bayer will be applying One Drop's platform in multiple indications, One Drop has traditionally focused on diabetes management. Its digital health offering includes coaching programs (with certified diabetes educators) and a mobile app that tracks blood sugar, medications, food, and activity, and incorporates artificial intelligence-based behavioral recommendations. The company also provides test strips, glucose meter start kits, and lancets. In addition to signing the licensing agreement, Bayer also led a $40m series B round for One Drop.

CLEARSIDE BIOMEDICAL INC.
REGENXBIO INC.

REGENXBIO Inc. received an option to license exclusive global rights (including sublicensing rights) to **Clearside Biomedical Inc.**'s *SCS Microinjector*. (Sep.)

Should REGENXBIO exercise its option, it would pay Clearside a fee plus up to $34m in development milestones and $102m in sales milestones as well as mid-single-digit sales royalties. REGENXBIO would use the *SCS Microinjector* to non-surgically deliver its own RGX314 adeno-associated virus 8 (AAV8) gene therapy to the suprachoroidal space (SCS) for treating wet age-related macular degeneration (wet AMD), diabetic retinopathy (DR), and other conditions for which anti-vascular endothelial growth factor (anti-VEGF) treatment is currently the standard of care. The company would be responsible for all development and commercialization activities for gene therapy product candidates, while Clearside will supply the *SCS Microinjector*.

FINANCINGS

DANAHER CORP.
Envista Holdings Corp.

Danaher Corp.'s dental subsidiary **Envista Holdings Corp.** (implants, orthodontics, and digital imaging technologies) netted $643m in its initial public offering of 30.7 million shares (including the overallotment) at $22, the middle of its anticipated $21-24 range. (Sep.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Credit Suisse Group; Evercore Partners; Goldman Sachs & Co.; JP Morgan & Co.; Jefferies & Co. Inc.; Morgan Stanley & Co.; Robert W. Baird & Co. Inc.; Stifel Nicolaus & Co. Inc.; William Blair & Co. (Envista Holdings Corp.)

INSULET CORP.

Insulet Corp. (developer of the *Omnipod* insulin management system) announced an upsized private placement of $700m (net $684.3m) aggregate principal amount of convertible senior notes due 2026. The notes bear interest at a rate of 0.375% and can be converted in cash, stock, or a combination. The conversion rate will initially be 4.4105 shares of common stock per $1k principal amount of notes, or $226.73 per Insulin share (its shares are currently averaging $154.65). The company is also granting the initial purchasers an option to purchase another $100m notes. Insult announced it is entering into capped call transactions and will use some of the proceeds to fund those transactions. Additional funds will be used to repurchase $225m aggregate principal amount of the outstanding 1.25% convertible senior notes due 2021. (Sep.)

ISTAR MEDICAL SA

Ophthalmic implants maker **iStar Medical SA** raised €40m ($44m) in its series C financing led by Life Sciences Partners and GIMV, which was joined by new backers Earlybird and BNP Paribas Fortis Private Equity, and returning shareholders Capricorn Partners, Walloon Region Investment Fund, and Belgian Federal Investment Fund. The company will use the proceeds for ongoing development of its *MINIject* as the company prepares to commercialize the device in the US and Europe. *MINIject* is designed to reduce intraocular pressure in glaucoma patients. (Sep.)

PHARMACEUTICALS

MERGERS & ACQUISITIONS

ANOKION SA
KANYOS BIO INC.

Four years after spinning out the company, **Anokion SA** has now acquired **Kanyos Bio Inc.** Financial terms were not disclosed. (Sep.)

Kanyos was formed in 2015 and tasked with developing celiac disease and Type

I diabetes candidates arising from a partnership between Anokion and **Astellas**. (Astellas had an option to buy Kanyos under terms of that deal.) Through the acquisition, Anokion gains KAN101, an antigen-specific celiac disease therapy for which an IND filing is expected by the end of 2019. The project will be developed alongside Anokion's ANK780, also an antigen-specific treatment that is in preclinical studies for multiple sclerosis. Concurrent with the Kanyos buy, Anokion announced a $40m Series B round.

ARTARA THERAPEUTICS INC.
PROTEON THERAPEUTICS INC.

Publicly traded **Proteon Therapeutics Inc.** is reverse merging with closely held **ArTara Therapeutics Inc.** in a stock swap. (Sep.)

Post-transaction, the combined firm will keep the ArTara name, trade on the Nasdaq under the ticker TARA, have its headquarters in New York City, and be led by currently ArTara CEO Jesse Shefferman. Mr. Shefferman will serve on the board along with five members designated by ArTara and one by Proteon. The company will be owned 90%/10% by ArTara and Proteon, respectively. The combined entity will focus on advancing ArTara's two assets. Lead program TARA002 (follow-on biologic of OK432 (picibanil), an attenuated strain of Streptococcus pyogenes) is a Phase III toll-like receptor 4 agonist for treating lymphangiomas.

CASTLE CREEK PHARMACEUTICALS LLC
FIBROCELL SCIENCE INC.

Castle Creek Pharmaceuticals LLC (CCP) agreed to acquire its partner, public US biotech **Fibrocell Science Inc.** (autologous cell-based therapies for skin and connective tissue diseases) for $3 in cash per share (a 60% premium). The deal was already unanimously approved by both boards and is expected to close in Q4 2019. (Sep.)

Including Fibrocell's net debt, the transaction is valued at $63.3m. Both companies have advanced candidates for multiple types of epidermolysis bullosa (EB), a rare genetic disease that leads to fragile skin prone to blistering, erosion, and peeling. The partners first collaborated in April 2019 when CCP in-licensed exclusive US development and commercialization rights to Fibrocell's lead potential gene therapy candidate FCX007, an autologous dermal fibroblast, which has US orphan, fast-track, rare pediatric, and regenerative medicine advanced therapy designations as well as orphan status in Europe. A Phase III trial in recessive dystrophic EB was initiated in July 2019 and a BLA filing is anticipated in 2021; with a 28% likelihood of approval (4% above average), according to Biomedtracker.

CURRAX PHARMACEUTICALS LLC
NALPROPION PHARMACEUTICALS INC.

Currax Pharmaceuticals LLC acquired 2018 start-up **Nalpropion Pharmaceuticals Inc.**. gaining worldwide rights to Nalpropion's sole product, the FDA-approved *Contrave* (bupropion/naltrexone; sold in the EU as *Mysimba*) weight-loss medication. (Sep.)

Currax's predecessor company Pernix (acquired by Currax after it filed for bankruptcy in February 2019) owned a 10% stake in Nalpropion, formed by Pernix in April 2018 as a special purpose vehicle to acquire the assets (mainly *Contrave* (NB32)) of the now-defunct Orexigen Therapeutics, after Orexigen itself filed for Chapter 11 in March 2018. *Contrave* was approved in 2014 for adult patients with a body mass index between 27 or greater (overweight) and 30 or greater (obese) who have at least one weight-related condition such as high blood pressure (hypertension), Type 2 diabetes, or high cholesterol (dyslipidemia).

GLAXOSMITHKLINE PLC
SITARI PHARMACEUTICALS

GlaxoSmithKline PLC is acquiring **Sitari Pharmaceuticals** for an undisclosed sum. (Sep.)

In 2013, Avalon Ventures and GSK created a venture in which they sought to create and fund at least ten biopharma start-ups in the San Diego area to be incubated by COI Pharmaceuticals. (To date they established eight companies.) Under the agreement, Avalon identified and assessed early drug development candidates and granted GSK an option to acquire each company at the point of lead clinical candidate identification. Sitari was formed in late 2013 and was the first company born out of that collaboration. At the time Sitari received $10m in Series A funding. The firm's intellectual property comes out of research from **Stanford University** surrounding the transglutaminase 2 (TG2) pathway. When exposed to gluten, the TG2 enzyme in the gut triggers an immune response that results in intestinal inflammation and disease pathogenesis. Sitari has been using the IP to develop TG2 inhibitors for celiac disease. The lead program is in preclinical studies.

H. LUNDBECK AS
ALDER BIOPHARMACEUTICALS INC.

Neuro-focused Danish pharmaco **H. Lundbeck AS** agreed to acquire public US biotech **Alder BioPharmaceuticals Inc.** for up to $20 in cash per share. The transaction was already unanimously approved by Alder's board and is expected to close in Q4 2019. (Sep.)

Lundbeck is mainly interested in Alder's eptinezumab (ALD403), an intravenous monoclonal antibody (mAb) candidate for migraine prevention, that targets the calcitonin gene-related peptide (CGRP). Alder submitted a BLA to the FDA for eptinezumab in February 2019, with a PDUFA action date of February 21, 2020. It has a 91% likelihood of approval (8% above average). Once approved, eptinezumab will be the first US-marketed IV CGRP therapy for migraine prevention. For the acquisition, Lundbeck will begin a tender offer of $18 in cash per share (a 97% premium) initially (equal to $1.5bn), plus one non-tradeable contingent value right (CVR) that entitles Alder to an additional $2 per share (another $167m) upon EMA approval of eptinezumab. Net of cash, the total transaction value is $1.95bn. Lundbeck will fund the deal using both existing cash and additional financing. Lundbeck expects to submit an MAA for eptinezumab in the EU during 2020, followed by regulatory submissions globally, including China and Japan.

SWEDISH ORPHAN BIOVITRUM AB
DOVA PHARMACEUTICALS INC.

Swedish Orphan Biovitrum AB (Sobi) signed a definitive agreement to acquire **Dova Pharmaceuticals Inc.**, a public three-year-old hematology drug company. The total potential value of the deal could hit $915m, including $27.50 per Dova share in cash (a 55% premium to the 10-day pre-announcement market average) and contingent value rights entitling Dova shareholders to $1.50 per share. (Sep.) Dova was formed by PBM Capital in 2016 to commercialize the thrombocytopenia therapy *Doptelet* (avatrombopag), a thrombopoietin receptor agonist that is approved in the US and EU for thrombocytopenia in adults with chronic liver disease and in the US for chronic immune thrombocytopenia (EU filing is expected next year).

VERTEX PHARMACEUTICALS INC.
SEMMA THERAPEUTICS INC.

Vertex Pharmaceuticals Inc. is paying $950m in cash to acquire closely held diabetes-focused firm **Semma Therapeutics Inc.** (Sep.)

Post-transaction, Semma will operate as a Vertex subsidiary and its current president and CEO Bastiano Sanna, PhD, will continue in the president role. In addition, Semma's founder and SAB chair Douglas Melton, PhD, will keep his position and offer oversight and guidance on the R&D programs. Semma is focused on using encapsulated stem cell-derived human islets as a curative treatment for Type I diabetes. The company has found a way to produce large amounts of functional human pancreatic beta cells that can restore insulin secretion and ameliorate hypoglycemia. Its encapsulation technology offers a way to protect the cells from the immune system and allow for implantation of an islet-cell filled device without the need for patient immunosuppression.

ZHEJIANG HISUN PHARMACEUTICAL CO. LTD.

Hisun BioRay Biopharmaceutical Co. Ltd.

Private equity firm PAG will pay $540m to take a majority stake (58%) in **Hisun BioRay Biopharmaceutical Co.**, a division of **Zhejiang Hisun Pharmaceutical Co. Ltd.**

(which retains a 42% ownership). (Sep.)

Hisun BioRay was formed earlier this year to develop, manufacture, and sell antibody therapeutics for cancer and autoimmune diseases. The company's first drug on the market, *Anbainuo* (recombinant human tumor necrosis factor-a receptor II), is an etanercept biosimilar for autoimmune conditions including psoriasis, ankylosing spondylitis, and rheumatoid arthritis. Hisun BioRay has more than ten other projects in its pipeline, with the *Humira* biosimilar *Anjianning* due to hit the market in China near year-end. The investment by PAG (which came after Hisun entertained offers from 40 other interested parties) marks the largest ever for a Chinese biotech and provides Hisun BioRay with funds to accelerate R&D activities and expand the company's presence in the biosimilars and biologics markets.

ALLIANCES

3B PHARMACEUTICALS GMBH
CLOVIS ONCOLOGY INC.

Clovis Oncology Inc. licensed global rights (excluding Europe) to a peptide-targeted radionuclide therapy and an imaging agent targeting fibroblast activation protein alpha (FAP) from **3B Pharmaceuticals GmbH**. (Sep.)

Under terms of the deal, the partners will also discover and develop radiopharmaceuticals for three other undisclosed targets, to which Clovis will have worldwide rights. Clovis pays $12m up front, milestones, and royalties ranging from the single to low-double digits. (*Strategic Transactions* estimates 1-29%.) Clovis is responsible for three 3BP FTEs in addition to external costs during the preclinical stage of the deal. FAP is highly expressed in cancer-associated fibroblasts found in epithelial cancers including breast, lung, colorectal, and pancreatic tumors. Using a FAP-targeted radiopharmaceutical agent results in the emission of ionizing radiation by cancer-associated fibroblasts surrounding the targeted area, resulting in DNA damage to tumor cells. A review of 3B's pipeline notes that the companies have named two preclinical solid tumor projects under their deal, 3B201 and 3B202. Clovis moves into the radiopharmaceuticals arena via the deal with 3B.

ABBVIE INC.
IDERA PHARMACEUTICALS INC.

Idera Pharmaceuticals Inc. and **AbbVie Inc.** forged a trial collaboration to study combinations of ABBV368, tilsotolimod, nab-paclitaxel, and/or ABBV181. (Sep.)

The parties seek to determine whether or not the combinations can stimulate the immune system and produce anti-tumor responses. The collaboration will study three treatment arms: AbbVie's Phase I OX40 agonist ABBV368 plus Idera's Phase I TLR-9 agonist tilsotolimod; ABBV368 plus tilsotolimod and the chemotherapy nab-paclitaxel; and ABBV368 plus tilsotolimod, nab-paclitaxel, and AbbVie's Phase I programmed cell death 1 (PD-1) antagonist ABBV181. The planned Phase Ib trial will determine the safety, tolerability, pharmacokinetics, and preliminary efficacy of combinations of ABBV368 plus tilsotolimod in patients with recurrent or metastatic head and neck squamous cell carcinoma. Idera will supply tilsotolimod and AbbVie will conduct the study.

ALEXION PHARMACEUTICALS INC.
BRIDGEBIO PHARMA INC.
Eidos Therapeutics Inc.

Eidos Therapeutics Inc. licensed **Alexion Pharmaceuticals Inc.** exclusive rights to develop and commercialize AG10 in Japan. (Sep.)

Eidos gets $25m up front, an equity investment of $25m, plus milestones and royalties. AG10 is designed to bind and stabilize transthyretin (TTR) protein in the blood to treat transthyretin amyloidosis (ATTR). The compound is currently in Phase III in the US and Europe for ATTR cardiomyopathy and is expected to enter Phase III for ATTR polyneuropathy by the end of 2019.

AMERIGEN PHARMACEUTICALS INC.
INVENTIA HEALTHCARE LTD.

Amerigen Pharmaceuticals Inc. licensed exclusive US sales, marketing, and distribution rights to India generics company **Inventia Healthcare Ltd.**'s paliperidone extended-release (ER) tablets and tolterodine ER capsules. (Sep.)

Inventia retains manufacturing rights and will supply the products. It has an Indian manufacturing facility to formulate approved oral products across a range of delivery dosage forms. A generic equivalent to **Janssen**'s *Invega*, the paliperidone ANDA was approved in the US in June 2019. The 5-HT2 and partial dopamine D2 antagonist is an antipsychotic medicine for schizophrenia. The ANDA for tolterodine, a generic to **Pfizer**'s *Detrol LA* for overactive bladder, was approved just last month. Tolterodine is commercialized in India by **Dr. Reddy**. The current deal enables Inventia to increase its global reach, while allowing Amerigen to expand its portfolio, which is mainly focused on externally sourced orally formulated APIs that are challenging to develop, require specialized technologies to manufacture, or have other regulatory and intellectual property difficulties in gaining US and Chinese approval.

AMPLYX PHARMACEUTICALS INC.
NOVARTIS AG

Amplyx Pharmaceuticals Inc. licensed exclusive worldwide rights to **Novartis AG**'s monoclonal antibody, MAU868, for treatment and prevention of BK virus (BKV)-related disease. (Sep.)

Novartis was assessing safety, tolerability, and efficacy of the compound in preclinical studies for the prevention of BKV infection in kidney transplant recipients before suspending development for unknown reasons late last year. A polyomavirus, initial BK infection is asymptomatic, but it can remain dormant in the kidney or bladder; if reactivated by a weakened immune system, serious disease may result. MAU868 targets VP1, the major viral capsid protein of BKV, necessary for the virus to bind to and infect new cells. Amplyx believes MAU868 will protect against BKV reactivation in kidney transplant and hematopoietic stem cell transplant patients, thus preventing, respectively, renal allograft failure and hemorrhagic cystitis (an inflammatory bladder disease). Amplyx anticipates initiating two Phase II proof-of-concept studies of the mAb by year end.

ATOMWISE INC.
JIANGSU HANSOH PHARMACEUTICAL GROUP CO. LTD.

AI-focused drug discovery start-up **Atomwise Inc.** and Chinese biotech **Jiangsu Hansoh Pharmaceutical Group Co. Ltd.** (Hansoh) agreed to collaborate on the design and discovery of potential drug candidates for up to 11 undisclosed target proteins across numerous therapeutic areas, including oncology. (Sep.)

Researchers from both companies will partner their respective capabilities with an aim to improve the chances for success and decrease discovery and development timelines. Atomwise will perform direct hit discovery, hit-to-lead selection, and lead optimization. Hansoh contributes its biological assay and medicinal chemistry expertise and will be responsible for leading preclinical and clinical development activities for potential compounds to which it receives worldwide development and commercialization rights in all fields. Atomwise will receive undisclosed technology access and option exercise payments, royalties, and potential fees from future sublicensing or sale of assets. The total potential value of the deal if all projects succeed is expected to reach blockbuster potential, according to the companies. Atomwise's *AtomNet* structure-based drug design platform, based on deep convolutional neural networks, can analyze a chemical space of billions and billions of compounds to identify a small subset with high specificity.

BIOMOTIV LLC
BRISTOL-MYERS SQUIBB CO.

Bristol-Myers Squibb Co. agreed to become a limited partner in **BioMotiv LLC**. Together they will establish start-ups, which BMS might eventually buy. (Sep.)

BioMotiv was founded in 2012 around the business model of in-licensing assets from academic institutions, developing programs through proof-of-concept studies, and then out-licensing the drugs or technologies to a partner. It has done such deals with **Takeda** and **Biogen**. Now, BioMotiv has given BMS

the option to fund selected projects (targeting great unmet need), around which the partners would form and fund new companies. Once a preclinical candidate is identified, BMS would have the option to acquire that company under pre-agreed terms. Therapeutic areas were not disclosed, although BioMotiv's previous alliances with Takeda and Biogen involved immunology, inflammation, and cardio-metabolic and neurological diseases. BMS is currently most active in oncology.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
INFLAMMASOME THERAPEUTICS INC.

Boehringer Ingelheim International GmbH and **Inflammasome Therapeutics Inc.** agreed to co-develop up to three candidates for retinal diseases. (Sep.)

BI will provide up to $160m in up-front, R&D, and milestone payments, plus tiered royalties and additional commercialization milestones. The deal combines compounds from the Big Pharma's retinal disease pipeline with Inflammasome's intravitreal (IVT) drug delivery technologies.Inflammasome's long-acting degradable IVT implant enables the administration of compounds to the eye as sustained-release depot formulations. Although specific candidates weren't disclosed, BI has compounds for retinal diseases in various phases of development, including Phase II BI1467335 for diabetic retinopathy, Phase I BI754132 for age related macular degeneration (AMD), and BI836880, in Phase I for wet AMD.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
LUPIN LTD.

Boehringer Ingelheim GmbH licensed exclusive worldwide development and commercialization rights to **Lupin Ltd.**'s LNP3794 mitogen-activated ERK kinase (MEK) inhibitor compound for difficult-to-treat cancers. (Sep.)

In exchange, Lupin gets $20m up front, specified clinical, regulatory, and sales milestones of more than $700m, plus double-digit royalties. LNP3794 has demonstrated preclinical activity as a single agent as well as in combination with other therapies. MEK inhibitors and BI's own K-Ras inhibitors are known to have complementary mechanisms of action. Ras is the most frequently mutated oncogene known in cancer, with K-Ras being the most common subtype occurring in cancers of the pancreas, colon, biliary tract, and lung. BI plans to develop LNP3794 in combination with one compound from its pipeline to treat K-Ras-dependent gastrointestinal and lung cancers.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
ONCOHEROES BIOSCIENCES INC.

Boehringer Ingelheim International GmbH licensed **Oncoheroes Biosciences Inc.** exclusive worldwide R&D and commercialization rights (and related IP) to its volasertib (BI6727), a polo-like-kinase 1 (PLK1) inhibitor for cancer. (Sep.)

The Big Pharma was advancing the compound in several cancer indications, but suspended development following a 2016 Phase III study in adult acute myeloid leukemia patients that failed to meet its primary endpoint. Oncoheroes plans to further develop and eventually sell volasertib for rhabdomyosarcoma (RMS), the most common pediatric soft tissue sarcoma, and other childhood cancer indications. BI's additional studies of volasertib (all since suspended) included a Phase I European study of the compound as a single agent in children with leukemia or refractory solid tumors. A recommended Phase II dose for children has been defined. Because of preclinical evidence demonstrating volasertib's ability to reduce the activity and stability of the fusion proteins thought to be responsible for many cases of the disease, it might prove an effective therapeutic agent against RMS. Clinical studies are expected to begin in 2020.

CIDARA THERAPEUTICS INC.
MUNDIPHARMA INTERNATIONAL CORP. LTD.

Cidara Therapeutics Inc. licensed **Mundipharma International Corp. Ltd.** exclusive global rights outside the US and Japan to develop and commercialize intravenous rezafungin for treating invasive fungal infections. (Sep.)

For the rights, Mundipharma will pay Cidara $30m up front and make a $9m equity investment in the firm. Cidara is also eligible for $42.4m in development funding to support the global Phase III ReSTORE and ReSPECT trials, up to $534.4m in development, regulatory, and commercial milestones, plus sales royalties in the teens. In addition to IV rezafungin, Cidara also granted Mundipharma an option to obtain exclusive licenses to develop, register, and commercialize rezafungin in subcutaneous and other formulation for administration. Mundipharma also has a co-exclusive worldwide license to manufacture the drug. Cidara will continue to lead the Phase III development programs with the support from Mundipharma. The parties may choose to pursue additional indications or formulations of rezafungin.

COPERNICUS THERAPEUTICS INC.
CAN-FITE BIOPHARMA LTD.
Wize Pharma Inc.

Copernicus Therapeutics Inc. licensed **Wize Pharma Inc.** exclusive global rights to develop, manufacture, and commercialize non-viral gene therapies for choroideremia (CHM) based on Copernicus' technology. Wize also has the right to sublicense. (Sep.)

Wize will pay an undisclosed up-front fee, development milestones (in cash or stock), and high-single or low-double-digit sales royalties (*Strategic Transactions* estimates 7-29%). Wize will also pay Copernicus fees to fund and execute the development plan leading to the completion of the Phase I/II clinical trial. Copernicus's technology enables the development of effective non-viral gene therapies for ophthalmic indications without toxicity. CHM is a rare, degenerative, inherited retinal disorder that mostly affects males and leads to blindness. There are no FDA-approved treatments for the condition.

CURRAX PHARMACEUTICALS LLC
OPTINOSE INC.

Currax Pharmaceuticals LLC (formerly Pernix Therapeutics) gained exclusive US, Canadian, and Mexican marketing rights to **OptiNose Inc.**'s *Onzetra Xsail* (sumatriptan) dry powder formulation acute migraine treatment. (Sep.)

Currax will provide $4.48m up front ($750k of which will be held in escrow), a $1m regulatory milestone, plus a one-time 10% royalty on net sales in excess of $3m during calendar year 2020. FDA-approved in 2016, *Onzetra Xsail* is administered via OptiNose's breath-powered powder exhalation delivery system (EDS), which consists of a reusable device with a flexible and adjustable fit mouthpiece with an assembly to pierce the medication capsule. Currax also has a license to certain patent rights to the EDS. Pernix--Currax's predecessor company, which filed for bankruptcy in February 2019 and was acquired by Currax after that--has US rights to another marketed migraine therapy, *Treximet* (naproxen sodium/sumatriptan), which it gained from **GlaxoSmithKline PLC** under a 2014 deal.

DAIICHI SANKYO CO. LTD.
MITSUBISHI CHEMICAL HOLDINGS CORP.
Mitsubishi Tanabe Pharma Corp.

Mitsubishi Tanabe Pharma Corp. granted **Daiichi Sankyo Co. Ltd.** commercialization rights in Brazil for an intravenous infusion formulation of edaravone for amyotrophic lateral sclerosis (ALS). (Sep.)

Edaravone (MCI186) was first approved for ALS as *Radicut* in Japan in June 2015, followed by South Korea (12/15), the US (5/17) and Canada (10/18)--it's marketed in the latter two territories as *Radicava*--Switzerland (1/19), and most recently, China (8/19). The drug is a free radical scavenger that protects motor neurons from oxidative stress to delay ALS disease progression. Daiichi also has rights of first negotiations for commercialization of the IV dosage form in Central and South American countries other than Brazil as well as for other dosage forms of edaravone in countries in Central and South America, including Brazil. Daiichi is responsible for filing a regulatory application and will commercialize the product in Brazil upon its approval.

EVOTEC SE
TAKEDA PHARMACEUTICAL CO. LTD.

Evotec SE and **Takeda Pharmaceutical Co. Ltd.** entered into a multi-year agreement for the discovery and development of new therapies across a variety of indications. (Sep.)

Under terms of the deal, Evotec will use its drug discovery technologies to uncover up to five programs in the areas of oncology, gastroenterology, neuroscience, and rare diseases. Takeda has options at lead series and upon delivery of preclinical candidates to license development and commercialization rights to any candidates. Takeda made an undisclosed up-front payment and could hand over up to $170m per program in total milestones ($850m for all five) plus tiered royalties. Takeda and Evotec have worked together in the past. In 2003, **Evotec Neurosciences** and Takeda penned a four-year collaboration to discover new treatments for Alzheimer's disease.

FLEXION THERAPEUTICS INC.
XENON PHARMACEUTICALS INC.

Flexion Therapeutics Inc. gained exclusive worldwide development and commercialization rights to **Xenon Pharmaceuticals Inc.**'s XEN402, a NaV1.7 sodium channel inhibitor for the non-opioid management of post-operative pain. The license includes associated patents and related non-clinical, clinical, and manufacturing assets. (Sep.)

Xenon gets $3m up front; up to $9m in manufacturing, development, and regulatory milestones (through the initiation of a Phase II proof of concept trial); up to $40.75m in development and regulatory milestones (following Phase II PoC); up to $75m in commercialization milestones; plus future sales royalties ranging from the mid-single to low double-digits (*Strategic Transactions* estimates 4-29%). Flexion will also assume Xenon's remaining obligation under a 2012 agreement (since terminated) to pay a low single-digit percentage sales royalty to **Teva Pharmaceuticals**. XEN402 was previously tested in multiple human clinical trials, which demonstrated good efficacy when delivered to the target site at high concentration. The candidate had reached Phase II trials before it was suspended after failing to meet primary and secondary endpoints in osteoarthritis (OA), post-herpetic neuralgia, and neuropathic pain indications. Flexion plans to conduct a preclinical program called FX301, in which it will formulate XEN402 as an extended-release hydrogel.

GLAXOSMITHKLINE PLC
VBI VACCINES INC.

VBI Vaccines Inc. and **GlaxoSmithKline PLC** are teaming up in a trial collaboration to study the combination of VBI1901 cancer immunotherapy with GSK's AS01B adjuvant system. (Sep.)

VBI1901 incorporates VBI's enveloped virus-like particle (eVLP) technology and has demonstrated potency in the Phase I/IIa trial for treating recurrent glioblastoma (GBM). VBI1901 is administered intradermally when adjuvanted with granulocyte-macrophage colony-stimulating factor. AS01B has shown its ability to boost T-cell mediated immunity. This is GSK's first partnership with a biopharma company to evaluate AS01B in the clinic and the first time it will be studied in oncology for GBM patients. AS01B has proven effective in combination with the gE antigen in GSK's shingles vaccine *Shingrix*.

GRUNENTHAL GMBH
MESOBLAST LTD.

Grunenthal GmbH licensed exclusive European and Latin American development and commercialization rights to **Mesoblast Ltd.**'s MPC06ID (rexlemestrocel-L), an injectable cell therapy for chronic low back pain (CLBP) due to degenerative disc disease. (Sep.)

MPC06ID uses allogenic mesenchymal precursor cells (MPCs), which secrete multiple factors that stimulate new proteoglycan and collagen synthesis by chondrocytes. MPCs have also been shown to produce anti-inflammation factors. In a US Phase II trial (completed in 2013), MPC06ID demonstrated that a single intra-discal injection resulted in significant improvements in CLBP intensity, functionality, and disc stability for at least three years. The candidate is currently undergoing a US Phase III trial with top-line results expected in 2020. MPC06ID has a 54% likelihood of approval (2% above average). Both companies will collaborate on the study design for a European confirmatory Phase III trial. Mesoblast will get $15m up front, up to $1bn in total milestones (includes $135m in precommercialization milestones, including $20m upon approval to begin the confirmatory Phase III trial in Europe and $10m for certain clinical and manufacturing outcomes), plus tiered double-digit sales royalties.

IFM THERAPEUTICS LLC
IFM Due
NOVARTIS AG

IFM Therapeutics LLC, through its **IFM Due** division, agreed to collaborate with **Novartis AG** on the development of cGAS/STING (cyclic GMP-AMP synthase/stimulation of interferon genes) pathway inhibitors to treat various inflammatory and autoimmune diseases. (Sep.)

Through fixed payments, Novartis will fully fund IFM Due's R&D costs for the cGAS/STING program in exchange for the option to acquire the subsidiary company outright. If Novartis exercises that purchase option, it will pay a total of up to $840m (including an up-front option closing fee and other contingent consideration). Within the innate immune system, the cGAS/STING pathway functions to sense cytosolic DNA (a signal of cellular danger) and thus triggers an inflammatory response. Mutations in the activation of this pathway can lead to excessive production of interferon and other pro-inflammatory cytokines that can cause a range of rare diseases, including Aicardi-Goutieres syndrome (AGS), STING-associated vasculopathy with onset in infancy, and systemic lupus erythematosus, as well as more common conditions such as nonalcoholic steatohepatitis, chronic obstructive pulmonary disease, age-related macular degeneration, and Parkinson's disease. Founded in February 2019, IFM Due houses its parent company's two small-molecule preclinical pipeline programs: STING antagonists to prevent the stimulation that leads to an excessive immune response (expected to enter the clinic in 2021), and cGAS inhibitors, which aim to block the pathway at a more upstream node. Back in April 2019, Novartis paid $1.58bn to acquire one of IFM's other subsidiaries, **IFM Tre**, which is focused on inhibition of the NLRP3 inflammasome, a multi-protein intracellular innate immune signaling receptor.

INTELLIPHARMACEUTICS INTERNATIONAL INC.
TRIS PHARMA INC.

Just a month after their first agreement, **Tris Pharma Inc.** licensed exclusive US marketing, sales, and distribution rights to a second CNS generic from **Intellipharmaceutics International Inc.**; this time gaining the latter's depression drug desvenlafaxine succinate extended-release (ER) tablets in the 50mg and 100mg strengths. The partners also entered a concurrent commercial supply agreement. (Sep.)

Desvenlafaxine succinate received tentative ANDA approval from the FDA for major depressive disorder in February 2019. The dual serotonin and norepinephrine reuptake inhibitor is the generic equivalent to **Pfizer**'s *Pristiq*. Back in August, Tris licensed exclusive US rights to Intellipharmaceutics' quetiapine fumarate ER tablets, a generic equivalent to **AstraZeneca**'s *Seroquel XR* schizophrenia drug. Under 2016 deal, Intellipharmaceutics had a long-term profit-sharing arrangement and US licensing arrangement with **Mallinckrodt** involving desvenlafaxine (as well as quetiapine fumarate and lamotrigine (a generic to **GlaxoSmithKline**'s *Lamictal XR* for epilepsy), but that agreement was terminated in April 2019.

JW PHARMACEUTICAL CORP.
SIMCERE PHARMACEUTICAL GROUP

JW Pharmaceutical Corp. licensed **Simcere Pharmaceutical Group** exclusive rights to develop and commercialize its Phase IIb gout candidate URC102 in China, Hong Kong, and Macau. (Sep.)

JW will receive an undisclosed up-front payment, milestones, and sales royalties. Simcere will conduct clinical trials and handle registration and commercializa-

tion of URC102 in the licensed territory. URC102 is a small molecule inhibitor of the urate transporter protein (URAT-1) designed to reduce the serum uric acid levels in gout patients.

KEMPHARM INC.

KemPharm Inc. granted an affiliate of VC firm Gurnet Point Capital (GPC) exclusive worldwide rights to its KP415 and KP484 prodrug candidates for attention deficit/hyperactivity disorder (ADHD). (Sep.)

With an NDA submission expected by the end of this year, Phase III KP415 is an oral, thin film prodrug of methylphenidate (MPH) generated using KemPharm's *LAT* (*Ligand Activated Therapy*) prodrug technology. Preclinical KP484 is a super-extended release prodrug of d-threo-MPH. KemPharm receives $10m up front, up to $63m in regulatory milestones (both prior to and upon approval), US sales milestone up to $420m, plus tiered royalty payments on a product-by-product basis ranging from the high-single-digits up to a mid-twenties percentage for US sales, and in the low-to mid-single-digits in each country outside the US. GPC also has the option to exclusively license any other candidate developed by KemPharm containing serdexmethylphenidate (a prodrug of d-MPH) to treat ADHD or any other CNS disorder, including preclinical KP879 (for stimulant use disorder) and KP922 (for ADHD and Tourette's syndrome). KemPharm will manage all development activities, with GPC reimbursing the company for all development, regulatory, and commercialization expenses. A joint steering committee will be established to monitor development progress of the KP415 and KP484 programs. Investment Banks/Advisors: RBC Capital Markets

NEUCYTE INC.
TRILLIUM THERAPEUTICS INC.

NeuCyte Inc. licensed exclusive worldwide development and commercialization rights to **Trillium Therapeutics Inc.**'s undisclosed refractory epilepsy compound for Dravet syndrome and related disorders. (Sep.)

In preclinical studies conducted by the **National Institutes of Health**'s **National Institute of Neurological Disorders and Stroke** (NINDS), the compound demonstrated safety and efficacy in both anti-seizure effectiveness over benchmark anti-epileptic drugs in eleven animal models and in NIH animal studies for drug-resistant epilepsy. NeuCyte's *Syn-Fire* cell-based translational technology generates induced pluripotent stem cell (iPSC)-derived neural cells that exhibit the main characteristics of human neurons for target identification and validation, efficacy testing, in vitro disease modeling, neurotoxicity assessment, and disease modeling.

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EDITORIAL OFFICE
605 Third Avenue, Floor 20-22
New York, NY 10158
invivo.pharmaintelligence.informa.com

CUSTOMER SERVICE
clientservices@pharma.informa.com

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US Toll-Free: +1 888 670 8900 | US Toll: +1 908 547 2200 | UK & Europe: +44 (20) 337 73737

Australia: +61 2 8705 6907 | Japan: +81 3 6273 4260

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