In Vivo
Informa Pharma Intelligence

VOLUME 38
NUMBER 03

MARCH 2020

UNMET NEEDS IN 2020

Exploring What Innovation Means Today

Underserved Areas: Looking Beyond Cancer And Rare Diseases

Discussing The Past, Present And Future Of Cell And Gene Therapies

Focusing On Collaborative Not 'Innovative' Ways To Pay

PAGE LEFT BLANK INTENTIONALLY

invivo.pharmaintelligence.informa.com

In Vivo

Informa Pharma Intelligence

March 2020

UNMEET NEEDS IN 2020

Exploring What Innovation Means Today

In Vivo
Informa Pharma Intelligence

March 2020

DEPARTMENTS

AROUND THE INDUSTRY

INFOGRAPHIC: UNMET NEEDS IN 2020

40 ON THE MOVE

44 DEAL-MAKING

EXCLUSIVE ONLINE CONTENT

invivo.pharmaintelligence.informa.com

From The Editor

LUCIE ELLIS

This month, *In Vivo* is focusing on the theme of unmet needs in 2020. We are looking at how the biggest issues for patients have evolved and whether the strategies of pharmaceutical and medtech companies are aligned with what society needs today.

Ed Silverman examines the formulas used by drug developers when making R&D decisions, while Melanie Senior analyzes where money is spent in drug development and whether a shift is occurring – pulling investment away from the overcrowded oncology pipeline.

Expanding on the topic of unmet need, Leela Barham looks at 21st century approaches to market access agreements. She asks the questions, have "innovative" models had their day? And does the terminology matter?

In a face-to-face interview, Keith Thompson, founding-CEO of the UK's Cell and Gene Therapy Catapult (CGT Catapult), discusses the journey of cell and gene R&D in the UK since 2012. Thompson will step down as CEO in April 2020, he highlights the greatest achievements of the Catapult so far and discusses steps the sector still needs to take to get more advanced therapies to more patients.

Also included in this issue: an infographic looking at rare disease indications that have seen treatments reach the market for the first time, including reactions from patient advocacy groups; and an exclusive interview with Patrick Boisseau, MedTech Europe's director of European research and innovation partnership policies, about the latest European public-private health care research partnership to launch under Horizon Europe.

As always, there are many more features and news articles that are not included in this issue. Go online to get all *In Vivo* content in one place, including a fact file on coronavirus, an analysis of Novartis's attempts to make a shift in workplace culture and more: invivo.pharmaintelligence.informa.com.

Up-Front

SNAPSHOTS FROM MARCH'S CONTENT

Investment in cell and gene manufacturing has been transformational for the UK market. "It has unlocked hundreds of millions of pounds in investment by venture capitalists, and accelerated firms to get into manufacturing at scale a lot earlier than they ever would have done otherwise."

PAGE 14

– Keith Thompson, founding-CEO of the Cell and Gene Therapy Catapult

"Sweden is a small country, comprising 10 million people. The Swedes have very good stewardship around antibiotics and have very low levels of resistance, so their key issue is access."

PAGE 24

– Colm Leonard, consulting advisor at NICE

INFOGRAPHIC: PAGE 8

42%

OF THE DRUGS APPROVED BY THE FDA WERE INDICATED FOR RARE DISEASES IN 2019

BEVERLEY FRANCIS-GIBSON AND OTHER PATIENT ADVOCACY LEADERS COMMENT ON NEW TREATMENTS FOR RARE DISEASES

76

THE NUMBER OF ORPHAN DRUG-DESIGNATED PRODUCTS APPROVED BY THE US FDA FOR THE FIRST TIME BETWEEN JAN 2016 – JAN 2020

Five areas being prioritized by MedTech Europe as a part of the new Horizon Europe Partnership for Health Innovation scheme:

1. Harnessing synergies
2. Patient-centric, integrated care solutions
3. Applying Big Data and advanced analytics
4. Empowering patients
5. Value initiatives

PAGE 34

Around The Industry

Redbiotec Pivots Toward HSV-2 And Oncology

Redbiotec has reached a new inflection point as it progresses two key programs in herpes and cancer. The company's CEO and CSO explain how it hopes to use bacteria as a delivery system for genes or proteins to treat cancer.

Having successfully sold its cytomegalovirus vaccine business to Pfizer Inc. in 2015, Zurich, Switzerland-based Redbiotec AG is again approaching key business inflection points with the new technologies it has in development.

This time around Redbiotec is developing two potential technologies: a therapeutic vaccine for HSV-2, a viral infection that has proven difficult to address successfully with conventional treatment approaches; and the use of bacteria as delivery systems for genes and proteins to treat cancer.

Redbiotec was first spun out of the Swiss science and technology university ETH Zurich back in 2006. At that time, it was conducting research mainly into the expression of multiprotein complexes, and was backed by both institutional and private investors, including Zurcher Kantonalbank and a European seed and early-stage venture capital firm, Redalpine Capital.

In the following years, Redbiotec collaborated with a number of pharmaceutical companies, and forged ahead with a cytomegalovirus (CMV) vaccine project.

"CMV is a very complex virus with multiple surface proteins and we were able to make protein complexes and virus-like particles that mimicked CMV," recalled Christian Schaub, co-founder, CEO and president of Redbiotec.

Because the project was much further ahead than others at the biotech, it was spun out into a separate company, Redvax GmbH, which was then acquired by Pfizer for an undisclosed amount.

This event was a turning point for Redbiotec. "Our shareholders, our investors, got some return on their investment, and they reinvested in Redbiotec," noted Schaub. "We had money from our investors and also their trust, because they saw that we could develop something valuable and lead our business to a transaction with a major pharmaceutical company. Our challenge was to find the next big thing."

SOURCE: Redbiotec AG

One challenge that Redbiotec decided to take on was finding a therapeutic vaccine, or immunotherapy, against HSV-2 infection, or genital herpes, for which there is still no vaccine on the market and better treatment options are needed.

One of the key issues is recurrence, with patients suffering repeated bouts of infection, indicating that they do not develop an effective immune response against the virus, which is good at hiding in bodily tissue. And a number of biotech and pharmaceutical companies have tried and failed to move HSV-2 therapies through the clinic.

"People were focusing on the wrong antigens for so long," said Redbiotec's chief scientific officer, Lilli Stergiou. "HSV-2 is a complex virus because of the latency associated with it, and initially researchers have concentrated on developing an antibody-based vaccine. But more recently, researchers have started looking at T-cell-based approaches, with antigens that give rise to strong cellular immune responses."

Redbiotec believes it has come up with a combination of antigens that appear to be highly potent.

Talks have started with investors and pharmaceutical companies on funding or collaborating on the next stage of development, validation of Redbiotec's approach in the clinic. Schaub said he was encouraged by big pharma maintaining a "watching brief" in the area.

A second therapeutic area that Redbiotec is exploring is the use of bacteria to fight cancer. "We are convinced that bacteria can play a major role in fighting cancer," said Schaub. "Some bacteria have a natural tropism to proliferate at tumor sites, and if we can engineer them to enter tumor cells and release agents to trigger the effect you want, then we believe we have a powerful weapon to fight cancer alone, or work in combination with chemotherapy," he explained.

Stergiou added that Redbiotec's engineered bacteria accumulate in tumors because of their immunosuppressive, hypoxic and nutrient-rich micro-environments, and wild-type strains are used to which patients should not have already mounted an immune response. The bacteria are engineered to express a ligand, which means they can bind to and get internalized within tumor cells, and also engineered to deliver mRNA or protein cargo, which are then released within the tumor cells.

Other companies are evaluating the use of bacteria in cancer, although usually in the cancer vaccine setting.

The lead program Redbiotec is currently evaluating is a candidate therapeutic against pancreatic cancer, a tumor that is difficult to treat and has an immunosuppressive micro-environment, Schaub noted.

The next few months are expected to be busy for Redbiotec; as well as fundraising to develop two assets, an immunotherapy against herpes and an oncology program against pancreatic cancer, Schaub said he would be spending time identifying those pharmaceutical companies that might benefit from Redbiotec's technology.

IV124467

JOHN DAVIS

Are Incentives Out Of Balance With Patient Need?

Incentives matter; they motivate us to do things. There is renewed interest in just what motivates the life sciences industry to make the choices it does when determining the diseases it will focus on, and how much effort it puts in. This stems from concern about too much effort going into some areas, and too little into others.

Concerns have emerged that today there are too many incentives for companies developing orphan drugs – those to treat rare conditions – to the cost of pursuing the remaining unmet needs in some of the more common diseases.

Rarity, in the past, was seen as problematic because the potential revenues could be small. Specific policies have been introduced to make tackling rare diseases economically attractive to the commercial industry.

Under the US 1983 Orphan Drug Act (ODA) incentives include reduced regulatory fees and seven years of market exclusivity. In Europe, the 2000 Orphan Regulation includes lower regulatory fees and 10 years market exclusivity.

Many see the incentives for tackling rare conditions and bringing orphan drugs to market as successful. FDA stats show that the Center for Drug Evaluation and Research (CDER) approved 125% more new orphan drugs during 2012–2019 than in 2004–2011 (142 products versus 63). In Europe, the nearest comparable figures based on data from Orphanet show an increase of 268% from 2013 to 2019 versus 2007 to 2012 (81 versus 22).

Adam Hutchings, managing director of rare disease market access consultancy Dolon, pointed out that this track record is the very thing that policy makers wanted. "The policies have worked pretty well. Companies have responded to messages that payers didn't want 'me toos' but wanted new drugs for rare diseases," he said.

The future looks rosy too with some analyses putting worldwide sales of orphan drugs at $242bn by 2024. This is, in part, due to the higher prices orphans command.

Have the incentives for orphans been too successful? Debate on the ODA has been ongoing since its introduction, but there has been more intense scrutiny in recent years. Organizations like *Kaiser Health News*, a non-profit news service, raised the profile of the US orphan drug incentives back in 2017. Their work suggested gaming of the ODA by companies. In 2018, the US Government Accounting Office looked into the processes used to give orphan drug status by the FDA and found them wanting.

Now in 2020, fresh concerns have been raised. Peter Bach, a physician working at the Memorial Sloan Kettering Cancer Center in New York, said in an interview for *WGBH* that there is not enough attention being given to more common diseases including heart disease, cancer and diabetes.

Central to Bach's view is presumably that there is scarcity of R&D resources, and companies will inevitably look to what seems to offer the best bang for the buck. With prices for orphan drugs hitting new records almost every launch, the idea that there are only modest revenues for tackling some of the rarest conditions now seems topsy-turvy. Novartis hit a new high asking for $2.1m for Zolgensma (onasemnogene abeparvovec-xioi) for babies with spinal muscular atrophy (SMA), an orphan drug approved in the US in May 2019, but not yet approved in Europe.

Rob Nauman, a US based industry expert at BioPharma Advisors, pointed out that while the economic incentives mattered, there was also real value being created with orphan drugs. He said, "There's a lot of venture capital in this space because there is the prospect of charging millions of dollars for a product, but there is also interest in personalizing treatments through understanding genetics. There's tremendous value in creating a treatment that can cure a patient."

There is potential value that can be created too for more common conditions, according to Hutchings. He said, "If a company could make a cure for Alzheimer's disease they'd be the wealthiest life sciences company in the world." Alzheimer's affects around 44 million people worldwide. There is currently no cure. With many countries having aging populations, the unmet need is only going to grow over time.

When it comes to which targets to chase, unmet need is relevant (*see page 10*), but so too are diminishing marginal returns to R&D. "Companies have come out and said we are not going to chase targets in common diseases, diabetes and heart disease, anymore because it's now more challenging to get results to prove efficacy and effectiveness than it has been in the past," Nauman explained. Hutchings shares this view, pointing out that "companies focus on where there is the most opportunity. In a lot of common diseases there has been innovation over decades and it's increasingly hard to chip away further at the remaining unmet need."

In 2020, there is no consensus on whether there is an imbalance when it comes to incentives for rare versus common conditions. Still, reforms are being put on the table for the US. For Bach, value-based pricing is part of the solution.

Just as in the US, debate continues on the incentives for orphan drugs in Europe. The European Public Health Alliance (EPHA), a member-led group of non-government organizations, patient groups, health professionals and disease groups, called for changes to the EU orphan drug legislation because of concerns about gaming. One of the reforms EPHA is seeking, is dropping the patent exclusivity term from 10 to six years.

The EU is actively looking at the orphan legislation with some hoping that changing the legislation could change orphan drug pricing. The prospects are unclear with preliminary reports on options due out during the first half of 2020, according to Hutchings. He also warned that if changes are too harsh it could push the pendulum too far and put orphan drugs out of favor. "Prices for orphans need to be at a certain level to make them economically sustainable – although companies should not be given a free pass. If price goes down, then something else, like longer IP is needed to balance it out," he said.

Next steps in the US and Europe on orphan drug changes are not immediate, but it is clear that the debate will continue and reform is likely to follow.

IV124454

LEELA BARHAM

Bringing A Different Science Into Solid Tumor Treatment

Depending on the regulatory jurisdiction, Nanobiotix's radiation-activated cancer nanotechnology may be a drug or a device. But regardless of classification, it offers a physical solution to problems that chemistry and biology cannot solve.

As far as unmet needs in health care go, nanotechnology company Nanobiotix SA (Paris, France, and Cambridge, MA) has set out to address one of the biggest.

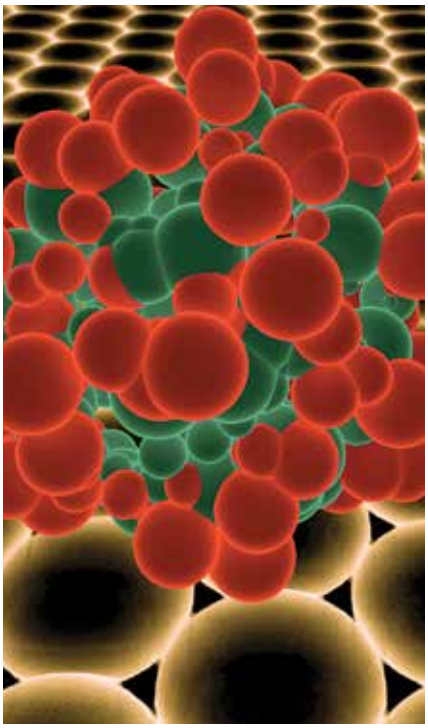
The clinical-stage company is pioneering new approaches to the treatment of cancer, in the knowledge that, although 60% of cancer patients receive radiation therapy, its efficacy levels are uncertain. On the other hand, potential toxicity is a known risk.

Nanobiotix's solution is to use nanoparticles to enhance the efficacy of radiation therapy in the treatment of tumor cells, without increasing the dose received by surrounding healthy tissues, says Nanobiotix CEO Laurent Levy.

The premise of solving this unmet medical need is to rely on physical rather than pharmaceutical or biological approaches in developing a highly effective solution that also has broad clinical potential. Nanobiotix's product candidate is a first-in-class technology called Hensify/NBTXR3. "We believe that combined with radiotherapy, it can become a new standard of care in the treatment of cancer," said Levy.

Already with EU Phase III approval for use in soft tissue sarcoma (STS) – as the first radiotherapy enhancer to demonstrate clinically meaningful benefit for patients with locally advanced STS compared with radiotherapy – the company is forging ahead with the next part of the strategy. It will start applying the product in head and neck squamous cell carcinoma (HNSCC) cancer. Promising results have been observed in a Phase I EU trial, and the US FDA in February accorded it Fast Track designation, underscoring the perceived need for new treatment options for this patient group.

The Euronext Paris-listed company, not yet revenue-generating, has struck an alliance with the University of Texas MD Anderson Cancer Center in Houston. It is a large-scale, comprehensive, clinical research deal covering nine new Phase I/II clinical trials in the US, across head and neck, pancreatic, thoracic, lung, gastrointestinal and genitourinary cancers. "It's a very strong collaboration that will provide a lot of feasibility data – every radiation oncology type is there," said Levy.



"We have no competition but we need to work harder than others as there is no reference."
– Laurent Levy

Elsewhere, the company is doing trials at other institutes across the world, including Institut Curie, Paris, and with hospitals in Europe and the US. Nanobiotix's partner company, PharmaEngine, is developing the technology in Asia. It generates data and pays Nanobiotix, the IP-owner, milestones and royalties. This range of partners will help spread the use of indications and supplement the "limited resources" at Nanobiotix, a company of around 100 staff.

DEMONSTRATING MODE OF ACTION

Critical for the company now is to demonstrate that the product, with its new mode of action, works in a major disease: the nanoparticles – "super absorbers" of X-rays – are injected directly into the tumor, once, before the first radiation treatment, where they deliver a strong dose of radiation to the tumor. "For grade II or III sarcoma – a hard disease to crack – you get a complete pathological response multiplied by four," Levy noted.

The company's Phase III STS trial clearly established the mode of action of the product. "But we needed an indication where we could demonstrate maximum medical benefit, in overall survival, progression-free survival and quality of life. Head and neck was perfect for that."

The head and neck market sees 900,000 new cases per year in the US and Europe. Targeting the large population of frail, elderly patients who are unable to receive chemotherapy or cetuximab in head and neck, Levy saw a "complete and sustainable response." Cancers were being stopped and patients were able to eat and drink again, he said.

A good way of visualizing the value of the product to head and neck patients is that most of the head and neck patients who receive radiation – 74% of the total – get it as first-line treatment, said Levy. There is no alternative to radiation, surgery or chemo; and there are no pharma or biotech industry solutions for first-line patients. "No one is targeting this patient group."

Nanobiotix has set a number of milestones this year in head and neck, and the priority, as soon as the Phase III head and neck trials have started in the US and Europe, will be to extend the product across oncology indications as soon as possible. "We are waiting for feedback from the FDA on the design of the trial, so our timings are not yet known." Europe will follow, with the same trial (although the US study is classed as a pharma trial and the European version will be geared toward device approval).

"We believe there is strong potential for reimbursement based on conversations with the European Network for Health Technology Assessment [EUnetHTA]," Levy said. Production is a secondary issue for Nanobiotix at present.

BROAD POTENTIAL

Nanobiotix was incorporated in 2003 and has focused on realizing the potential of NBTXR3 since 2007. In the interim, it has built a network of affiliate companies in the US, France, Spain and Germany. Its first positive Phase III US data came in 2018, and EU CE mark approval in STS was granted in 2019. "From concept to positive Phase III it was 10 years. We think we've been very efficient in developing this new concept, which could benefit millions of patients," Levy said.

He explained that Nanobiotix has potential beyond cancer. "It is one technology for mass medicine – we can combine our product with radiation and, technically, it can work in any kind of cell." For instance, the company has been developing a technology for CNS disorders, in a bid to change the way the brain communicates from one neuron to another. The product's physical mode of action points to applications in Alzheimer's disease, Parkinson's disease and dementia generally.

Another application is what Levy calls "nano-chewing gum" – an intravenous (IV) injection technology that occupies the liver while the drug is circulating. Often only a very small part of a drug reaches its target. Now, the drug can be more effective because a lower proportion will be retained by the liver while the nanoparticles are present. The principle is: the same amount of drug, more efficacy; or less drug, same efficacy, said Levy. "It can apply to every product out there." This project is now being run by wholly owned Nanobiotix spin-out, Curadigm.

Nanobiotix is also running an immuno-oncology development program, having received FDA approval for a clinical trial of NBTXR3 activated by radiotherapy in combination with anti-PD-1 antibodies in locoregional recurrent or recurrent and metastatic HNSCC. The IO program has the potential to bring a new dimension to cancer immunotherapies.

VALUE IS THE TARGET

The company will continue to seek EU and US funding until it reaches sustainability – but value, rather than sustainability, is Levy's target: "As long as we move into different indications, we are creating more value for everyone."

The company has 14 or more trials ongoing in prostate, hepatocellular, liver, lung and rectal cancer, among others. "We cover almost all solid tumors with our product. But technically, any patient receiving radiation could use its help."

It is a new concept, but not necessarily a new idea. "If you want change, you need to bring another science into the game. That's what we did by bringing nanotechnology and physics into the biology game," Levy explained. The company has looked at the problem from a different angle, and found that it could use the same target for many different drugs. "We have no competition, and looking at the problem from the physical angle, we think that with one technology we can treat millions of patients."

Market response so far has been cautious but encouraging. While still seen as "revolutionary," the concept is no longer dismissed by physicians as impossible, instead it is viewed as having useful potential. The reaction has been similar among investors and the pharma industry. "We are really just at the birth of something big," said Levy.

But Nanobiotix's biggest advantage is also its biggest hurdle: "We are different, alone, we have no competition," he said, adding "but we need to work harder than others as there is no reference."

The mixed classification of the technology alone – a drug in the US, a device in Europe – is an indication of the "new limits" approach Levy and his team are pursuing with NBTXR3. However, the FDA and EU agencies have been helpful in moving the technology forward, as they can see possibilities of serving large populations of patients with unmet needs.

As to the company's market strategy, it plans to build its own direct sales capabilities, but will also reach out to the pharma industry, with which it is in discussions at present. "Ideally, we would like to be a tumor-agnostic company, and given the potential of the product, we would need a good number of partners on a non-exclusivity basis," said the chief executive.

The product was, in fact, showing the very highest value in oncology – in its impact on patient survival, he said. "Our healthtech industry experience has told us that the revolution never comes from the players already in place," Levy noted. "We are close to a point where our product is recognized as beneficial for the whole oncology world."

IV124464

ASHLEY YEO

US FAST TRACK DESIGNATION

Nanobiotix's FDA Fast Track designation recognized the population-need for NBTXR3 – a viable option in a space where there is no solution. FDA Fast Track is a process designed to facilitate the development and accelerate the review of drugs for serious conditions that have the potential to address unmet medical needs. The purpose is to expedite the availability of new treatments for patients. Eligible products entitle the company to frequent FDA meetings and written communications on clinical trial design and the use of biomarkers. They are also eligible for Accelerated Approval and Priority Review; and for Rolling Review, whereby as soon as they are complete, individual sections of the New Drug Application (NDA) can be submitted to the FDA.

"Zolgensma represents a breakthrough toward the promise of safe and effective gene therapies, and it may catalyze the development of other gene therapies to treat a range of rare neuromuscular diseases."

LYNN O'CONNOR VOS
PRESIDENT & CEO
MUSCULAR DYSTROPHY ASSOCIATION

76

THE NUMBER OF ORPHAN DRUG-DESIGNATED PRODUCTS APPROVED BY THE US FDA FOR THE FIRST TIME BETWEEN JAN 2016 – JAN 2020

MAKING PROGRESS AGAINST RARE DISEASES

BIOPHARMACEUTICAL COMPANIES DOUBLED DOWN ON RARE DISEASE TREATMENTS DURING THE LAST FIVE YEARS,THANKS TO A POTENT COMBINATION OF SCIENTIFIC DISCOVERY AND APPEALING BUSINESS INCENTIVES.

42%

OF THE DRUGS APPROVED BY THE FDA WERE INDICATED FOR RARE DISEASES IN 2019

"Sickle cell disease is a devastating, lifelong, inherited blood disorder ... After decades of waiting, we now have a treatment option that could change the course of this disease."

BEVERLEY FRANCIS-GIBSON
PRESIDENT & CEO
SICKLE CELL DISEASE ASSOCIATION OF AMERICA

THE FIRST GENE AND CELL THERAPY APPROVALS GRANTED BY THE FDA - SPARK THERAPEUTICS' LUXTURNA AND NOVARTIS'S KYMRIAH - ARE BOTH INDICATED FOR RARE DISEASES

"For those living with intractable seizures caused by Lennox-Gastaut Syndrome and Dravet syndrome, Epidiolex represents a true medical advancement."

PHILIP GATTONE
PRESIDENT & CEO
EPILEPSY FOUNDATION

SOURCES: Biomedtracker; Cystic Fibrosis Foundation; Epilepsy Foundation; FDA; Muscular Dystrophy Association; Sickle Cell Disease Association of America

DESIGN: Gayle Rembold Furbert/Informa Pharma Intelligence Design Team

KEY FDA APPROVALS FOR RARE DISEASE PRODUCTS SINCE 2016

4/11/16

VENCLEXTA

Chronic Lymphocytic Leukemia/ Small Cell Lymphocytic Lymphoma

Noteworthy: First FDA-approved treatment that targets the B-cell lymphoma 2 protein, which supports cancer cell growth and is overexpressed in many patients with CLL

12/19/16

RUBRACA

Ovarian Cancer

Noteworthy: Concurrent approval was granted for the FoundationFocus CDxBRCA companion diagnostic, the first next-generation-sequencing companion diagnostic approved by the FDA

3/30/2017

TAGRISSO

Non-Small Cell Lung Cancer

Noteworthy: First approved medicine in the US indicated for NSCLC patients who have tested positive for the EGFR T790M mutation

8/1/2017

KYMRIAH

Acute Lymphoblastic Leukemia

Noteworthy:
First FDA approved CAR-T cell therapy

11/16/2017

HEMLIBRA

Hemophilia A

Noteworthy: First new drug class targeting hemophilia approved in 20 years

2/25/2018

EPIDIOLEX

Dravet Syndrome/Lennox-Gastaut Syndrome ◆

8/23/2018

TAKHZYRO

Hereditary Angioedema

Noteworthy: First monoclonal antibody approved in the US to prevent severe swelling in patients 12 years and older

5/24/2019

ZOLGENSMA

Spinal Muscular Atrophy ✪

8/2/2019

TURALIO

Pigmented Villonodular Synovitis

Noteworthy: First systematic therapy approved for patients with symptomatic tenosynovial giant cell tumor

10/21/2019

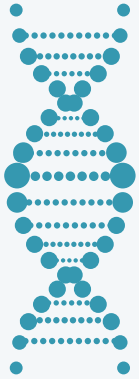
TRIKAFTA

Cystic Fibrosis ■

11/25/2019

OXBRYTA

Sickle Cell Anemia ✱



■ "This is a moment to celebrate and to reflect on how working together, and against great odds, we have effectively transformed a genetic disease in a single generation, making CF the greatest story in medicine. As we celebrate, we also vow to intensify our focus on finding a therapy for every individual in our community who is still waiting for a breakthrough."

MICHAEL BOYLE
PRESIDENT & CEO
CYSTIC FIBROSIS FOUNDATION

Defining Go And No-Go Disease Areas As An R&D Business

Some believe unmet need refers only to rare diseases and tiny patient populations. But it is more than this. In 2020, the term sits at the heart of decision-making for drug makers – along with cost, access and value, of course.

BY ED SILVERMAN

The calculus used to make fateful go or no-go decisions about medicines that could solve an unmet medical need is difficult to define.

The phrase unmet need generally refers to ailments without a salve. However, the term is also increasingly used to describe rare diseases, which address a decidedly narrower but potentially lucrative patient population.

The challenge is in balancing pressure from investors – and in large companies, from the commercial side – to explore certain diseases at the expense of others.

At first blush, the antibody looked promising and Chris Garabedian was optimistic it could be a winner.

The molecule was advanced enough to be ready for clinical testing, the management team was strong and, initially, there seemed to be sufficient upside to invest. Although there are plenty of multiple sclerosis treatments on the market, by his reckoning there is room for still another medication to tackle what is known as relapsing remitting MS, which is when the disease flares up.

But after mulling it over yet again, he passed.

"It was just too risky," said Garabedian, who once ran Sarapta Therapeutics, a rare disease drug maker, and is now chief executive officer at Xontongeny, which provides funds and guidance to early-stage life science companies. "There could have been lots of upside if it worked. But when you're in the early stages of developing a drug and don't have a clinical data set, it's all about the probability that it will work."

Garabedian continued: "In this case, even if this target and technology was successful, we weren't convinced. I mean relapsing remitting MS still has unmet need. It all depends on how you want to define an unmet need, but if you talk to any patient, there's still a lot of room to improve on tolerability and toxicity. But we found that lupus had a bigger unmet need with fewer failures in the clinic than MS. In a way, there's a ranking order."

Such is the calculus used to make those fateful go or no-go decisions about medicines that could solve an unmet medical need (*see Exhibit 1*), a phrase that generally refers to ailments without a salve. However, the term is also increasingly used to describe rare diseases, which address a decidedly narrower but potentially lucrative patient population. Although the phrases are sometimes conflated, the emphasis has helped

transform the prism through which drug development is viewed.

How Unmet Need Has Changed

Over the past decade, in fact, rare disease drugs – which in the US are approved to target maladies affecting 200,000 people or less and fewer than five in 10,000 people in the European Union – have become something of a phenomenon and overtaken the notion of meeting unmet needs more broadly. This reflects a serendipitous convergence of scientific advances, pent-up investor demand, and subsequent flexibility in regulatory thinking about medical evidence and drug approval standards.

"The definition of unmet need has changed, or at least expanded," said Robin Feldman, a professor at the UC Hastings College of Law in San Francisco and director of the Center for Innovation, who has written *Drugs, Money & Secret Handshakes: The Unstoppable Growth of Prescription Drug Prices*. "Often, some people will say unmet needs refer to rare diseases and so we think of tiny patient populations, although it really is more than that. And it has become a huge business."

As of 2018, there were roughly 7,000 recognized rare diseases affecting up to 30 million people in the US alone – more than half of whom are children – but treatments were available for just 5% of them, according to IQVIA, the market research firm. Nonetheless, rare disease drugs, which are also known as orphan drugs, are anticipated to comprise one-fifth of worldwide prescription sales and amount to around $242bn in spending in 2024, according to market analysts.

The reason, of course, is that many of the treatments are priced at levels that are designed to generate a hefty return despite a relatively small number of patients. Sarepta, for instance, charged about $300,000, depending upon patient weight, for its drug for Duchenne muscular dystrophy, which affects approximately 1 in 3,500 male births worldwide. The betting, of course, is that payers will cover such drugs if they recognize they are likely to have few beneficiaries requiring such medications.

The Sarepta drug approval also exemplified an evolving regulatory view toward unmet needs. A behind-the-scenes drama erupted among high-ranking staffers inside the Food and Drug Administration over whether the medicine, known as Exondys 51, should have been approved due to disagreements over the validity of certain data in one small clinical trial. The controversy raised questions about the extent to which satisfying an unmet medical need might require a new approach to approval standards.

But while the high-profile dispute underscored mounting pressure from patient families and their supporters in Congress, this was hardly the only instance in which the regulator was set to hasten an approval. The Sarepta drug, which ultimately became available in 2016, had been granted accelerated approval. Like a related status called fast track, this FDA designation refers to medicines that treat unmet needs. And plenty of medicines have been granted such status in recent years.

Here are a few numbers: the FDA designated 17 of 48 novel drugs, or 35%, in 2019 as worthy of fast track status and approved nine of those medicines, or 19%, under the accelerated approval program. Ultimately, 21 of the medicines were approved to treat rare, or orphan, diseases.

The pattern has been consistent in recent years, too. In 2017, 18 of 46 novel drugs were fast tracked by the FDA, which greenlighted a half dozen under accelerated approved, with 18 approved to treat rare diseases. In 2015, fourteen of the novel drugs, or 31%, were designed as fast track, with six endorsed under accelerated approval and 21 approved to treat a rare disease.

The trend has clearly presented opportunities for drug companies – big and small – to focus more resources on such patient populations. In fact, the number of orphan drug designation requests has steadily increased from 2012 through 2016 and has remained greater than 500 annually for the past four years, according to the FDA. In 2019, the Office of Orphan Products Development received 533 new requests for designation, a 5% increase from 2018.

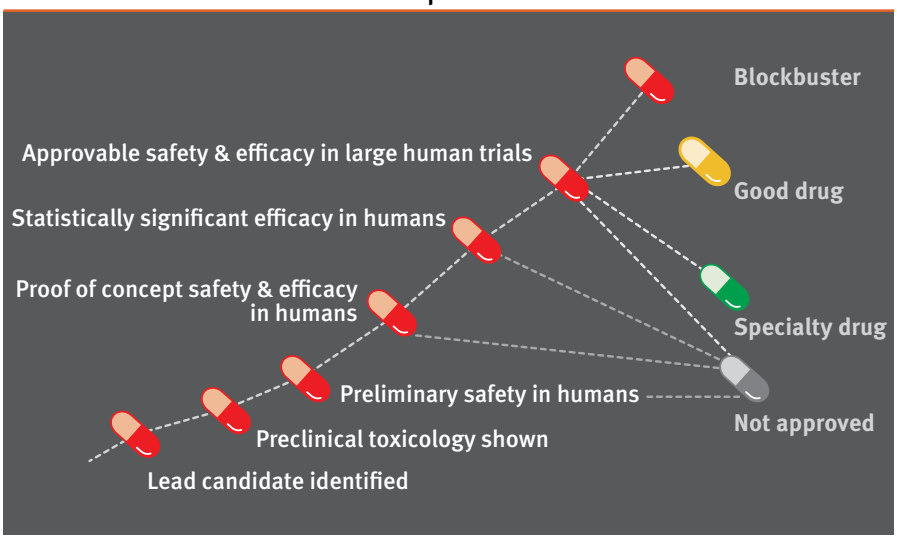
"This reflects instructions that FDA was given by Congress through legislation that requires the agency to take a different approach toward approvals," said Ira Loss of Washington Analysis, who tracks regulatory and legislative developments affecting the pharmaceutical industry for investors. "The 21st Century Cures Act was designed to speed [drug] approvals and unmet medical needs were the impetus for the legislation. And of course, investors like the sizzle."

A Perfect Formula Does Not Exist

Yet despite more receptive regulators, large fund investors eager for bigger returns, and growing piles of venture

Exhibit 1

A Basic Drug Development Risk: The Result And Thus The Return Is Unknown Until The End Of Development



SOURCE: Cognition Therapeutics

capital, settling on an appropriate drug and target is not always straightforward and there is really no formula that can be readily applied, according to John LaMattina, a former head of research and development at Pfizer, who now sits on the board of PureTech Health, a clinical stage company that seeks to develop medicines for hard-to-treat diseases.

"I'm not sure every company does it the same way," he said. "At Pfizer, the commercial team had a pretty big influence on what was worked on. The research teams would work on projects and when you got something into humans, then you would start attracting their attention. But even before getting to the next stage, we think about whether it would be useful and if the commercial team would do an analysis and express an interest. You had to think about the competition out there, weaknesses in those drugs, what your program hopes to accomplish with this new approach, and what else is in this area?"

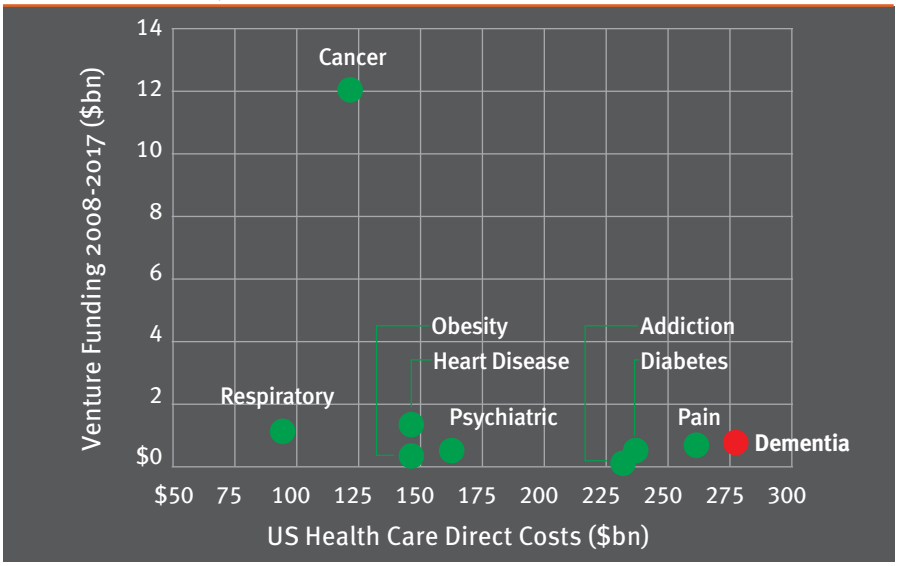
The bigger pharmaceutical companies, he continued, were largely concerned with medicines that aligned with existing product portfolios. There may be an unmet need to treat Alzheimer's disease, for instance, but developing a treatment to cure or mitigate the effects of this particular disease may be too high a risk, given that the field has been littered with clinical trial failures. More broadly, though, a growing number of the largest drug makers have been exiting neuroscience altogether, despite many unmet patient needs.

Smaller companies should take note that venture funding for oncology has outstripped money invested in various prevalent chronic diseases – such as diabetes, obesity, depression, pain, addiction, heart disease and Alzheimer's – by large margins (*see Exhibit 2*). In fact, approximately 20% of all investments in life sciences treatments were directed toward oncology in 2018, given the huge unmet need to tackle so many different cancers, according to the Biotechnology Innovation Organization.

"Oncology is really a series of rare diseases and unmet needs," said Ken Moch, who has led several biotechs and is currently chief executive at Cognition Therapeutics, which is developing an

Exhibit 2

US Health Care Spending Versus US Venture Funding



SOURCE: Cognition Therapeutics

Alzheimer's treatment. "But the reality is that there are highly prevalent chronic diseases for which therapies exist but are insufficient for many patients. And these are large patient populations with absolutely unmet needs. But even if these are treatments, and not cures, does that mean research should not continue?"

"The issue is how much pressure is there from investors – and in large companies, from the commercial side – to explore certain diseases at the expense of others? There is a profit motivation, after all. Everyone is looking for the best return on investment and the pressure is overt. If I'm an investor or I'm beholden to investors, I'm going to go with the highest probability of an extraordinary return. So we're letting economics dictate the funding of drug development."

This reality also shapes decisions made by small, early-stage companies, since their playbook often calls for developing a compound – often, the only compound in its labs – and eventually seeking to sell their company to a larger drug maker. But given the propensity of big drug makers to focus on specific therapeutic categories, a smaller company must tailor its decisions toward a buyout or convince its investors that a payout is possible by pursuing a particular disease and unmet need.

"I think it's an area that most smaller companies get wrong and there are a lot of reasons for that," said Jeffrey Aronin, CEO at Paragon Biosciences, which invests in and launches drug companies to develop novel therapies for severe medical conditions that do not have adequate treatments. "As someone investing in these companies, I want to know if the unmet need is important. Some of the patients with unmet needs are costing the system more than the medicines cost."

Aronin said he worked backwards. "We want to know if there is currently no available treatment or if what is available is unsatisfactory," he said. Aronin wants to see a scientific thesis, a patient need, but also a commercial thesis. "We also have to determine whether we can develop it, manufacture it and get it approved."

Getting The Data And Securing A Price

Although regulators may be more receptive to medicines for unmet needs – certain cancer treatments, for instance, have been approved with single-arm clinical trials – Aronin also pointed out that the investment needed for clinical testing can be daunting. There are never any assurances that a drug will pass muster, even if a regulator indicates approval may be possible. And sometimes the costs of running the necessary clinical trials can quickly dampen enthusiasm. Budgets are

budgets, after all.

Clinical trials for rare disease drugs take 131 months on average to complete, 68% longer than for medicines developed to target other diseases and 41% longer than for all cancer-related diseases, according to an August 2019 report issued by the Tufts Center for the Study of Drug Development, a think tank that is funded, in part, by drug companies.

And while regulatory reviews finish four months faster for rare disease drug applications than therapies for other maladies, the overall time spent on rare disease applications run four years longer than for all other diseases. Moreover, 81% of patients screened for clinical trials for rare diseases are not eligible to enroll, and 56% fail to be randomized. This is in stark comparison to the 57% screening rates and 36% randomization failure rates for other diseases. However, drop-out rates are lower in rare disease trials.

There is another looming factor to consider, of course, as companies make development decisions: will payers bite? Perhaps the most pressing issue facing the pharmaceutical industry is the ability to convince payers that reimburse for medicines that increasingly carry high prices tags – whether newly launched or existing treatments for which list prices are increased. As more medicines for unmet needs, notably rare disease drugs, win approval, the issue is a key point of debate and speculation.

Of course, more payers are willing to consider outcomes-based or value-based agreements in which the drug maker may offer a rebate if its medicine fails to perform as advertised. In some cases, payments may be spread out over time, which is increasingly being considered for pricey new gene therapies. But one payer complains that the deals are, by and large, insufficient to create a reliable template, partly because there is more desire to see longer term data to back up claims in product labeling.

"Generally speaking, the marketplace wants payers to cover everything, but no one has figured out how to do a bona fide value-based agreement," a chief medical officer at a pharmacy benefits manager told *In Vivo*. "The reality is we don't want trial results that make specific designs and don't necessarily match the FDA label. When you combine this scenario with accelerated approval, companies and patients are hoping for access in advance of long-term safety and durability."

"The reality is we don't want trial results that make specific designs and don't necessarily match the FDA label. When you combine this scenario with accelerated approval, companies and patients are hoping for access in advance of long-term safety and durability."

As a result, payers are trying to reposition themselves as more medicines for unmet needs become available, according to Randy Vogenberg, a principal at the Institute for Integrated Healthcare, a consulting and research firm that specializes in health plan benefit designs. Beyond clarity around safety and efficacy data, payers want to distinguish between medicines that are truly innovative – such as curing a disease – and those that are simply enhancements.

"You can have a drug for a rare condition or unmet need, whichever term applies, but does it really make a difference? Does it change the quality of life? There are treatments for hemophilia, for instance, but will a gene therapy offer a quantum leap and not just manage the disease? That could be a game changer," he said. "So companies have to be willing to provide not just enough trial data but real-world evidence to confirm the claims. There is going to be a lot more rigor around such things."

Indeed, these are among the factors that are increasingly giving biopharma execs and investors pause as they assess molecules and marketplaces. Yet despite scientific advances – such as precision medicine – patients will continue to clamor for help in addressing their unmet medical needs. And this presents opportunities to fine tune decision making and goals.

"If we believe in the technology and we have a drug that will make an impact and be the best in class, we may go after crowded disease areas, because we think we have something better," said Garabedian. "But there's always a tradeoff. Do we go for the bigger unmet need, but where there is a higher chance of failure? Or do we pursue some unmet need with a higher likelihood of success? Every company has grappled with that quandary when making decisions. And it's only going to get more exquisite."

IV124468

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

Discussing The Past, Present And Future Of Cell And Gene Therapies

KEITH THOMPSON

Founding CEO of the UK's Cell and Gene Therapy Catapult, Keith Thompson, will retire from the company this year. He looks back on the last eight years of progress for CGT Catapult and the advanced therapies sector – and provides words of wisdom for the challenges still to come.

BY LUCIE ELLIS

At the start of April, Keith Thompson will step down as CEO of the Cell and Gene Therapy Catapult (CGT Catapult), a global leading institute in the field of advanced therapies, having held the position since 2012.

He sat down with *In Vivo* to talk about the development and growth of CGT Catapult, actions the UK advanced therapies sector still needs to take and the future for cell and gene therapy.

A state of the art, GMP manufacturing facility, which opened in Stevenage in 2018, is a legacy Thompson is proud to leave behind as he moves on to new roles.

Thompson started his career in the biopharma industry, focused on biologics and monoclonal antibodies. However, in 2003 he took over the Scottish Blood Transfusion Service. "I set about doing a whole range of things, modernizing the service, dealing with the variant CJD [Creutzfeldt-Jakob disease crisis], for example," Thompson told *In Vivo* during an interview at Guy's Hospital in London, home of CGT Catapult.

"Among all the stuff that the Scottish Blood Transfusion Service was doing they had a good research group. Within that research group there were several advanced therapy projects, everything from trying to make red blood cells from embryonic stem cells, through to making corneal limbal stem cell graphs for blindness," he explained. The service put together one of the very first Epstein-Barr virus (EBV)-transformed T lymphocyte banks for the treatment of post-transplant lymphoproliferative disorders.

When the idea of a Catapult in the UK for advanced therapies was first mentioned, the organization was being called a "Technology Innovation Center." The idea was to propel the creation of a new industry by bridging the gap between research and full-scope commercialization, Thompson noted. "It seemed to me that the whole sector had been on the verge of doing something for years. I was very keen on using all the experience I'd had in both the blood transfusion service and in industry, particularly in monoclonals, to help stimulate the growth of an industry."

When Thompson was appointed CEO of the "Catapult" in 2012, he was "pretty much given carte blanche to write a business plan to create a sector. I initially asked for £70m [$90.5m] and managed to secure that. Then we started developing all the assets that we have."

In 2012, Thompson said there was not much of an industry for cell and gene thera-

pies. "There was quite a lot of academic activity. There were a few pioneering firms. But essentially it was regarded as a sector that was too risky to attract the kind of venture capital that would be able to stimulate the growth of an industry," he explained.

Thompson focused on a key question: "Why is an industry that has the potential to transform health care stuck?"

Three Main Problems

When creating CGT Catapult eight years ago, Thompson set out with a plan to tackle three key issues that were preventing the development of a strong advanced therapies market in the UK.

The first problem was uncertainty around regulation in clinical trials. At the time, "there was an absolute maze of regulations and different bodies. It took over a year to get through that maze to even get anywhere near a trial, going through the various labyrinthine procedures. Even if you got a regulatory go ahead, the hospitals did not really know how to run the trials," Thompson noted.

The second group of problems was focused on the question: "How to make a living medicine?" Industries were used to "making pills, potions and biologics" but facilities were not in place to develop cells as products and make them consistently to GMP standard.

The third key challenge centered on health economics. "By and large, modern medicines, apart from antibiotics and one or two other treatments, don't really cure you of anything. Most medicines keep the disease at bay." In 2012, health care systems were not used to the idea that a one-off treatment could cure a patient. "How would you pay for this one-off therapy; these things were going to be expensive."

Thompson's goal when establishing CGT Catapult was to make the UK *the* place to have a new industry – a place where businesses could launch, grow and confidently develop their advanced therapies and be able to deliver them to patients.

He began by creating three groups. "I got experienced industry executives in to help me and they've been fantastic." He organized a manufacturing technology group, a clinical trial and regulatory group and a business and health care economics group. The largest of these focused on the essential issue of manufacturing – an area that is still evolving for cell and gene therapy developers years later.

Exhibit 1

Research Hotspots Throughout The UK

Setting Goals

Thompson set a target for CGT Catapult to help foster a £10bn market. "We planned to measure things like company growth, the number of companies, the amount of money that they attracted and rise in employment," he noted. At the end of 2019, there were 70 cell and gene therapy companies operating in the UK: 56 with UK headquarters and 15 international companies with a UK presence. Across Europe and Israel, there are more than 230 active advanced therapy companies, but the UK has the major share.

Another thing he was keen to measure was the number and stage of clinical trials for advanced therapies in the UK.

"We were very fortunate, there was a lot of interest in the sector from stakeholders in the research councils and in government. The environment was positive but the ability to get it done was constrained." Thompson found that the sector was receptive to his plans to speed up processes for clinical trials.

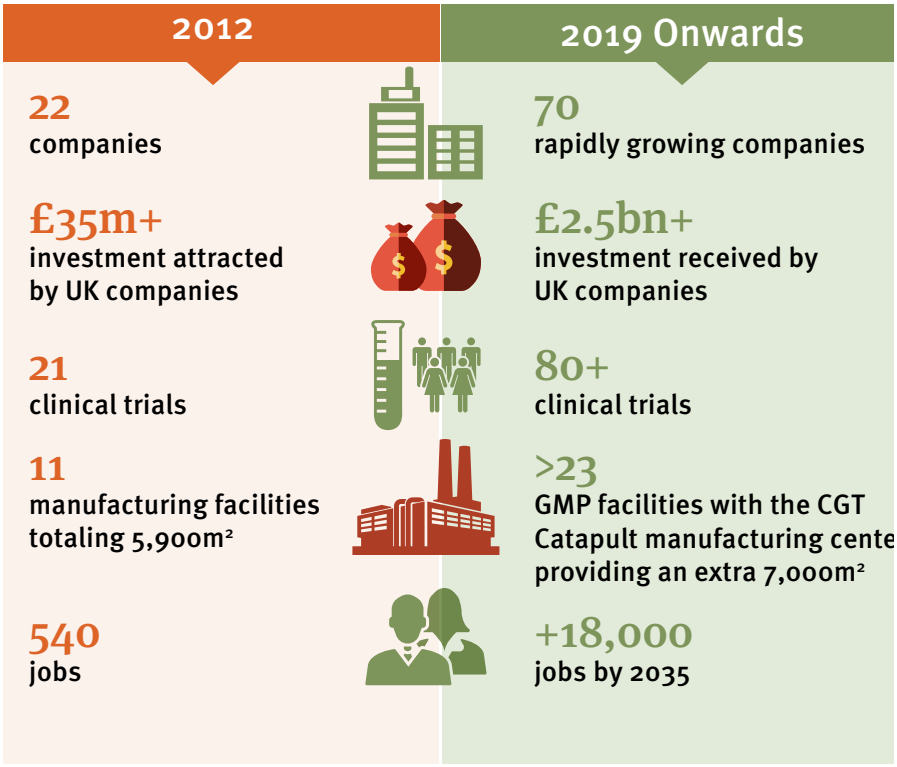
"I said, 'We'll set up a one-stop shop for advanced therapies.'" He added that clinical trial regulatory time scales had come down from over a year to less than two months.

Early on, the CGT Catapult team spent time taking stock of the number and type of facilities in the UK. It found there was a good stock of small-scale academic facilities, but there was a need to expand these offerings. "I was able to go to government to make the case for investing in a large-scale center." In the 2014 government budget, £55m was granted to build what has become the CGT Catapult manufacturing center in Stevenage."

This investment was critical. Feedback from venture capitalists at the time was that while interest in the cell and gene therapy space was strong, the risks were high and the facilities were lacking. "They said, 'Well, we like the space, but apart from all the other risks, every group that wants to spin out wants £25m to build a factory and we're venture capitalists, we're not in the bricks and mortar business.'"

Exhibit 2

The Growing UK Cell And Gene Therapy Industry



SOURCE FOR ALL EXHIBITS: Cell And Gene Therapy Catapult

Although that was true, it was about more than bricks and mortar. These aspiring start-ups saw the intrinsic value in the way that they manufactured therapies, and they wanted to be able to rapidly control the process, Thompson noted. "We came up with the idea of the Stevenage facility, which was a collaborative approach to manufacturing where these firms would be able to actually operate their own processes and be fully supported by us, whether it was advanced quality systems or supply chain," he said.

Thompson calls the Stevenage manufacturing center his greatest achievement. "It has been transformational for the UK market. It has unlocked hundreds of millions of pounds in investment by venture capitalists, and accelerated firms to get into manufacturing at scale a lot earlier than they ever would have done otherwise."

As well as the development of the Stevenage site, CGT Catapult began working with the UK pricing and reimbursement watchdog NICE to run mock health technology assessment (HTA) appraisals on CAR-T therapies to fine-tune their analytical methodologies, but also "to show that even the National Health Service [NHS] would pay for outstanding clinical benefits."

Around 2014/2015 the world started to see "really outstanding clinical results across cell and gene therapies" and cash started to pour into advanced therapy companies around the globe, Thompson said. "We created a strong environment for developing cell and gene therapies in the UK, and the UK certainly became the leading cluster within Europe, and probably the third largest cluster globally – alongside Boston and California."

Work To Be Done

CGT Catapult has named Matthew Durdy as its next CEO. Currently, the chief business officer for the organization, Durdy will take over from Thompson in April 2020.

In words of wisdom to a successor, Thompson said: "You have a great foundation, build on it." While there is now a good stock of companies in the UK working in cell and gene therapy, there remain challenges to overcome. Manufacturing issues are still top of the list. "It's a journey from handcrafted products that were made to treat a handful of patients, to the future of highly automated manufacturing that can bring the costs of goods right down. We are probably about halfway through that journey," Thompson noted.

He believes there are about another 10 years of work until these products can be made at a cost that allows them to be truly accessible to all. However, Thompson cited Oxford BioMedica as an example of progress, calling the company "probably the world's best manufacturer of lentivirus." That company now employs around 500 people across several sites. A few years ago, it had a team of just 100. But, Thompson said, there is "a huge amount of work still required on the manufacturing side."

Another area that continues to evolve is clinical practice. "You simply can't put these therapies through a wholesale distributor into a pharmacy and then wait a year for a junior doctor to prescribe them. We worked on this with Innovate UK to define a program for advanced therapy treatment centers, which have now gone into three major locations across the UK."

Thompson said work remains for CGT Catapult on developing systems for routine delivery of advanced therapies at scale. "If you're trying to treat 50 cancer patients it's relatively straightforward to get that done, but if you want to treat 5,000 patients that's a lot of work." There is development needed on aspects such as patient registries and technologies to track and trace treatment.

A handful of cell and gene therapies have been approved in the US and Europe in the last couple of years, but there are hundreds of product candidates on the horizon. "The next big move is going to be the gradual transition from the rare ultra-orphan diseases to diseases with a higher incidence," Thompson said. "The great thing is, not only are the science and investment looking good, but the appetite of health systems – including the NHS – to gear themselves up to deliver these seems quite remarkable."

Still, Thompson predicts that investment in the cell and gene space will slow down soon. "Money has continued to pour into the sector, particularly over the last few years. I can't imagine it will

keep going at the same rate. Everything slows down. But there is a good stock of well-funded companies now, in the UK and globally."

Getting Therapies To Patients

"The real acid test over the next two to three years is going to be how these products are adopted and accepted by patients, because that's going to be the real proof of the pudding," Thompson believes.

Cell and gene products approved to date all target relatively low incident diseases, so while they have been costly treatments the overall budgetary impact has been modest. "Health systems are geared to be able to deal with that," Thompson said. He added that there would always be an argument over price "because that's the way the world is," but so far this has not prevented the products being adopted.

"As companies move into larger-scale indications then the development of payment over time, or risk share models, will be a key feature of the landscape," Thompson said. "To really perform at scale, then treatments will have to get cheaper. The sector has to work out how to manufacture them cheaper."

Another challenge when moving into disease areas with higher incidence, is that many of these conditions will have other treatment options available. Thompson noted that when a patient would otherwise die or suffer a long-lasting illness – as with a number of the rare diseases being targeted by cell and gene therapy developers today – then the clinical decision is easier to make. "If you've then got a gene or cell therapy for a disease where there are alternative treatments, then the data around the benefit [cost benefit and patient benefit] are really going to have to be strong."

For example, in hemophilia it would be an easy clinical decision to try a gene therapy for somebody who has a really severe case where bleeding is a real problem, Thompson said. But with a hemophiliac whose disease is well-controlled on recombinant clotting factors, "you're going to have to work through a lot of cautious clinical adoption to justify treatment with a gene therapy."

He emphasized that it is not just about price but about the nature of the disease and the current treatments available for that condition. "It will be interesting to see companies navigate this path and to see what the patient demand for these therapies looks like."

Lessons From A CGT Leader

"I've learned a lot over the years and for me the key to success is focus, focus, focus. Stakeholders will respond to a compelling vision and actually buy into practical ways of moving it forward," Thompson said.

He added that communication is central to getting that kind of buy-in from stakeholders. "You need to be able to engage with that compelling vision of how it can be and of course, the great thing is that the advanced therapies sector is now set to become the fourth major pillar of health care, globally."

As CGT Catapult moves into the 2020s, a new era for cell and gene therapies worldwide, Thompson said its role will be to anchor large-scale industry. "The role is to take all of this current growth and actually turn it into an industry that sticks long term in the UK, rather than one that just gets to a point and dissipates. This is why manufacturing is so important because manufacturing is an anchor of long-term value."

He expects CGT Catapult to continue focusing on "lowering treatment costs and lowering the barriers, so that it becomes more and more routine to be able to see these products in use in the UK."

Although today's products appear to be safe and efficacious, Thompson warned against "letting up" on a cautious approach to their adoption. "Nobody wants to have a major safety failure." This concern is something he keeps front of mind.

Thompson will step down as CGT Catapult's CEO in a few weeks. After taking a well-earned break, he plans to work in a non-executive or board capacity in a small number of high-quality companies. "That's my next task, to try to find the right companies that would perhaps get some benefit from the experiences I've had, so I can help them develop."

IV124460

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

STEVENAGE MANUFACTURING CENTER

7,700m² manufacturing center designed specifically for cell and gene therapies

12 segregated large clean room modules

Secure supported collaboration model

Center of a cell and gene therapy cluster in UK

Underserved Areas: Looking Beyond Cancer And Rare Diseases

Oncology and rare diseases dominate the industry pipeline, fuelled by science, regulatory tailwinds and high prices. But as the world grapples with coronavirus, and with heart disease still the top killer, can our systems fund treatments for more prevalent conditions?

BY MELANIE SENIOR

The biopharma R&D pipeline is chock full of cancer and rare disease candidates, driven in part by the high prices such drugs can command.

Payers are starting to put on the brakes, but venture activity in these segments is still booming. Meanwhile, access to treatments for chronic, yet "silent" conditions like high cholesterol or NASH is tightening.

Precision therapies have set new benchmarks for impact and pricing. These will acutely challenge affordability and access as they expand into more prevalent diseases.

Cancer and rare disease drug candidates dominate the industry pipeline more convincingly than ever. In 2019, over a third of drugs in development were for cancer, according to Pharmaprojects (which counts preclinical as well as clinical-stage candidates). A third were for rare diseases. Although there is some overlap: 20% of cancer diagnoses in Europe are for rare cancers, according to Cancer Research UK. But the aggregate picture is reflected in the FDA's 2019 drug approval roster: 44% of the 48 new arrivals were for rare or "orphan" diseases affecting fewer than 200,000 people in the US.

The industry pipeline includes seven times as many immuno-oncology candidates as cardiovascular disease hopefuls – yet heart disease remains the leading cause of death worldwide. As coronavirus spreads across the globe, the number of anti-infectives in development has shrunk, according to PharmaProjects. Metabolic disorder candidates are down in 25th place, even though, by 2025, half of all US adults will be obese *(see Exhibit 1)*.

There are good reasons why the newest generation of drugs treat increasingly narrowly defined diseases. The first is science: genomics and precision medicine have helped uncover the genetic and molecular bases of cancer in particular – a mostly genetic-driven disease with measurable manifestations. This has sliced the condition into ever-narrower subtypes as its full complexity is better understood. Meanwhile, conditions caused by single (or very few) genetic mutations – like some rare, inherited disorders – are most amenable to new modalities such as gene therapy.

Policy and pricing have also driven the skew toward rare diseases and oncology. The FDA has five programs aimed at accelerating patient access to treatments for serious conditions with few or no alternatives. These include designation programs enabling faster development (Fast Track, Breakthrough Therapy), faster approval (Priority Re-

view) and Accelerated Approval (based on a surrogate endpoint). Orphan drugs – which often qualify for such programs – also enjoy longer market exclusivity. Anti-infectives, on the other hand, face massive commercial hurdles, including restrictive use policies.

Incentives for addressing niche unmet needs have worked very well. Two of the 2019 FDA approvals – Vertex Pharmaceuticals Inc.'s cystic fibrosis therapy Trikafta (elexacaftor/ivacaftor/tezacaftor), an orphan, and metastatic breast cancer treatment Enhertu (fam-trastuzumab deruxtecan-nxki), an antibody-drug conjugate developed by AstraZeneca PLC and Daiichi Sankyo Co. Ltd. – made it into the top-10 fastest approval decisions since 2010, according to Evaluate. Almost a quarter of 2019's submissions were approved in less than six months.

These drugs are not just getting to the market fast, they are also racking up huge sales – a reflection of unmet need, but also of hefty price tags. The average annual per-patient cost of an orphan drug in the US in 2018 was over $150,000, according to Statista. The top-10 best-selling orphans all generate well over $1bn annually – Merck & Co. Inc.'s cancer therapy Keytruda (pembrolizumab) pulled in $11.1bn in 2019 *(see Exhibit 2)*. The first four of those qualify as top-10 selling drugs outright (Keytruda, Revlimid, Opdivo and Rituxan).

Let us be clear: many of these treatments have transformed patient outcomes. Mortality rates for several cancers have declined considerably; in some categories, for example, breast cancer: five-year survival rates are over 90% for those diagnosed at early stages. Trikafta will be life-changing for many CF patients whose disease subtype meant they did not qualify for earlier treatments.

Yet as more high-priced cancer and rare disease drugs are approved, they continue to challenge affordability and access. This can have a knock-on effect on funding for other conditions. Payers have, until recently, accepted high price tags for rare disease drugs given the relatively small numbers of patients involved – and, in some cases, clear biomarkers to help define which individuals will respond.

That is now changing. "We're putting in

Exhibit 1

Top 25 Therapeutic Categories

POSITION 2020 (2019)		THERAPY	NO. OF R&D PRODUCTS 2020 (2019)		TREND
1	(1)	Anticancer, immunological	3,434	(2731)	↑↑
2	(2)	Anticancer, other	2,510	(2450)	↔
3	(3)	Gene therapy	1,273	(864)	↑↑
4	(4)	Monoclonal antibody, other	1,009	(818)	↑↑
5	(6)	Ophthalmological, other	756	(690)	↑
6	(5)	Prophylactic vaccine, anti-infective	698	(702)	↔
7	(8)	Neurological	666	(567)	↑
8	(7)	Antidiabetic	589	(571)	↔
9	(9)	Immunosuppressant	544	(511)	↔
10	(10)	Anti-inflammatory	529	(473)	↑
11	(15)	Monoclonal antibody, humanized	508	(455)	↑
12	(11)	Musculoskeletal	504	(461)	↔
13	(20)	Reformulation, other	492	(408)	↑
14	(33)	Cellular therapy, chimeric antigen receptor	491	(276)	↑↑
15	(14)	GI inflammatory/bowel disorders	488	(459)	↔
16	(19)	Cardiovascular	468	(412)	↑
17	(13)	Cognition enhancer	466	(459)	↔
18	(12)	Monoclonal antibody, human	448	(461)	↓
19	(21)	Analgesic, other	448	(390)	↑
20	(18)	Biosimilar	442	(432)	↔
21	(24)	Neuroprotective	421	(386)	↑
22	(16)	Reformulation, fixed-dose combinations	419	(446)	↓
23	(29)	Hepatoprotective	418	(340)	↑↑
24	(30)	Dermatological	408	(339)	↑↑
25	(22)	Metabolic and enzyme disorders	400	(389)	↔

SOURCE: Pharmaprojects, January 2020

Exhibit 2
Top Best-Selling Orphans

NAME	SALES ($BN)	INDICATION
Keytruda	11.1	Several cancers including lung, melanoma, bladder and classical Hodgkin lymphoma
Revlimid	10*	Multiple myeloma
Opdivo	7.2	Several cancers
Rituxan	6.8	Blood cancers and RA
Imbruvica	4.67	Blood cancers
Soliris	3.94	Paroxysmal nocturnal hemoglobinuria
Darzalex	3	Multiple myeloma
Jakafi	2.8	Myelofibrosis
Pomalyst	2.65*	Multiple myeloma
Yervoy	1.48	Melanoma

*Estimates; as Celgene was acquired, figures reported by BMS as of November 2019.
SOURCE: Company reports

place oncology management programs," said Michael Sherman, chief medical officer at Harvard Pilgrim Health Care, a US payer. "There are double-digit increases in cost, without equivalent improvement in outcomes," he added. Even with convincing outcomes, such as in some rare diseases, there is a problem, because "collectively, rare diseases are not as rare as people think." The US-based National Organization for Rare Disorders (NORD) claims that 8% of the US population may have a rare disease, said Sherman. Six-figure price tags for even half of those would be unsustainable. The Institute for Clinical and Economic Review (ICER) in 2018 blasted Vertex for CF drug prices that were almost 80% above what was considered good long-term value for money by the US cost-watchdog. European payers have also resisted funding the drugs.

Neither US nor European health systems are equipped to pay for $1m to $2m one-time cures that some gene therapies purport to offer, or indeed for $500,000-a-year therapies. So they're finding ways to restrict treatment to certain subgroups, such as those who benefit most in trials. "We will see continued squeezing of subgroups and very complex definitions of who is eligible and who is not," said Ed Pezalla, previously a VP and national medical director at US payer Aetna (now part of CVS Health). Drug price-curbing policy ideas – some radical, some less so – continue to swirl around Washington in the heated lead-up to US elections.

Payer Bottleneck Is Not Curbing Early-Stage Investment

Despite this, many venture capitalists continue to double down on cancer and rare diseases.

Oncology-focused biotechs drew in over a quarter of all venture money in 2018–2019, according to Bay Bridge Bio, overshadowing all other categories. Rare diseases accounted for about 12%. There are more than 1,200 gene therapies in the pipeline, according to PharmaProjects – 50% more than in 2018. Among 35 portfolio companies at Cambridge, MA-based Atlas Venture, 28 classify as oncology, gene therapy or rare diseases. Syncona, headquartered in London, is exclusively focused on cell and gene therapy. *(Also see "Creating Stability In A Time Of Transition" - In Vivo, 19 Feb, 2020.)*

New modalities like gene and cell therapy and RNA interference do have huge potential. And the payer bottleneck is unlikely to impact private investors' returns: most will make their money well before therapies reach the market, given rich deal-making and IPO activity. Cancer companies accounted for half of the top-10 IPOs of 2019, according to Renaissance Capital, with genetic-disease-focused groups next. Among 2020's front-runners so far: precision-oncology-focused Black Diamond Therapeutics, which pulled in over $200m in its January debut on the US Nasdaq.

Some VCs, though, have steered clear of these hot spots, sensing that the music may stop. Giovanni Mariggi, a partner at London-based Medicxi, and Hakan Goker, executive director at Amsterdam-based M Ventures (the corporate venture arm at Merck KGaA), said they have avoided cell and gene therapy because of high manufacturing costs – and per-patient pricing that is "not sustainable," noted Goker, speaking at the LSX World Congress in London in February 2020.

Most of the industry's 17,500-plus pipeline programs won't see the light of day. Competition in some segments may help temper prices (as they did in hepatitis C) – although in many niches, such competition, if it exists, is likely to be weeded out well before the marketplace. But if the trend toward therapies with six-figure price tags continues, government action, including in the US, may be inevitable. "You run into a real possibility of legislative action to put a damper on drug prices," said Sherman.

Beyond Oncology

There are signs of a rebalancing away from oncology, as precision medicine tools are applied to other areas also. "Neurosciences are coming to the fore, and I sense respiratory, too, coming into focus," said Ben Thorpe, co-head of EMEA Healthcare at Goldman Sachs, at February's LSX World Congress.

BayBridge Bio data highlighted a slight rise in the funding going into neurology and neurodegenerative diseases in the first half of 2019, relative to 2018. Alzheimer's disease – labeled as a future epidemic, as populations age – attracted the seventh-highest number of active pipeline compounds in 2019, behind six cancers, according to Pharmaprojects, despite continued high-profile failures in the field. The US regulators' verdict

on Biogen's aducanumab, resurrected from failed late-stage trials, may prove a watershed in the field; filing is expected imminently.

The gut-brain-immune system axis has also emerged as a promising area of research, in conjunction with a growing understanding of the gut microbiome and its role in disease and health. Several companies are looking at the relatively new field of neuro-immunology – how the immune and nervous systems interact. Alector – whose $176m IPO in February 2019 made it into the year's top 10 – is harnessing the immune system to fight neurodegeneration, building on recent understanding of the role of immune system genes in nerve cell death.

Figuring out how to pay for a treatment for dementia would not be easy, either, though.

Applying precision medicine approaches to these chronic diseases – as both scientific and investor logic dictate – means new treatments will arrive initially for smaller, genetically defined slices of the population. Alector's lead Phase II compound, for instance, is for frontotemporal dementia patients with particular mutations. But, as many orphan drug trajectories have shown, smaller audiences mean higher prices, and lots of small audiences lead to unsustainable costs. "Instead of spreading the cost [for one drug] over an entire population for which it is available, populations are now being sliced and diced so that instead of one drug, you need 10," said Pezalla. "Since each one costs the same to develop, that means 10 times the cost."

Meanwhile, if a new drug is shown to work in a large population, like those with high cholesterol, the price tag needs to shrink considerably – well below the benchmarks that have come to be associated with novel therapies, especially biologics.

The PCSK9 inhibitor class, introduced in 2015, is a case in point. Both drugs in this latest generation of (injectable) cholesterol lowerers, Amgen Inc.'s Repatha (evolocumab) and Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab), were initially approved in a smaller group of patients, those with an inherited condition leading to high cholesterol. Both have been forced to cut their annual prices – initially in the $14,000 per year range – by over half as the target patient group expanded. But even then, they are in the wrong price bracket to enter a realm where pennies-per-pill generic statins are a treatment mainstay. Payers balked at paying even for higher-risk patients who could not control their cholesterol on statins alone. Combined annual sales of drugs that address the leading cause of death globally are barely $1bn.

Praluent and Repatha require once- or twice-monthly injection, so there was more than just the sticker price blocking adoption. Novartis hopes to lower adherence barriers with its twice-yearly administered inclisiran, recently filed for FDA approval. Inclisiran – which uses small-interfering RNA to target PCSK9 – was acquired via Novartis AG's $9.7bn purchase in November 2019 of The Medicines Company. The question remains whether the drug can be priced at a level that generates the returns that large companies need to stay in the game, while keeping payers on board.

Sanofi has decided that the math does not work in cardiovascular disease and diabetes. Last year, it stopped R&D in those areas, also pulling out of a 12-year partnership with Regeneron around Praluent. Instead, the French group is doubling down in oncology, rare disease and rare blood diseases such as hemophilia.

Conditions like high cholesterol remain underserved; that is clear from their prevalence. But they are invisible until they trigger serious complications, and there are cheap generics available. That makes it particularly challenging, within the current system, for payers to fund new, potentially more potent but also wildly more expensive treatments.

Budgeting For Extremes

Non-alcoholic steatohepatitis (NASH) is another unmet need in the highly prevalent, silent-killer category. Up to a quarter of the US population may be suffering from this fatty liver disease, which is strongly associated with obesity, but has few obvious symptoms until it becomes dangerous (NASH is the fastest-growing cause of liver transplants in the US).

The good news is that several late-stage development candidates are going after NASH, at biotechs as well as big pharma. Intercept is among the leaders with a Phase III candidate aimed at the subgroup of patients with advanced fibrosis, but payers are on guard. An expanding palette of high-priced oncology drugs continues to concern us, said Harvard Pilgrim's Sherman, but is now "baked into our psyche." *(Also see "Intercept's Early NASH Efforts Will Stress Advanced Fibrosis" - Scrip, 17 Dec, 2019.)*

NASH is a new type of worry – with high patient numbers even in restricted segments. Competition, which appears likely, may keep prices at bay. *(Also see "Zydus Cadila First Off The Block In NASH After India Approval" - Scrip, 6 Mar, 2020.)* But it can take a couple of years to arrive. "If a [potential NASH drug] is priced at $30,000, even if the condition affects only 3% of my covered universe, with 1 million patients that is still a significant budget impact. And it's a chronic condition so the costs would come year after year," said Sherman.

Hemophilia is also on payers' radars. "It's the extremes I'm worried about," summed up Sherman – highly prevalent conditions like NASH where volumes drive up budget impact, and rare diseases such as hemophilia, where sky-high prices for a few patients hit hard. Hemophilia, an inherited blood-clotting disorder, affects only 20,000 people in the US. But a gene therapy to treat most patients with the condition may cost between $2m and $3m. BioMarin's Valrox (valoctocogene roxaparvovec) was accepted for Priority Review by the FDA in February 2020.

Valrox, like many gene therapies, is designed as a single infusion – so that is in theory a lifetime cost. Factor VIII therapy – which patients currently need to take – costs $200,000 per year. If the gene therapy does last 10 years, which so far it has not demonstrated, then the math works. If not, it doesn't. And Valrox will not be the only option for most patients: two-thirds can use Factor VIII treatment. Roche/Chugai's Hemlibra (emicizumab) provides an alternative life-line for those who can't: it binds together two other coagulation proteins, Factors IX and X, and offers more flexible dosing options than Factor VIII – including a once-a-month prophylactic regime. In short: payers

should have some leverage. This potential new treatment era in hemophilia is unlikely to be a replay of Sovaldi in hepatitis C.

But with more drugs arriving at both ends of the spectrum – gene therapies for ultra-rare diseases, and more targeted therapies eating into ever-larger segments of widespread conditions – affordability issues won't go away.

Beyond The Drug Pipeline

The pipeline skew toward oncology and rare diseases is a reflection of science and market economics. These targeted treatments have set new benchmarks for both impact and pricing. Thus they highlight, and perhaps exacerbate, the real challenge: working out how to fund new drugs for silent, chronic conditions whose value lies in preventing expensive complications tomorrow, rather than today visibly shrinking tumors, freeing kids' breathing or transforming patients' ability to move.

Finding a way to pay only for what works becomes more urgent as more targeted, thus higher-priced drugs multiply. "Payers don't mind that there are so many immuno-oncology or rare disease drugs in the pipeline," said Kim Caldwell, previously VP, pharmacy professional affairs at US insurance company Humana, and now principal at Texas Star Healthcare Consulting. "They just don't want to pay for things that don't work."

Multiple experiments are underway to design and test new payment mechanisms for drugs. Meanwhile, for some chronic conditions, drug therapy may have reached its limits anyway. Tools to support lifestyle and behavior change, including healthy eating, are the next frontier for some segments of obesity and diabetes. Many of these tools have emerged from a burgeoning digital health sector.

Indeed, lifestyle change is likely to be tied to access to even more treatments than it is today. For example, some of the forthcoming NASH therapies may find themselves restricted to patients who undertake six months of a weight loss regime, suggested Sherman. UPMC Health Plan, in Pittsburgh, PA, in 2020 began offering some members reduced or zero co-pays on diabetes medications, alongside health coaching support and free gym access. Many other payers have similar incentives in place.

Digital modalities are also offering lower-cost, more accessible cognitive behavioral therapy for patients with depression.

FOLLOW THE MONEY

Contrast two of 2019's approvals: Trikafta (approved five months ahead of deadline) and Lilly's acute migraine treatment Reyvow (lasmiditan). Migraines affect one in seven Americans (about 46 million). Cystic fibrosis affects about 30,000. Trikafta trials enrolled 510 patients; Reyvow's more than 3,000. Reyvow's peak annual sales are pitched at less than $500m. Trikafta sold almost that much ($420m) in the two months after its late-October 2019 approval. Its peak sales are expected to exceed $8bn.

CF is a nasty, debilitating and sometimes fatal condition; it is a clear unmet need as some patients have no existing treatment options. Migraine is not fatal – though many find it debilitating. There are drugs available for the condition, but they are suboptimal for many. Sales of cholesterol-lowerers Repatha and Praluent are also in the Reyvow range – even with data that show they can reduce the risk of CV events and, in Praluent's case, reduce all-cause mortality.

Thriftier Innovation

Other thriftier innovations are emerging, too. The science of re-purposing and combining existing drugs to make new, better ones, has had a new lease of life thanks to deeper knowledge of both the therapies and the disease. Boston-based Karuna Therapeutics' Phase II schizophrenia program KarXT combines two tested molecules – a generic overactive bladder syndrome drug, and a compound originally investigated by Eli Lilly – to achieve an optimal efficacy-tolerability balance. Sweden's Cereno Scientific has re-formulated valproic acid, a generic treatment for bipolar, for preventing blood clots. It may one day offer a lower risk of bleeding complications than found with blood-thinning drugs and could have applications in atrial fibrillation, heart failure and chronic kidney damage.

These areas may not be where the majority of VC funding is going – for now. Nor do they show up prominently in the drug R&D pipeline. But as the scope of innovation is forced to expand beyond science into access, payment and policy, these economical approaches may provide the biggest impact, by benefiting the largest number of patients. That has to be part of industry's societal contract, too.

A sign of the times, perhaps: EQRx, launched in January 2020 by ex-Third Rock venture partner Alexis Borisy, with $200m from investors including GV (formerly Google Ventures), ARCH Venture Partners and Andreessen Horowitz. Its innovation: drugs that are "radically" cheaper.

IV124471

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

Pink Sheet
Informa Pharma Intelligence

Global Regulatory and Compliance Insight for Fast Regulatory Approval

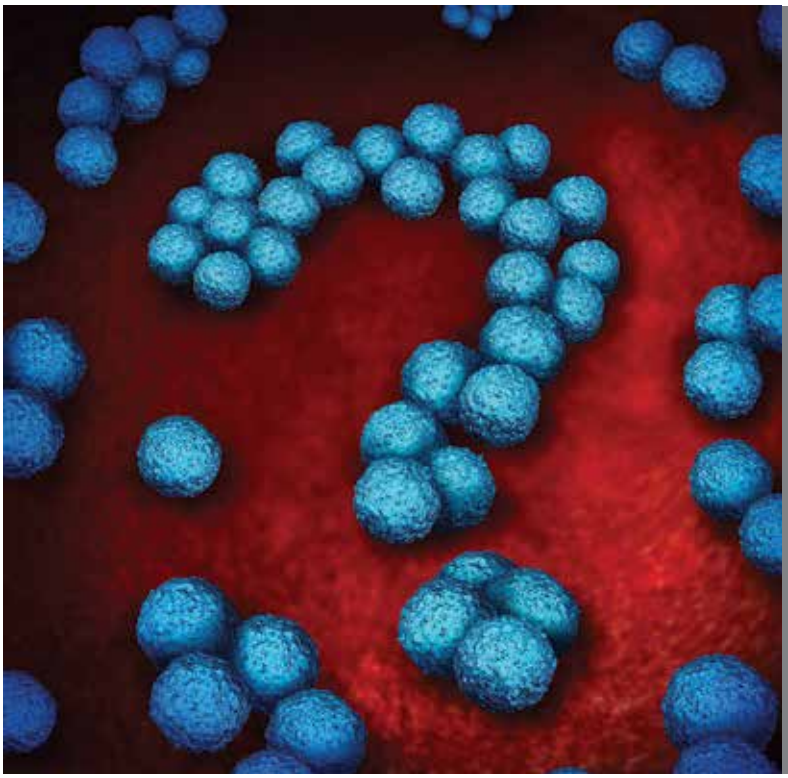
Successfully navigate the complex world of Pharmaceutical Regulatory and Compliance with access to worldwide intelligence for approved and pipeline drugs.

Tracking product progress from submission to approval, our exclusive network of worldwide analysts and journalists cover critical areas of regulatory insight and analyse the implications of worldwide developments on your business.

Anticipate challenges, minimize risks and maximize opportunities.

To find out more, visit:
www.pharmaintelligence.informa.com/pink-sheet

UK, Sweden Test Differing Antibiotic Market Models



Sweden and the UK are conducting differing 'develop and test' programs to assess so-called 'pull' incentives in which an antibiotics innovator will be paid an annual fee in return for an access guarantee for anti-infectives. The projects have drawn keen attention from other countries.

BY STEN STOVALL

2020 will be a key year for development programs in the UK and Sweden that are testing "pull" reward incentive mechanisms as ways to ensure adequate supply of antibiotics, a drug class which is dwindling dangerously.

But their approaches differ significantly, as the UK project aims to stimulate innovation for new antimicrobial drugs and incorporates health technology evaluation of the added value from the new antimicrobial, whereas the Swedish project does not.

Each program is exploring a method of paying the innovator of a chosen drug – or the current marketing authorization holder – an annual fee, in return for an access guarantee.

One key difference between the new incentives programs being trialed by the UK and Sweden is that the UK approach is focused on paying for the added value of a new antimicrobial by delinking volume of sales from reimbursement, with the aim of incentivising the research and development of new antibiotics. The Swedish program is aimed at ensuring the availability of already approved and existing antibiotics to the Swedish health system. Another key difference is the Swedish program does not involve a health technology assessment of any new antibiotics, whereas the British approach does.

The two programs do share the goal of finding ways to maintain a secure access to effective antibiotics at justifiable prices. And they have each attracted interest from other countries also struggling with how to meet the rising threat of antimicrobial resistance and spur improvements in the world's poor pipeline of new antibiotics.

"These programs are very different," said Colm Leonard, a consulting advisor at the National Institute for Health and Clinical Excellence (NICE) and project manager for the UK AMR pilot. "In some ways they send out a similar signal, but they are inherently different because the rationale for each is very different. And the mechanism for each is significantly different," he told *In Vivo* in an interview.

The UK and Swedish projects are being conducted amid increasingly urgent warnings of the threat from antimicrobial resistance (AMR), which is growing as supplies of existing antibiotics fall and the pipeline of new antimicrobials shrinks, largely due to a dysfunctional marketplace.

"The key evidence of that [situation] is the bankruptcies of two US companies in the last 12 months," Leonard said. "Both of those companies had brought to market new antimicrobials that were of some additional value but failed, basically because their sales were

low and hundreds of millions of dollars had been spent on developing them, so they just weren't sustainable in that situation."

Leonard was referring to US-based Melinta Therapeutics Inc. which went into administration in December and smaller Achaogen Inc. which went bankrupt in April last year. Experts foresee more biotech casualties this year unless viable reward systems are put in place for commercializing novel antibiotics.

The UK and Swedish projects must find a balance between supply and demand that reflects the fact that antibiotics tend to be for short courses and are relatively inexpensive. Novel antibiotics must be used sparingly to restrain the spread of antimicrobial resistance to existing antibiotics. Small innovating biotechs cannot survive on revenues that do not cover operational costs. That imbalance dissuades investors from backing them further. And when these companies go either bankrupt or move onto other therapeutic areas, their products may be no longer accessible to patients needing alternative anti-infectives.

Big pharmaceutical groups have meanwhile largely abandoned R&D in innovative antibiotics, due to the absence of adequate reimbursement for the associated investment outlays. This dearth of innovation is occurring despite significant increases in so-called "push funding" for AMR-related R&D over the past five years from publicly and philanthropically financed entities.

Tale Of Two Projects

It is against that background – and amid expectations that antimicrobial resistance will only increase its threat to modern medicine – that Sweden and UK have launched separate national programs to test "pull incentives" in hopes of finding viable reward mechanisms that would ensure adequate access to important antibiotics to meet their national needs.

Both the UK and the Swedish models are assessing de-linkage or partial de-linkage to volume of sales, within an arrangement where a national entity will negotiate with drug companies to ensure national access to important antibiotics. The assumption is that any negotiated payments must be high enough to cover the production and distribution costs, as well as provide some profit margin for the company, project leaders said. Another assumption is that other countries will also procure enough of the same antibiotics to ensure the viability of the drug's producers.

"Sweden is a small country, comprising 10 million people. The Swedes have very good stewardship around antibiotics and have very low levels of resistance, so their key issue is access," explained Leonard. "Because they are a small country, and because there isn't a problem with antimicrobial resistance there is very little incentive for a company to launch a new antibiotic in Sweden. That's a key difference."

Leonard added: "The UK is a bigger country and we do have an issue around antimicrobial resistance, and in general all new antibiotics have been launched in the UK, so the issue is not about access."

The UK project is "absolutely to stimulate research and development by showing that there is potentially a viable market for a drug, because we'll assess the added value that it brings, and then give some level of fixed payment regardless of the volume of prescribing, to allow stewardship while also allowing reimbursement for the company," he said.

UK Program Outline

One of the key points Lord Jim O'Neill identified in the UK Government-commissioned Review On AMR (which started back in 2014), was a broken market leading to a poor antimicrobial development pipeline. In the UK, drug companies are currently paid by volume of antibiotics sold. The "subscription" style payment model that is being developed in the UK by NICE, NHS England and the Department of Health and Social Security is suited for new antibiotics that would be appropriately stewarded on market entry to avoid early emergence of resistance, which currently limits the ability of companies to recoup their investment, Leonard explained.

The UK project is looking at the potential of this approach with a novel value assessment and some level of upfront guaranteed payments to improve the market entry environment and thus encourage companies to invest in the development of new antimicrobial drugs. The aim is to have companies submit products that they want to be considered for the first phase of the test, which is likely to initially involve one recently approved antimicrobial and one soon-to-be-approved antimicrobial.

The exercise will examine the potential to adjust prices of new antibiotics to be commensurate with the value not only for the patient but also society.

"How it will work is that there will be a value assessment that will assess not just the antibiotic's ability to cure Patient A from Infection B but will take on board additional treatment value; like whether the antibiotic will stop transmission to other patients; that there's an enablement value around antibiotics allowing procedures such as hip replacements or transplants or chemotherapy to be given. And there's a diversity value from having new antimicrobials in addition to an insurance value in case Armageddon happens in terms of antimicrobial resistance," Leonard explained.

It is expected that the pilot will introduce better value assessment that will then inform a commercial negotiation with the company. After which, an agreement can be made for some level of fixed payment each year for a set number of years along with very strict stewardship guidance.

"Basically, the company will eventually be signing a contract with the NHS to agree access to the product in a particular indication and in return that company will receive some level of fixed payments for a defined number of years, with options for that arrangement to be reviewed on both sides should information change," he said.

Swedish Pilot Plans

The Swedish program's approach is more narrowly focused.

"The model which we are piloting does not focus on incentives for research and development of new antibiotics. Rather, it is focusing on ensuring the availability of already approved and existing antibiotics in the Swedish health system," explained Jenny Hellman, who is project managing the study at the Public Health Agency of Sweden (PHAS).

"However, we understand and applaud the importance of work, such as that being conducted in the UK, that focuses on facilitating development of new antibiotics," she added. The overall goal of this current Swedish program is

to formulate a concrete recommendation by the end of 2022. "This model would ideally be something we should extend and implement throughout the country," she explained. "If it proves viable, the model could act as a blueprint for other countries," Hellman added.

Sweden has been actively preparing the ground for a pull mechanism antibiotics program since 2014. The government mandated the current pilot in June 2018. "In this pilot study in Sweden, we are evaluating whether the model can ensure availability of new antibiotics that are regarded as having special medical value, and where the availability of those drugs risks being insufficient on a national level," Hellman said in an interview.

The pilot involves the "testing of a contracting process and associated legal aspects." During the pilot, PHAS will run monitoring and evaluation studies of the effects of these methods and if they improve availability of antibiotics.

PHAS is using a bespoke algorithm to identify antibiotics that need special mechanisms in order to secure their availability. "First, we identify antibiotics with low sales turnover and antibiotics that have few marketing authorization holders, with a view to identifying products that might have availability problems," Hellman said. "Secondly, we assess antibiotics with regards to their special medical value. To do that, we have created an algorithm that includes evaluation for activity against bacteria with identified high-risk resistance, the drug's ecologic profile and its role in Swedish medical treatment guidelines," she said.

UK Time Frame

The UK project was first announced last July and was a direct result of the influential Review on Antimicrobial Resistance commissioned in July 2014 by the then UK Prime Minister David Cameron and chaired by Lord Jim O'Neill, and which made proposals covering the 10 main areas in which action was required to address the imminent threat posed by AMR. *(Also see "Lord O'Neill Blames Governments And Pharma For Faltering AMR Progress " - Scrip, 9 Oct, 2019.)* The UK exercise involves close collaboration between NICE, NHS England and the Department of Health and Social Care.

"It's a very joined-up piece of work," Leonard said, adding: "NHS England and NHS Improvement, the Department of Health, and NICE have committed to delivering on this. There is a real commitment both organizationally and with the expectation of financial backing behind it to deliver the novel assessment and reimbursement for these two products, and the hope is that it would inform future assessments in antimicrobials. There will be more information in this regard shared in the market engagement stage in March 2020."

> *"...The aim then is that the whole assessment will inform commercialization, and that we will have the final contract, payment and stewardship arrangements in place in the first quarter of 2022."*
>
> COLM LEONARD

The current timeline is for market engagement to begin in March between the program team and interested pharmaceutical companies and other stakeholders, "just to share all the process documents and selection criteria to pick the first two products. There will also be draft documents around the evaluation framework and commercial negotiation framework and we have allocated time to respond to feedback from that engagement," Leonard explained.

Companies would then be formally invited at the end of April 2020 to put their product forward for one of the two slots for project's initial phase, the invite appearing as a notice in the Official Journal of the European Union.

"Then there will be a selection phase that will happen over the course of the summer and the plan is that we will have then selected two products in 2020 to undergo a type of novel health technology assessment in 2021. The aim then is that the whole assessment will inform commercialization, and that we will have the final contract, payment and stewardship arrangements in place in the first quarter of 2022," Leonard explained.

He said the exact reimbursement mechanisms will become clearer as the UK project evolves, as the UK team recognizes that a "one-size-fits-all" approach may not be appropriate. "We will need to be flexible. We haven't decided which two products we'll be looking at. There is an assumption that there will be some level of fixed payments each year to the company regardless of the volume of prescribing. In that sense it takes the form of a subscription model. But each product will be assessed on its own merit," he said.

Leonard added that in theory there could be a product where the nature of payments may have a fixed element and non-fixed element. It could also be that the agreement is dependent on performance and/or outcomes, or a payment based partly on fixed payments and partly on unit price. "There will be a clear component of this model's output that meets the definition of subscription, because there will be some level of de-linkage of payment to the company from volume of medicine prescribing, but we are well aware that we will have to be flexible and accepting of the fact that there are different mechanisms for subscription and different ways of doing that – some of which might be performance related and dependent on other different outcomes."

"It will essentially depend on what two products we look at," Leonard concluded.

IV124465

Comments:
Email the author: *Sten.Stovall@Informa.com*

Pharma Intelligence
Informa

Intelligence with a Global Perspective

The Premier Resource in the Life Sciences Industry.

- » Biomedtracker
- » Datamonitor Healthcare
- » In Vivo
- » Generics Bulletin
- » HBW Insight
- » Meddevicetracker
- » Medtech Insight
- » Pink Sheet
- » Pharmaprojects
- » Scrip
- » Sitetrove
- » Trialtrove

To find out more, visit:
www.pharmaintelligence.informa.com

Focusing On Collaborative Not 'Innovative' Ways To Pay

Innovation is defined by the Cambridge dictionary as "(the use of) a new idea or method." The term is bandied about a great deal in the life sciences industry. Is it actually helpful to use the term so widely, or does the sector risk overlooking true innovation? This can be applied not only to the drugs coming to market, but how they are paid for as well.

BY LEELA BARHAM

Innovative pricing agreements have been used in Europe for more than 20 years. Can something that has been around for so long still be considered innovative?

The UK is one market that can lay claim to at least trying out novel approaches. Still, what is telling about the UK's early experience with innovative ways to pay is that they have not proliferated. The trend over time has been towards simple discounts.

"Innovative" as a description for access agreements appears to have had its time. Companies are shifting their focus to models that respond to the main concerns of payers and that are more collaborative.

Innovation in life sciences is important; breaking new ground when it comes to meeting an unmet need can mean preventing suffering and saving lives. Innovation has also been applied to finding new ways to pay. Actions that have come about in response to the financial pressures faced by health care systems, uncertainties in the performance of drugs in the real world, and newer challenges related to huge upfront costs for potential cures.

Innovative Ways To Pay

The European Commission has looked specifically at innovative payment models for high-cost medicines. They commissioned the expert panel on effective ways of investing in health to look at the issue in 2018. Their list of innovative payment models included price-volume agreements, outcome guarantees, coverage with evidence development and disease management programs.

Industry uses the terminology too; the US industry association PhRMA has a value collaborative that wants to advance "policy ideas to find new and innovative ways to pay for medicines." There are also companies who have people in job roles including "Associate Director, Innovative Contracting."

Swap the term payment models to contracting and agreements and you will still find the word innovative in front of them. Innovative financing is also another buzz phrase being used.

Confusingly, the definition for traditional payment models can take in the very same models others describe as innovative. Traditional can mean volume based agreements, cost or patient capping, and discounts/rebates. Omar Ali, head of payers at Verpora, a consultancy focused on supporting manufacturers with construction and deployment

of *innovative* contracts, said "the simplest definition is that it's anything that's not a traditional price volume contract."

Innovative pricing agreements have been used in Europe for more than 20 years. Can something that has been around for so long still be considered innovative?

Raf De Wilde, senior executive advisor at Valid Insight, a market access consultancy that helps pharmaceutical companies overcome market access challenges, notes that the word innovative is not always a fair reflection of the deals being struck. He said, "We started with these 20 years ago. Innovative may be true for a country, but globally there are lots of schemes that have already been done." Ali concurs, he said, "They are not really that innovative."

Disappointing Experiences With 'Innovative' Models

The UK is one market that can lay claim to at least trying out novel approaches. A well-known example – but not the first outcomes-based approach according to De Wilde – was the multiple-sclerosis (MS) risk sharing scheme in 2002. This deal saw Biogen Inc., Schering, Serono and Teva Pharmaceutical Industries Ltd. agreeing to link prices to the outcomes generated by their treatments, Avonex (interferon-beta 1a), Betaferon (interferon-beta 1b), Rebif (interferon-beta 1a), and Copaxone (glatiramer acetate). Outcomes were monitored through a registry over 10 years. The aim was for prices to be in line with a cost-effectiveness threshold of £36,000 per Quality Adjusted Life Year (QALY).

The MS risk sharing scheme was not supported by all. It experienced some real challenges along the way. These ranged from the time taken to recruit patients, the academic group responsible for analysis dropping out because of concerns about data access and publication rights, to a damning verdict that it was costly failure. This last view was according to a 2010 piece published in the British Medical Journal written by Professor James Raftery, a professor in health technology assessment at the University of Southampton.

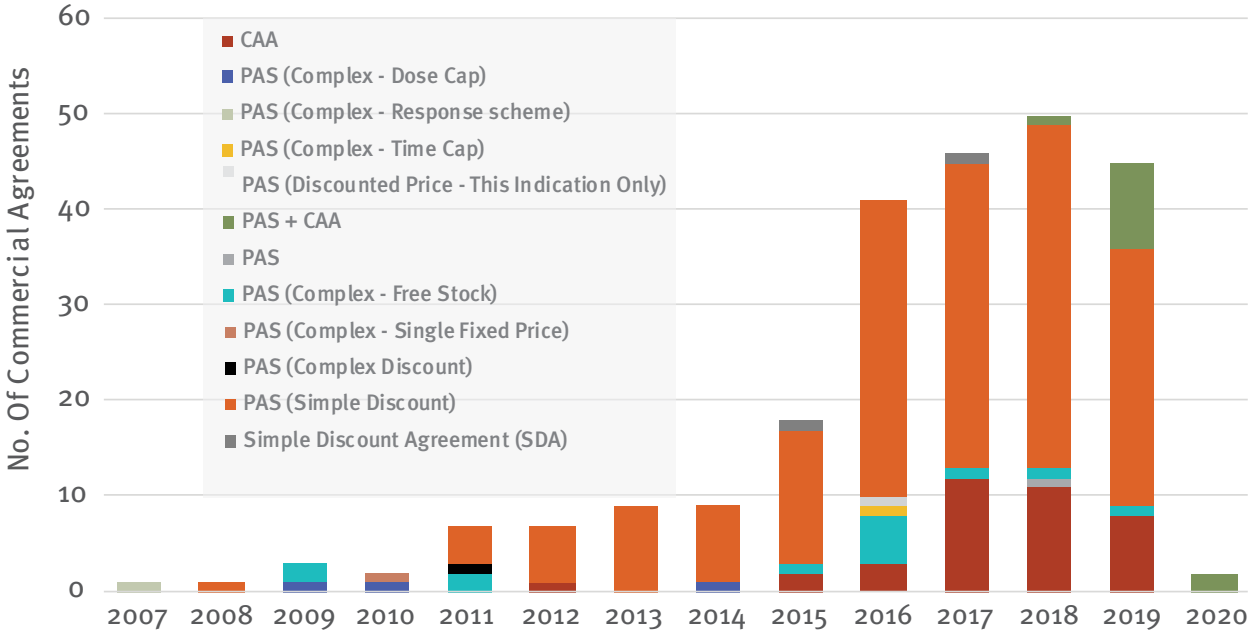
The final results for the MS risk sharing scheme, in relation to patient outcomes, came out in 2018, 16 years after the scheme was agreed. It showed that the treatments were beneficial to patients and could slow disease progression, albeit that further study was needed to explore the benefits of treatment waning over time. That study did not address whether the new payment model really worked, or not, and from whose perspective.

The UK followed up with a response scheme in 2007. The deal was struck between Janssen-Cilag GMBH and the English national health service for Velcade (bortezomib) in the treatment of multiple myeloma. The scheme centered on serum M-protein, measured routinely with a blood test and so added no further clinical costs to the NHS, although the admin was a bugbear for many professionals working on the scheme in the NHS.

The innovative element to the Velcade scheme was having Janssen-Cilag agree to rebate the cost of Velcade for patients who did not respond after four cycles of treatment. De Wilde was involved in developing the Velcade scheme, and he noted that the name it was given – a response scheme – was deliberately different to the MS risk sharing scheme because "the MS risk sharing scheme was seen so negatively by the NHS." It is also clear that the scheme was a far simpler approach, used a routine clinical measure that is needed for managing patients anyway, and one that would take far less time to determine if the drug worked when compared to the

Exhibit 1

Evolution In Commercial Arrangements Agreed As Part Of NICE Appraisals



2020 data is for January only

SOURCE: *In Vivo* analysis using NICE data

MS risk-sharing scheme.

What is perhaps telling about the UK's early experience with innovative ways to pay is that they have not proliferated. The trend over time has been towards simple discounts *(see Exhibit 1)*. There have been no further response schemes. According to the UK's health technology agency, NICE, of the 241 schemes that were still in play up to January 2020, 70% were simple discounts.

Similar trends have been noted elsewhere. The Netherlands, for example, tried out performance-based approaches; they discontinued this method in 2012. A 2019 OECD review of managed entry agreements (MEAs) – another name for innovative contracts – suggests that Sweden too has been moving away from schemes that intended to generate more evidence on performance of drugs which, in the end, did not provide the information that was hoped for.

Even Italy – a country alongside the UK, credited with leading the way in MEAs – has seen debate about whether performance-based approaches really can generate the necessary evidence. Italy has seen fewer outcome based agreements over time, there were no outcome based agreements agreed in 2017 or 2018, according to analysis from IQVIA. There were outcome-based agreements struck every year between 2008 and 2016. On the upside, there is evidence that there is faster patient access when agreements are used.

Dominance Of Tried And True Ways To Pay

Real life experience has seen the financial-based payment models not only growing in their use, but they are dominating in the mix of payment models being used for drugs. The OCED found that its financial payment that are most often used across OECD countries, with 28 allowing financial-based schemes versus 23 permitting performance-based schemes. There is variation though; some countries permit both financial and performance-based MEAs, whereas others only permit performance-based, and there is a lack of data for some countries (*see Exhibit 2*).

Hard Work For Payers When Using Innovative Ways To Pay

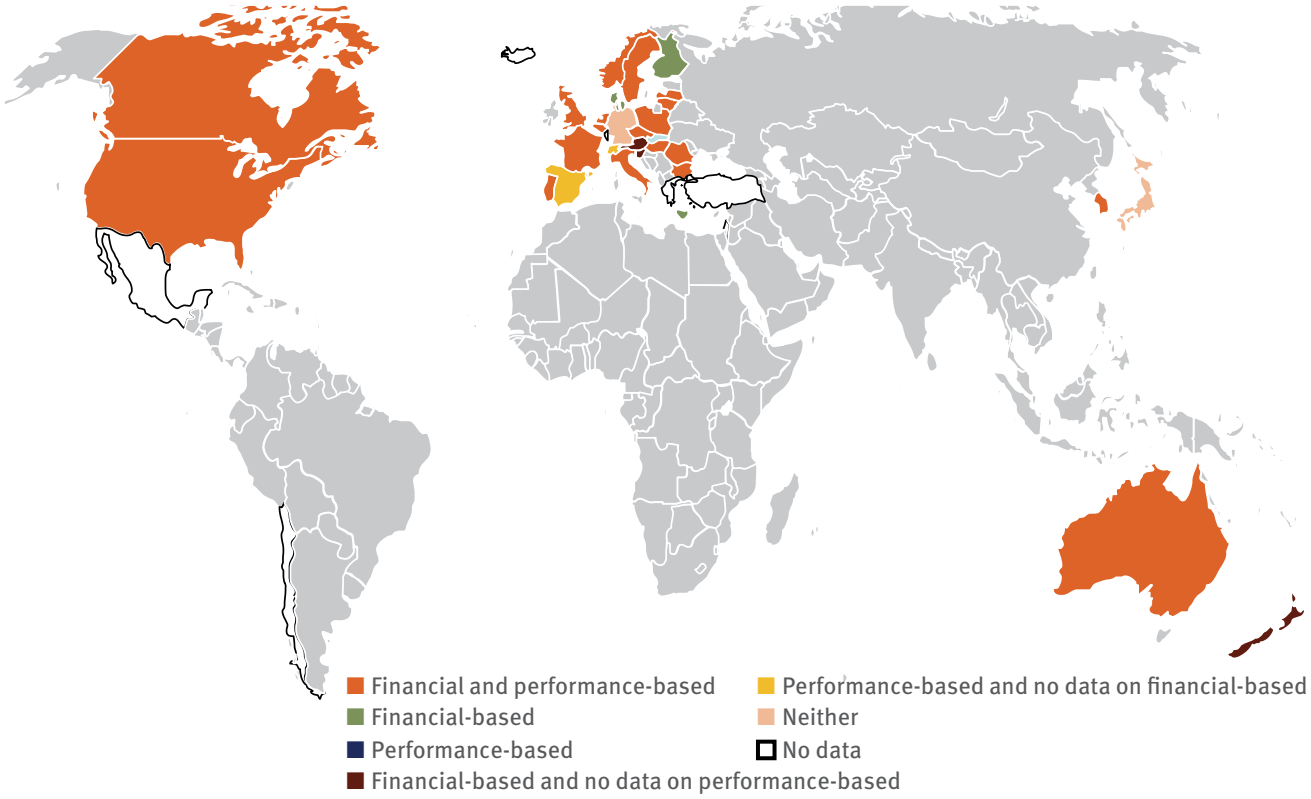
Collective experience in Europe reinforces the notion that in reality, innovation is not a driving force in payment models. The reason? There is a lot of work for payers in implementing and running anything but the traditional discounts. According to those working in Spanish hospitals and surveyed from December 2017 to March 2018 by researchers from the Universidad de La Rioja, drawbacks of risk-sharing agreements range from persuading clinicians to prescribe the drugs covered by the agreements to administration in following up.

In the US too, there are a host of reasons why payers reject value-based contracts (yet another term to capture the concept of paying for performance). According to researchers from Precision Value and Health, a US based market access consultancy, who surveyed 25 pharmacy directors the reasons included:

- the difficulty of defining or agreeing an outcome measure;
- the value in dollar terms does not jus-

Exhibit 2

Map Of OECD Countries' Use Of Financial And Performance-Based Ways To Pay



SOURCE: *In Vivo* using data from OECD (2019)

tify the effort to adjudicate the deal;
- lack of data infrastructure;
- complexity;
- lack of trust;
- uncertainties including whether patients adhere to treatment;
- plus, the silo nature of medical and pharmacy budgets.

Even in Italy there remains admin despite it being a trail blazer using flexible web-based registries. "Web registries make it possible to apply any new scheme," said Fabrizio Gianfrate, who formerly worked at the Italian Medicines Agency, AIFA, and is now a market access consultant. Yet he concedes that the issue of admin and workload applies even with the capabilities in the Italian system. He explained, "It's a lot of work for the treating doctors. They are reluctant and not very happy to update the registry." With a focus on interoperability it could become easier as systems essentially talk to one another without the need for the current step of inputting data.

Despite the disappointments of the past, there has been a resurgence of interest in innovative ways to pay. Novartis funded researchers from the UK-based think-tank the Social Market Foundation (SMF) to look at introducing outcomes-based ways to pay in the NHS in 2017. Their conclusion was that, with lessons learnt, the benefits of an outcomes-based model would be to help address affordability challenges, reduce risks for the NHS, and improve outcomes for patients.

Others have looked at the potential for outcomes-based models too. The Office of Health Economics (OHE) and Rand Europe, both UK-based research groups, funded by Cancer Research UK and the Greater Manchester Health and Social Care Partnership, have looked at how to make outcome-based payment a reality in the NHS. Their 2019 report suggests that outcomes-based pricing schemes have not been used systematically reflecting a lack of consensus.

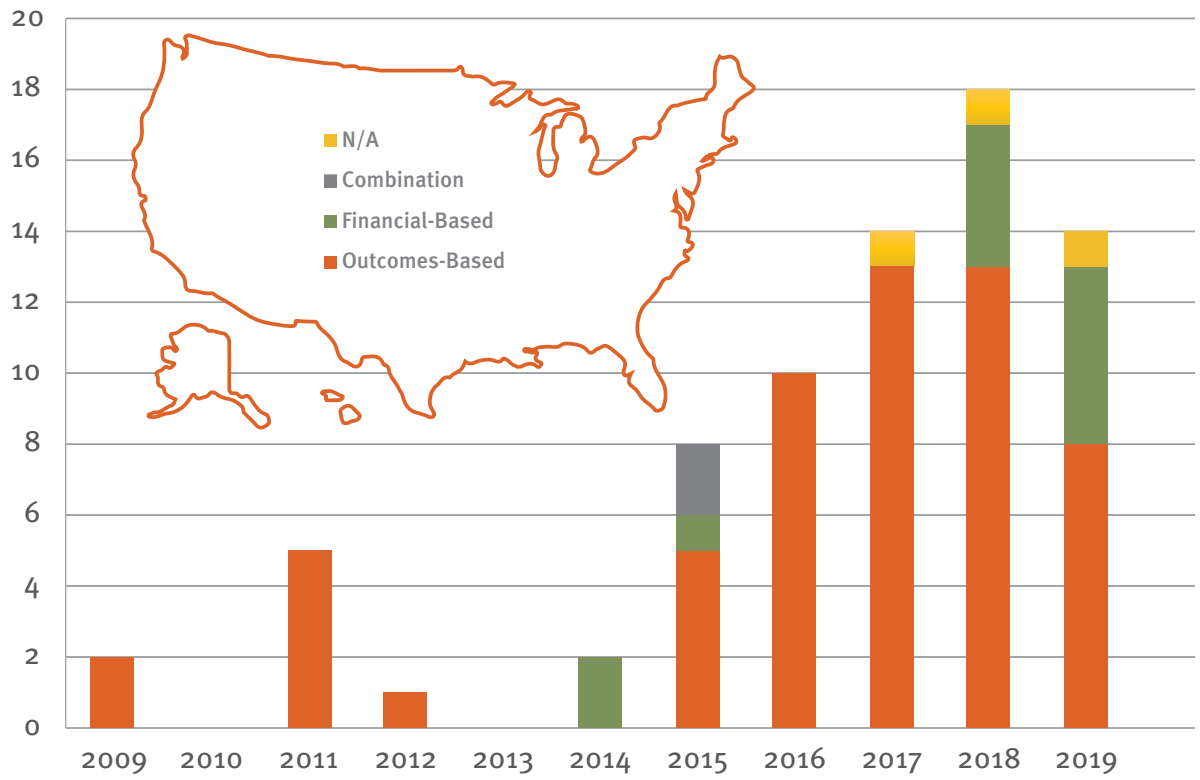
Implicit to both the SMF and OHE/Rand reports is that, in essence, this time it is different. In technology terms, that must surely be the case compared to early outcomes-based agreements like the MS risk sharing scheme. Such is the belief in the potential, OHE, working with others, have secured funding to follow-up their work and will be piloting an outcome-based payment scheme in the Greater Manchester region of England.

It is not just the UK either. There is interest in innovative agreements between hospitals and pharmaceutical companies in the Netherlands, according to Vintura, a life sciences and health consultancy based in the Netherlands. It said, interest in what is arguably still the most experimental – on outcomes – is seen only amongst a few. Vintura's 2019 survey of 30 hospital-based professionals suggested that 20% were interested in outcomes-based discounts because this was seen as picking up on innovation. That compared to around half of those surveyed having a preference for a flat discount since it is simple and predictable. Almost a third could be interested in volume-based discounts reflecting the opportunity to secure a higher discount.

The US has seen an increase in the number of agreements, known locally as value-

Exhibit 3

Number And Type Of Publicly Disclosed Value-Based Contracts In The US, 2009-2019



SOURCE: Data from Verpora VBA tracker

How best to pay for cures – when it is not yet evident that they really are cures because there is no lifetime data to draw upon – has re-invigorated the debate.

based contracts, since 2009. Just over 75% of these have been outcomes-based, bucking the trend in Europe (*see Exhibit 3*). Given the complexity of the US market with its many payers, plus the confidentiality that surrounds agreements struck, this may well be an under-estimate. It may not be a fair reflection of the types of agreement made either. Ali believes that that there could be as many as eight to 12 deals made that remain confidential, for every one that is in the public domain.

Arguably much of the renewed interest in finding new ways to pay reflects the new drugs coming to market. How best to pay for cures – when it is not yet evident that they really are cures because there is no lifetime data to draw upon – has re-invigorated the debate. That debate has moved beyond talk and into new payment models. For example, AIFA struck for the first time a model it calls payment at results for Novartis' T-cell therapy, Kymriah (tisagenlecleucel), for adult patients with diffuse large B-cell lymphoma (DLBCL) and for patients aged up to 25 years old with B-cell acute lymphoblastic leukemia (ALL) in August 2019.

Focus On Collaboration

Payers too use the term innovation in relation to payment models. For example, NHS England – the biggest buyer of specialty drugs in the NHS – has referred to its own innovative approach when it came to an agreement for a population level trial of not-yet approved cholesterol treatment inclisiran with Novartis in January 2020. Novartis also spoke of the innovative approach in their press release. Yet both organizations led with a different message to innovation in the payment model; instead both emphasized collaboration.

NHS England has also focused on what it sees as "smart procurement." Examples include a deal agreed with Vertex for their cystic fibrosis products announced in October 2019, where all clinically eligible patients can access Orkambi (lumacaftor/ivacaftor), Symkevi (tezacaftor/ivacaftor) and Kalydeco (ivaftor). Another is an agreement with Roche on Ocrevus (ocrelizumab) for multiple sclerosis, signed in May 2019. Details on the agreements in the public domain are minimal.

De Wilde believes that rather than what payment models are called, what matters more is tackling head-on the concerns of payers and working collaboratively. He said, "Innovative as a term has had its time. Companies need to focus on models that respond to the main concerns of payers." From a payers' perspective, the focus is not on striking an innovative payment arrangement but on companies engaging constructively and striking the right deal.

Gianfrate concurs that the real target should be meeting payer needs. He points to the AIFA deal struck for Kymriah . He explained, "The mix of the outcomes-based payment with instalments is based on the specific need to manage uncertainty on long-term efficacy, and a high upfront cost that is hard to manage in one year."

Companies need to think collaboration, not innovation, when it comes to ways to pay.

IV124455

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

In Vivo
Informa Pharma Intelligence

Follow us online and be a part of hot topic discussions on the matters impacting Pharma and Medtech today

Join us on LinkedIn:
https://www.linkedin.com/company/in-vivo-pharma

Join us on Twitter:
https://twitter.com/INVIVOnow
@INVIVOnow

EU Health Innovation Partnership Reflects Medtech's Role In Unmet Needs

The EU Partnership on Health Innovation, a new public-private health care research partnership, is in the final drafting phase before its launch under Horizon Europe. *In Vivo* asked the partnership's medtech industry lead, Patrick Boisseau, to set out the innovation challenges for participants as they address unmet health care needs in Europe.

BY ASHLEY YEO

The EU's forthcoming Partnership for Health Innovation will break new ground, as it establishes a program to address emerging health care challenges over the next seven years in five priority areas of unmet needs.

This public-private partnership awaits the final go-ahead from the European Commission and member states, including budgetary decisions, but its Strategic Research Agenda will be available soon.

Crucially, the partnership calls for major input from the medtech and the pharma sectors, as it broaches needs across the health care continuum, with solutions expected to come from the genomics, prevention, diagnostics and therapy disciplines, as well as digitally enabled care and "smart health."

Health care in Europe faces increasing challenges on a number of fronts, but it is clear that technological and scientific advances offer the main route to solving the growing needs of patients. Identifying these unmet needs and putting into action a strategic plan around how and with whom the solutions can be developed have previously failed, as a process.

In the past, the European Union has set up targeted research programs, from FP6, to FP7, to Horizon 2020. These have all offered grant-funded research and innovation (R&I) experts the opportunity to engage with academia, providers and other health care stakeholders in embarking on joint approaches to tackling health care's unmet needs.

These seven-year programs have bridged some of the gaps that arise in health and translational challenges. That is being continued within the Horizon Europe Framework Programme (2021-2027), the new tentative €80bn-100bn ($90bn-113bn), EU R&I funding program, within which the novel public-private partnership (PPP) on Health Innovation will sit.

Some 8% (€7.7bn) of Horizon Europe's budget is currently planned to be allocated to health projects. This is subject to change, however, as the final budget amounts can only be set after the EU's Multiannual Financial Framework has been decided at EU council level. This has been delayed and, in early March, was still awaiting finalization.

Lead Role For Medtech

Europe's leading medical technology industry federation, MedTech Europe, has, along with COCIR (the European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry), taken a lead role in organizing the new Health Innovation PPP. These two organizations have split the industry input into the task 50:50

with European pharmaceutical trade body EFPIA (the European Federation of Pharmaceutical Industries and Associations). These three will jointly oversee the industrial input from the larger manufacturers, while the European Commission will co-fund for smaller companies and the non-commercial inputs.

The work areas were proposed in a draft Strategic Research Agreement (SRA) in October. This split the initiative into five areas of need. "Delivering the SRA was a major achievement," said Patrick Boisseau, who was commissioned by MedTech Europe to spearhead the medtech side of the scheme.

Speaking to *In Vivo*, Boisseau described the SRA document as "a scientific road map and a description of high-level priorities." It was opened for public consultation in October 2019, and led to a 15-page document that describes the five areas of actions – the "priority" areas. It received some 100 comments with which to craft the final SRA.

It was to be posted on www.euhealthppp.org in late January 2020, but that, too, has been subject to a slight delay. The final document will still be released on that website, but it will not be published on the commission's website, however, as the associated budgetary issues might mean the PPP having to reduce its scope, which might lead the SRA to being revised.

The industry groups in the partnership will, however, publish it, with a disclaimer, and it will be updated, probably after a couple of years. The commission's delay was not related to the recent coronavirus outbreak, and was not a reprioritizing of commission's resources, MedTech Europe asserted.

Despite these minor hiccups, Boisseau regards the ethos and the set-up of the new PPP as game-changing for medtech in Europe, especially when compared with the Innovative Medicines Initiative (IMI), the preceding scheme for EU health care. "In the past, the medtech sector did not engage with EU support instruments as actively as some other industries. But that is changing," he said.

Boisseau's career and track record made him an ideal candidate to lead the medtech industry's input into the PPP. His 40 years of industry experience include 32 at the European Atomic Energy Commission (CEA), working on technology research in life sciences, academic research and R&D with and for industry. For the past 18 years, he has had a role on European R&D collaborations in nanomedicine, which provided him with knowledge and insight into European funding programs.

PATRICK BOISSEAU: AN IDEAL TRACK RECORD TO LEAD A MAJOR MEDTECH RESEARCH PROJECT

Patrick Boisseau has managed many EU collaborative projects, research infrastructures, coordination actions and networks of excellence. Initially specializing in agronomy and environmental engineering in France, he later develop scientific and technical expertise in nanomedicine, drug delivery, medical imaging and innovative medical technologies.

A French national, Boisseau is the past chair of the European Technology Platform on Nanomedicine. He is MedTech Europe's Inter-Association Task Force representative for the public-private partnership on Health Innovation within Horizon Europe, and joined MedTech Europe on 1 September 2019 as director of EU R&I partnership policies.

His remit is to develop and lead the medtech industry in EU R&I partnerships and programs, liaise with the European Commission and help coordinate European funding projects at EU level for the medtech industry.

In 2012, he became head of strategic planning for health care at CEATech, the technology research division of CEA, the European Atomic Energy Commission. He was most recently VP, Europe, at CEATech.

Start Of The Venture

Five years ago he was approached by the European Commission about taking a role in the forthcoming Horizon Europe PPP for European medtech. That led him to contact MedTech Europe chair Serge Bernasconi.

"That was the start of the venture. But what is really new is that, for the first time

ever, medtech is actively shaping the PPP, both in creating it, and later on in the governance of it," Boisseau highlighted. Six months into his new role at MedTech Europe, Boisseau said, "This is my best experience ever," adding that he was gratified by "the strong push by our MTE members to be part of this EU funding program."

He said, "The basis of my job is trying to explain, prepare and train our members [150, including 50 associations] to take advantage of opportunities."

A significant part of medtech research done by some large companies takes place in the US rather than in Europe. For this reason, the US-headquartered groups have had little knowledge of the processes and programs at EU level.

"For them, [the premise of the PPP] is not necessarily an easy thing to assimilate because, for many, it is the first time they have been able to consider collaborative research in Europe," Boisseau said. Most medtechs have not really addressed European R&I, as this is seen as the responsibility of their US teams. "This new opportunity has led to them to reconsider, and many are doing internal reflections on how they can work on a collaborative basis in Europe. It is a very interesting phase." It might even see companies transferring some research from the US back to Europe, Boisseau believes.

An R&I committee of some 23-25 companies has done a lot of preparatory profiling of opportunities and assessment of potential engagement levels for the medtech side of the PPP.

The Value Of Joint Research

The value and purpose of EU health care funding initiatives has been brought into sharp focus with the ongoing coronavirus outbreak. In late January, the European Commission released €10m initially, and later another €37.5m, for research on vaccines, new treatments and diagnostics. *(Also see "Stark COVID-19 Drug Shortages Warning From Senior EU Regulator" - Pink Sheet, 6 Mar, 2020.)*

Boisseau has a leadership and coordinating role at the Health Innovation PPP. "The great challenge is that this partnership is not a simple extension of the IMI," he said. "We started 16 months ago, with tripartite negotiations featuring the commission, pharma and devices, with pharma and devices meeting every week, and then both of them with the commission every two weeks, to define step-by-step the rules and objectives of the PPP."

A lot of effort was devoted to the strategic objectives, and to the level of research needed, and it took much time before agreement was reached, said Boisseau, as R&D is performed in a very different way by the two commercial sectors. "But we are progressing," said Boisseau, adding that the months ahead will be used to finalize all the details and rules that will apply for the next seven years.

"The medtech sector needs to be active now," he said. "All our members need to be ready on 1 January 2021, that is my objective. And companies are learning very quickly."

Delivering the SRA was the first tangible, major milestone, he said. Up ahead lies the work of finalizing the governance structure, the priority-setting processes, the participation of stakeholders, and the funding mechanisms. The process has involved workshops with pharma and medtech companies, to survey their suggestions on the top five challenges they saw in their area of activity in the coming seven years, and how to address them collectively.

The principle of the PPP is that the risks are shared by companies, and the partnerships that happen take place in the "precompetitive" area. It is better to co-invest collectively so everyone will benefit, saving time and/or accelerating progress, said Boisseau. These can then be translated into proprietary products that are developed by companies individually.

The basis of the contributions is that the commission will invest cash up to the estimated value of 50% of the project's funding for the non-industrial partners, the hospitals, the universities and the start-ups, etc. On the industrial side, the major companies involved in the project will invest 50% of the budget of projects in kind.

Five Priority Areas

"The ideas have been discussed, and now we have five priority – or action – areas. Every year, the five areas will yield calls for probably 10 to 20 projects, which will be published in the expectation that all kinds of stakeholders will apply," Boisseau explained.

The five action areas that have been prioritized in the SRA are:

1. Harnessing advances in, and synergies between, genetics, biology and technology innovations for more precise and effective prevention, diagnosis, treatment and care, and interfacing the disciplines. This action area also includes healthy ways of living and factoring in environmental issues that might need addressing.

2. Developing patient-centric, integrated care solutions along the entire health care continuum, which is a new trend. Looking at it from the patients' viewpoint, Boisseau said the aim is for all the different steps to be aligned and consistent, whether a pharma or a medtech solution. "Consequently, we need to develop interconnected solutions with the support of both pharma and medtech industries."

3. Digitization. This relates to collecting Big Data in new ways and combining it with advanced analytics/artificial intelligence to enable research, development and business opportunities, which, in turn, promote new, integrated health care approaches. Artificial intelligence will deepen the impact in the health care sector, with issues being addressed by the pharma and medtech industries together. This cross-sectoral approach has not been a feature of research programs so far, Boisseau observed.

4. Empowering citizens and patients to effectively engage and improve their own health, which is also a new way of considering health management, not only through the use of apps, but generally through giving patients more information. In this way, patients become key players in their own heath management.

5. Reinforcing value initiatives to guide investment, and rewarding innovation in health and social care. These very much play into the value-based health care concept. "There is a consensus that value will drive the future of health care. At present, it is still a concept, but we want to achieve that aim," said Boisseau.

Innovation Discussions, Focus Groups And Selection Criteria

The individual health care projects within these five priority areas will be discussed every year of the PPP, including with external stakeholders (patients, pay-

ers, health care professionals, research organizations, hospitals, universities, regulators and EU member states, etc).

There will also be focus groups – technical groups where the ideation process will take place – similar to the strategic governing groups (SGG) used in the IMI initiative. The title and the remits of these groups could evolve over time. "We are trying to find the right granularity, so we cover the full SRA in a manageable way," Boisseau said.

The topics of the call for projects will be shortlisted each year, and the governing board of the PPP will take the final decision. One criterion is that the commission and industry should agree to fund the budget for a topic equally. If industry is not prepared to invest in a particular topic, it might be moved to another program of the commission's health cluster, to give it another chance, said Boisseau.

The PPP process will be managed by a central office, yet to be set up, similar to the structure within the IMI model. The process is still being fine-tuned into "a management process that will deliver." But Boisseau said that a lot has been learnt from the IMI and ECSEL partnerships. "Past experience has helped to design the process and organization for the Health Innovation PPP."

In addition, the PPP will communicate with other partnerships, on food and the environment, and not focus solely on actual treatment, but rather on the whole continuum of care.

Adoption Of Solutions

The question of how solutions that emerge from the individual projects will be adopted is highly relevant. What will finally reach the patient and consumer? Companies will want to know the answer to this question. Boisseau said the commission was putting more pressure on ensuring deliverables for patients, i.e. products that will reach the market. Industry, for its part, will be eager to get a return on investment.

The research would not always deliver products, Boisseau cautioned, but it may instead deliver a method or process that can be further developed. The partnership is currently defining key impact indicators, to monitor the projects and collaborations. It also wants an indicator to monitor the

Five Action Areas: Potential Outputs

1 Harnessing synergies:
- Increased understanding of human disease biology
- New tools and technologies for personalized/ precise prevention and treatments
- Novel treatment paradigms for non-communicable diseases
- Better preparedness for infectious disease outbreaks

2 Patient-centric, integrated care solutions:
- Pathways for the combination of products and integrated solutions for diseases
- Integrated solutions to support more efficient operational and workflow
- Integrated medical and non-medical solutions for improved patient outcomes
- Setting up the environment, infrastructure and standards for integration

3 Applying 'Big Data' and advanced analytics:
- A roadmap for implementing data standards harmonization
- Auxiliary data tools
- An incentive system for buyers of health technologies to be compliant with data standards and quality
- Deployment of the IT infrastructure necessary within health care for AI and machine learning

4 Empowering patients:
- Greater understanding and knowledge among patients
- A "facilitating environment"
- A strong case for patient empowerment

5 Value initiatives:
- A harmonized definition of value for products, services and their combinations
- Tools and methodologies for value-based assessment, procurement and financing
- Facilitation of value-based decision-making
- Pilots for innovation financing to accelerate access

impact of the funding granted. "We are driving for rules that that will ensure best use of the money invested."

There is a growing trend in European funding of going closer to the market, but product development is the responsibility of the industry, so public money should not fund it, Boisseau asserted. For its part, the commission is aiming in the pre-competitive space to facilitate all necessary steps that accelerate or promote the new medtech and digital solutions being made available.

The two major founders in the PPP are the commission and large medtech companies, with the cash from the commission being used to financed substantially all of the public partners' inputs, the start-ups and the SMEs. Start-ups and SMEs would have to apply for funding, and if successful, would be granted costs by the commission.

"The most successful projects are run by consortia where large and small companies, and regulators and others, all become used to meeting on a regular basis, enabling them to deepen their relationships at an early stage in the development of the technology," Boisseau said.

A lot of R&D in the medtech sector is done by start-ups, but when they get closer to the market and need to embark on clinical validation, the smaller ones tend to get taken over to enable their technology to continue its route to the market. This is the framework which start-ups and large companies live together in and are accustomed to, Boisseau observed.

But he is enthusiastic about the possibilities for medtech in the PPP. It is the first time in many decades in the industry that medtech has been invited to actively contribute and shape the R&D and innovation thrust in healthtech at EU level. "We hope this new plan will encourage more investment and commitment in the next seven years," said Boisseau. "It really is a change for medtech, and for Europe, and, of course, for the patients and the health care systems."

> *"Together, we will help to design cross-sectorial R&I programs on prevention, diagnostics, treatment, monitoring of patients, as well as socio-economic studies on value and digitization of health care."*
>
> Patrick Boisseau

This is because, for the first time, medtech companies are being strongly encouraged to take an active role in shaping an EU research partnership, to ensure it meets their needs and expectations. "Together, we will help to design cross-sectorial R&I programs on prevention, diagnostics, treatment, monitoring of patients, as well as socio-economic studies on value and digitization of health care," said Boisseau. It will be a big part of the process of solving unmet patient needs. Solving tomorrow's health care challenges requires a broad coalition of stakeholders to explore new approaches that can combine devices, diagnostics, medication, digital tools and big data. That is precisely the remit of the Health Innovation PPP, he said.

Unmet Needs In Focus

In reality, any topic of interest to both industry and the commission under the PPP could be called an "unmet need," Boisseau observed. But if a project merely "improved" an existing market, the commission may not be favorable to funding half of its budget.

Equally, some projects may be seen by companies as too risky or too early-stage to take on under their own funding. "In this case, we have asked that the regulation establishing the PPP could make room for exceptions, and allow industry to be granted funding to use its resources to address these needs, as has happened under IMI," said Boisseau.

In the meantime, MedTech Europe will host webinars, organize training, offer access to support tools and official templates, and make available details of work programmes, "for medtech innovators of all sizes."

IV124470

Comments:
Email the author: *Ashley.Yeo@Informa.com*

Meddevicetracker

Informa Pharma Intelligence

Meddevicetracker: Medical Device Intelligence and Forecasts

Stay up-to-date and get a complete view of the continually evolving medtech landscape with access to real-time market intelligence on product and company developments across the medical devices, diagnostics and advanced delivery systems markets.

Anticipate upcoming filings, clinical trials dates and data, and access market size information and expert forecasts all in one place, helping you assess the competition, track key events and make better-informed decisions.

To find our more visit:
pharmaintelligence.informa.com/Meddevicetracker

On the Move

Recent executive appointments in the life sciences industry

NIKOLAUS BEYER

TIMM CROWDER

LISA GELLER

TOM GRIFFIN

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Timm Crowder	Aerami Therapeutics	Chief Operating Officer	Spyryx Biosciences	Chief Operating Officer	5-Feb-20
Cecilia Ahlin	AroCell AB	Chief Medical Officer	Novartis	Medical Head, Oncology Sweden	10-Feb-20
Blaine Davis	ArTara Therapeutics Inc	Chief Financial Officer	Insmed	Vice President and Head, Investor Relations and Corporate Communications	11-Feb-20
Kristin Yarema	Atara Biotherapeutics Inc	Chief Commercial Officer	Amgen	Vice President and Therapeutic Area Head, Global Product Strategy and Commercial Innovation, Hematology and Oncology	18-Feb-20
Joseph Baroldi	Avidity Biosciences	Chief Operating Officer	Ionis Pharmaceuticals	Vice President, Business Development	12-Feb-20
Bijoy Sagar	Bayer AG	Chief Information Technology and Digital Transformation Officer	Stryker Corp	Chief Digital Technology Officer	1-Jun-20
Craig T. Basson	Boston Pharmaceuticals	Chief Medical Officer	Novartis Institutes for Biomedical Research	Global Head, Translational Medicine, Cardiovascular and Metabolism	3-Feb-20
Elisabeth Leiderman	Complexa Inc	Chief Business Officer	Fortress Biotech	Head, Corporate Development and Senior Vice President	7-Feb-20
Bob Howe	Conformis Inc	Chief Financial Officer and Treasurer	NxStage Medical Inc	Vice President, Finance and Corporate Controller	5-Feb-20
Kenji Hashimoto	Crescendo Biologics Ltd	Chief Medical Officer	Roche	Associate Clinical Director	3-Feb-20

READ MORE ONLINE

Take an interactive look at recent executive-level company changes and promotions in the biopharma, medical device and diagnostics industries.
Visit: invivo.pharmaintelligence.informa.com

P.J. HALEY

JURIS HMELNICKIS

JAMES NICHOLS

DAVID HORN SOLOMON

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Alison L. Hannah	CytomX Therapeutics Inc	Chief Medical Officer and Senior Vice President		Pharmaceutical and Biotech Consultant	3-Feb-20
Pascal Wotling	DBV Technologies	Chief Technology Operations Officer	Novartis	Head, External Supply Operations, Asia-Pacific, Middle East and Africa	1-Apr-20
David Morris	Enterprise Therapeutics Ltd	Chief Medical Officer	Novartis Venture Fund	Managing Director	10-Feb-20
Theresa Heggie	Freeline Therapeutics	Chief Executive Officer and Director	Alnylam Pharmaceuticals	Head, CEMEA and Senior Vice President	4-Feb-20
Lisa Geller	Frequency Therapeutics	Head, Intellectual Property	Casebia Therapeutics	Head, Intellectual Property	7-Feb-20
Wendy Arnold	Frequency Therapeutics	Chief People Officer	Kaleido BioSciences	Senior Vice President, Human Resources	7-Feb-20
Vesa Kataja	Kaiku Health	Chief Medical Officer	Central Finland Health Care District	Chief Medical Director	1-Feb-20
Rob van Maanen	Khondrion BV	Chief Medical Officer	Astellas Pharma	Senior Medical Director	5-Feb-20
Kristen Stants	Magenta Therapeutics	Chief People Officer	Alexion Pharmaceuticals	Head, Talent Strategy	5-Feb-20
Ian Ball	Medicom Healthcare	Commercial Director and Executive Committee Member	Aeques Pharmaceuticals Inc	Chief Commercial Officer	1-Feb-20
Jon Dill	Midmark Corp	Chief Financial Officer	Orchard Holdings	Operating Executive	3-Feb-20
Christophe Arbet-Engels	Millendo Therapeutics Inc	Chief Medical Officer	Poxel Pharmaceuticals	Chief Medical Officer, Executive Vice President, Late Development and Medical Affairs	10-Feb-20

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Tom Griffin	Nuvaira Inc	Chief Financial Officer	Avedro Inc	Chief Financial Officer	4-Feb-20
Francois Martelet	Oasmia Pharmaceutical AB	Chief Executive Officer	Nivigenix SA	Non-Executive Director	15-Mar-20
Peng Lu	Pharvaris BV	Chief Medical Officer	Takeda	Vice President, Global Program Lead, Rare Diseases	7-Feb-20
Rajiv Patni	Portola Pharmaceuticals Inc	Chief Medical Officer and Executive Vice President	Adamas Pharmaceuticals	Chief Medical Officer	3-Feb-20
Ranjay Radhakrishnan	Reckitt Benckiser plc	Chief Human Resources Officer	InterContinental Hotels Group	Chief Human Resources Officer	1-Mar-20
James Nichols	Relay Therapeutics	Head, Genetic Diseases	Warp Drive Bio	Chief Operating Officer	4-Feb-20
Nikolaus Beyer	Safe Orthopaedics SA	Chief Commercial Officer	K2M	General Manager, Central and Northern Europe	3-Feb-20
Andrew Smith	Santhera Pharmaceuticals Holding AG	Chief Financial Officer	Allecra Therapeutics GmbH	Chief Financial Officer and Chief Operating Officer	1-Apr-20
Archelle Georgiou	Starkey Hearing Technologies	Chief Health Officer		Consultant	10-Feb-20
Heinz Ruch	Starkey Hearing Technologies	Chief Business Development Officer	HRC Independence llc	Managing Partner	10-Feb-20
Neal Bibeau	TARGET PharmaSolutions Inc	Chief Executive Officer	Symphony Health Solutions	Chief Executive Officer and President	13-Feb-20
Tim Sawyer	Teligent Inc	Chief Executive Officer and President	Barr Laboratories	Executive Vice President, Global Generic Sales and Marketing	5-Feb-20
Scott Applebaum	Trevena Inc	Chief Legal and Compliance Officer and Senior Vice President, Regulatory Affairs	Context Therapeutics	President	13-Feb-20
David Zaccardelli	Verona Pharma plc	Chief Executive Officer, President and Director	Dova Pharmaceuticals Inc	Chief Executive Officer and President	1-Feb-20
Robert Abraham	Vividion Therapeutics	Chief Scientific Officer	Pfizer	Senior Vice President and Group Head, Oncology Research and Development	11-Feb-20

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Stephen A. Trowbridge	AngioDynamics Inc	Chief Financial Officer, General Counsel and Executive Vice President	Senior Vice President, General Counsel, Associate Secretary and Interim Chief Financial Officer	5-Feb-20
Lila Corwin	Biodex Medical Systems Inc	Head, Global Physical Medicine Sales	Senior Vice President, Marketing Communications	5-Feb-20
Tom Mander	Domainex Ltd	Chief Executive Officer	Chief Operating Officer	1-Apr-20

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
P.J. Haley	Exelixis Inc	Executive Vice President, Commercial	Senior Vice President, Commercial	1-Feb-20
Yijun Huang	EyeKor llc	Chief Executive Officer	President and Chief Technology Officer	11-Feb-20
Hans van Schijndel	HAL Allergy Group	Chief Research and Development Officer and Director	Principal Scientist/Head, Preclinical Research	1-Feb-20
Lauren M.G. Burt	Kemin Industries Inc	Head, Worldwide Communications	Manager, Worldwide Communications	14-Feb-20

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Scott Brun	Axial Biotherapeutics Inc	Director	12-Feb-20
Avner Lushi	Brainsway Ltd	Director and Member, Audit Committee	10-Feb-20
Jim Schuermann	CorWave SA	Independent Director	11-Feb-20
John Pedersen	DYSIS Medical Ltd	Chairman	10-Feb-20
Kevin C. O'Boyle	GenMark Diagnostics Inc	Chairman	10-Feb-20
Ronnie Hershman	Hemostemix Inc	Director	10-Feb-20
Juris Hmelnickis	JSC Grindeks	Chairman	4-Feb-20
Doug Manion	Kleo Pharmaceuticals	Chairman	14-Feb-20
Christine Seidman	Merck & Co Inc	Director	16-Mar-20
Kathy Warden	Merck & Co Inc	Director	16-Mar-20
Alex C. Sapir	PhaseBio Pharmaceuticals Inc	Director	13-Feb-20
David Horn Solomon	Rexgenero Ltd	Chairman	10-Feb-20
Huw Jones	Rexgenero Ltd	Non-Executive Director and Chairman, Remuneration Committee	12-Feb-20
John Markels	Sangamo Therapeutics Inc	Director	12-Feb-20
David McIntyre	Starpharma Holdings Ltd	Non-Executive Director	1-Mar-20
Paul Walker	Trillium Therapeutics Inc	Director	6-Feb-20

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Michael Briskin	Obsidian Therapeutics Inc	Chairperson, Scientific Advisory Board	5-Feb-20
Andreas Harstrick	Orion Biotechnology	Scientific Advisory Board Member	6-Feb-20
Anne J. Ridley	RhoVac AB	Scientific Advisory Board Member	6-Feb-20
Maksim Mamonkin	Xenetic Biosciences Inc	Scientific Advisory Board Member	13-Feb-20

Deal-Making

Covering deals made February 2020

IN VITRO DIAGNOSTICS

MERGERS & ACQUISITIONS

Meridian Bioscience pays $49M for **Exalenz**

MEDICAL DEVICES

FINANCINGS

NuVasive nets $436M via sale of debt

PHARMACEUTICALS

MERGERS & ACQUISITIONS

Catalent buys cell therapy CDMO **MaSTherCell** for $315M

Merck spins out women's health and other mature businesses into newco

Takeda exercises option to acquire celiac disease drug developer **PvP**

ALLIANCES

Aimmune licenses rights to **Xencor**'s mAb for food allergies

Collegium buys US rights to *Nucynta* from partner **Assertio**

RedHill gets rights to OIC drug *Movantik* from **AstraZeneca**

Bicycle Therapeutics finds a third Big Pharma partner in **Roche**'s **Genentech**

Biogen pays **Sangamo** $350M up front for up to 12 CNS programs

BI, **Trutino** pen discovery-stage immune-oncology deal

EyePoint gets global rights (excluding Greater China) to vorolanib from **Equinox Science**

Seattle Genetics licenses antibodies from **Five Prime** for ADC development

GSK, **Immatics** team up in discovery and development of adoptive cell therapies for cancer

Nestle Health Science gets rights to diabetes candidate from **Valbiotis**

Vir Bio, **WuXi** enter coronavirus collaboration

FINANCINGS

ADMA Biologics nets $88.9M via FOPO

Adverum nets $141.2M through FOPO

AGTC nets $30.5M via FOPO

AVROBIO nets $94M via FOPO

Beam Therapeutics goes public via $192.5M IPO

Catalent raises €825M in debt offering

To help fund **MaSTherCell** acquisition, **Catalent** nets $493.9M in FOPO

Catalyst Biosciences nets $32.4M through latest public offering

Collegium secures $339M through term loan agreement, public debt raise to finance *Nucynta* deal

Deciphera nets $164.5M through public stock sale

EyePoint nets $20.4M via FOPO

Moderna nets $479.8M via FOPO

Orphazyme raises DKK745M through PIPE

PPD nets $1.5bn in IPO

RAPT Therapeutics nets $70.5M via public offering

RedHill enters $115M term loan agreement with **HealthCare Royalty**; $30M drawn down up front

Revance closes upsized $250M notes offering to support *DAXI* commercialization

Initial public offering nets $254.5M for **Revolution Medicines**

Schrodinger nets $216M in IPO

Theravance nets $139.6M via FOPO

Valneva gets initial $60M in debt finanicng from Deerfield and OrbiMed

Xeris nets $39.1M via FOPO

Public offering nets $85M for **Ziopharm**

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

FINANCINGS

Public offering nets $140.5M for **Twist Bioscience**

IN VITRO DIAGNOSTICS

MERGERS & ACQUISITIONS

MERIDIAN BIOSCIENCE INC.
EXALENZ BIOSCIENCE LTD.

In an effort to become a leading provider of gastrointestinal diagnostic products, **Meridian Bioscience Inc.** is paying $49M in cash ($1.78 per share) to acquire Israeli firm **Exalenz Bioscience Ltd.** (Feb.)

Exalenz offers diagnostic tools and management devices for patients with liver and stomach disorders. Its leading product is the *BreathID* urea breath test platform for detecting Helicobacter pylori, which is often associated with peptic ulcers and gastric cancer. The *BreathID* system facilitates easy patient sample collection and provides real-time patient monitoring in a physician's office setting. It is complementary to Meridian's own stool antigen tests and non-invasive diagnostics for H. pylori. Meridian will fund the acquisition through cash on hand and debt under an existing credit facility that is being expanded to $160M. Exalenz reported $14M in 2019 revenues. Investment Banks/Advisors: LCF Rothschild & Co. Inc. (Meridian Bioscience Inc.); William Blair & Co. (Exalenz Bioscience Ltd.)

MEDICAL DEVICES

FINANCINGS

NUVASIVE INC.

NuVasive Inc. (spine technologies) netted $435.9M ($450M gross) through the private sale of 0.375% convertible senior notes due 2025 to qualified institutional buyers. The initial conversion rate is 10.7198 shares of common stock per $1k principal amount of notes, equivalent to $93.29 per share (NuVasive's stock is currently averaging $76.88). Concurrently the company entered into privately negotiated convertible note hedge transactions and warrant transactions with certain parties. NuVasive will use some of the proceeds to repurchase shares of its common stock and to pay for convertible note hedge transactions. (Feb.)

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.

For information about access please contact Customer Care at 888-670-8900 or PharmaNewsSales@informa.com

PHARMACEUTICALS

MERGERS & ACQUISITIONS

CATALENT INC.
ORGENESIS INC.
MaSTherCell Global Inc.

In another unsurprising sign of the continued consolidation in the advanced therapy manufacturing market, **Catalent Inc.** bought privately held Belgian cell therapy CDMO **MaSTherCell Global Inc.** for $315M in cash. Catalent is funding the transaction through a concurrent FOPO. The company also received a $200M loan commitment from JP Morgan. (Feb.)

Catalent itself has been part of the manufacturing frenzy, having paid $1.2bn for **Paragon Bioservices** in April 2019. Other recent cell and gene therapy manufacturing deals have included **Thermo Fisher**/**Brammer Bio** for $1.7bn and **Cognate BioServices**/**Cobra Biologics**. Driving these agreements is the estimated 70% of cell and gene therapy developers that outsource manufacturing. With the current deal, Catalent says it now has a more complete end-to-end offering with respect to development, manufacturing, analytical, fill-finish, and clinical supply services. Spun out of **Universite Libre de Bruxelles** in 2011, MaSTherCell operated independently until 2015 when it was bought by **Orgenesis** through a stock swap worth $24.6M. (For Orgenesis, the divestment means it will focus more on its point-of-care cell therapy business and development of advanced therapies.) MaSTherCell currently operates or is building three major manufacturing facilities, of 25k- (clinical services), 32k- (development-scale), and 60k- (commercial-scale) square feet sizes, and specializes in both autologous and allogeneic therapeutics such as CART, T-cell receptors, tumor-infiltrating lymphocytes, and mesenchymal stem cells. Its overall services include cell collection, process industrialization, analytical services, cGMP manufacturing, and in-house quality control, and the company counts **Iovance Biotherapeutics**, **CRISPR Therapeutics**, **Servier**, and **Txcell** among its clients. Great Point Partners and SFPI-FPIM are investors.

MERCK & CO. INC.

Merck & Co. Inc. is joining the downsizing trend by spinning off its women's health, legacy brands, and biosimilars businesses into a separate as yet unnamed publicly traded company. (Feb.)

Key brands that will housed be under the new entity include the *Nexplanon* (etonogestrel implant) birth control device, biosimilars *Renflexis* (infliximab-abda) and *Brenzys* (etanercept) in immunology and *Ontruzant* (trastuzumab-dttb) in oncology with partner Samsung Bioepis, and other strong brands including the cholesterol drugs *Zetia* (ezetimibe) and *Vytorin* (ezetimibe/simvastatin). Approximately 75% of the new firm's sales will be generated from ex-US markets, with estimated 2021 revenues between $6bn-$6.5bn. Merck will retain its existing lead businesses of diabetes, oncology, vaccines, hospital, and animal health. Its current key brands include *Keytruda* (pembrolizumab), *Lynparza* (olaparib), *Lenvima* (lenvatinib mesylate), *Gardasil* (Human Papillomavirus Vaccine, Recombinant), *Bridion* (sugammadex), *Zerbaxa* (ceftolozane/tazobactam), and *Bravecto* (fluralaner). The new company will be headquartered in New Jersey, US, and staff approximately 10k employees. Kevin Ali will be at the helm as CEO, with Carrie Cox as chairman. The spin-off is expected to be completed during 1H 2021.

PVP BIOLOGICS INC.
TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. acquired **PvP Biologics Inc.**, a private firm developing an investigational treatment for celiac disease. (Feb.)

Takeda paid an undisclosed amount up front and will hand over up to $330M in earn-outs based on the achievement of development and regulatory milestones. In early 2017, Takeda and PvP entered into an agreement surrounding the development of PvP's KumaMAx (Kuma062/TAK062), an oral enzyme designed to break down the immune-reactive parts of gluten in the stomach and prevent gastrointestinal reactions in patients with celiac disease. Takeda paid $35mm for PvP's expenses related to the therapy's early development, and got an exclusive option to acquire PvP following a Phase I proof-of-mechanism study. The study has now completed, and Takeda has exercised its option to buy PvP.

ALLIANCES

AIMMUNE THERAPEUTICS INC.
XENCOR INC.

Aimmune Therapeutics Inc. licensed exclusive global rights to develop and sell **Xencor Inc.**'s humanized monoclonal antibody XmAb7195 for food allergy indications. Xencor will rename the project AIMab7195. (Feb.)

Xencor was originally developing the candidate--which uses three mechanisms of action to reduce blood serum IgG and suppress IgE-producing cells--in Phase I studies for allergic asthma. Aimmune now plans to develop AIMab7195 as an adjunct therapy to its own *Characterized Oral Desensitized ImmunoTherapy* (*CODIT*) programs including *Palforzia*, a recently approved immunotherapy for peanut allergy in patients ages 4 through 17 years. Under terms of the deal, Aimmune will bear all development costs. It paid $5mm in cash up front and issued $5mm of its shares (156,238 common at $32; market average). Beginning with the initiation of Phase II trials, it could also hand over up $385mm in development, regulatory, and sales milestones plus high-single to mid-teen royalties (*Strategic Transactions* estimates 7-16%).

ASSERTIO THERAPEUTICS INC.
COLLEGIUM PHARMACEUTICAL INC.

Collegium Pharmaceutical Inc. acquired outright US rights to oral opioid analgesic *Nucynta* (tapentadol) from its 2017 US commercialization partner **Assertio Therapeutics Inc.** (Feb.)

In 2015, Assertio (then known as Depomed; it changed names in 2018) paid $1.05bn up front to gain exclusive US rights to *Nucynta* from **Janssen Pharmaceuticals**, which had licensed the drug from **Grunenthal** (its originator) in 2003. Under a late 2017 deal, Assertio granted Collegium an exclusive sublicense to commercialize both immediate-release (IR) and extended-release (ER) formulations of *Nucynta* in the US for $10mm up front, up to $135mm annually in licensing fees, plus royalties. The 2017 commercialization deal has been terminated upon the signing of the current asset purchase agreement, which has Collegium paying Assertio $375mm in cash up front,

without the requirement to pay Assertio ongoing royalties. In addition, Collegium will pay Grunenthal a flat 14% royalty on net sales instead of the $34mm (annual) royalty obligation previously owed on sales equal to or greater than $180mm under the former deal. The present arrangement is expected to increase Collegium's cash flows more than four-fold. Collegium already sells pain drug *Xtampza ER*, an abuse-deterrent, extended-release, oral formulation of oxycodone launched in 2016, with expected 2020 revenues between $150-160mm. The 2020 *Nucynta* revenues are anticipated in the range of $170-180mm. Collegium is financing the transaction with cash on hand and $339mm in committed debt financing, including a concurrent $200mm term loan facility from BioPharma Credit PLC and a $139mm public offering of convertible senior notes. Investment Banks/Advisors: Stifel Nicolaus & Co. Inc. (Assertio Therapeutics Inc.); Jefferies & Co. Inc. (Collegium Pharmaceutical Inc.)

ASTRAZENECA PLC
REDHILL BIOPHARMA LTD.

RedHill Biopharma Ltd. licensed worldwide rights (excluding Europe, Canada, and Israel) to the GI drug *Movantik* (naloxegol) from **AstraZeneca PLC**. (Feb.)

Movantik, a peripherally acting mu-opioid receptor antagonist (PAMORA), is approved to treat opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Under terms of the deal, RedHill pays $52.5M upfront, and a non-contingent payment of $15M 18 months after the deal closes. RedHill will finance the deal through a concurrent $115M royalty-backed term loan from HealthCare Royalty. AstraZeneca originally licensed *Movantik* from **Nektar** in 2009; RedHill now assumes sales-based royalty and milestone payments due to Nektar. Additionally, AZ granted **Daiichi Sankyo** co-commercialization rights in the US under a 2015 collaboration. As a result of the new deal, RedHill assumes US rights and leads US commercialization, but will continue to share costs and pay sales-related commissions to Daiichi.

BICYCLE THERAPEUTICS PLC
ROCHE
Genentech Inc.

Roche's **Genentech Inc.** and **Bicycle Therapeutics PLC** agreed to discover, develop, and sell bicyclic peptide immuno-oncology therapies against multiple targets chosen by Genentech. (Feb.)

Bicycle, which completed an IPO last year, already has two Big Pharma partners including a $1B deal with **AstraZeneca** focused on multiple therapy areas, and a $466M sickle cell/hemophilia agreement with **Bioverativ**, which was later bought by **Sanofi**. The new partners will jointly conduct discovery and preclinical studies, with Bicycle responsible for the discovery, lead optimization, and early preclinical work up to the point when Genentech may exercise an option to select a candidate for exclusive worldwide licensing. The agreement will include two immuno-oncology targets; Genentech has the option to add an additional two targets for a cost of $10M per program. Genentech will then take over remaining development and commercialization. Bicycle gets $30M up front; $10–12M per program (a maximum total of $48M); $200M in development, regulatory and first sale milestones per program; $200M in commercial milestones for each product; and tiered mid-single-to-low-double-digit royalties. *Bicycles* are short peptides developed as either stand-alone candidates or linked together to enable binding to two or more tumor antigen targets. One key advantage of *Bicycles* is that they are excreted by the kidney, not the liver, and therefore avoid immunogenicity issues. In oncology, Bicycle is exploring *Bicycle* toxin conjugates in which the peptide is linked to a toxin that is later cleaved and destroys the tumor (Bicycle's internal oncology programs are not part of the Genentech alliance). Roche and Genentech are quite active in immuno-oncology, particularly with their marketed PD-L1 inhibitor *Tecentriq*, which is approved in many cancers and being investigated as a monotherapy and combination in multiple tumor types. Roche/Genentech are also investigating other mechanisms; most recently Genentech teamed up with **Xencor** in the area of IL-15 bispecific cytokine therapeutics. The tie-up with Bicycle comes days after Roche signed another peptide-focused deal with **Nimble Therapeutics**.

BIOGEN INC.
SANGAMO THERAPEUTICS INC.

Sangamo Therapeutics Inc. licensed **Biogen Inc.** exclusive global rights to develop and commercialize preclinical ST501 for tauopathies including Alzheimer's disease (AD) and ST502 for synucleinopathies including Parkinson's disease (PD), plus an undisclosed neuromuscular disease target. Biogen also has exclusive rights to nominate up to nine other undisclosed neurological disease targets over a five-year period. (Feb.)

Biogen will shell out $350M up front in the form of $125M in cash and a $225M equity investment in Sangamo (24M shares $9.21 each; a 25% premium). Sangamo is also eligible for up to $925M in development and regulatory milestones, $1.45B in commercial milestone payments, and royalties in the high-single-digits to sub-teen double-digits (estimated at 7-12%). Under the agreement, Sangamo will conduct early research activities to be funded by both companies. Biogen is responsible for performing and funding IND-enabling studies, clinical trials, regulatory activities, and worldwide commercialization. Sangamo will manufacture clinical supplies of the initial three products, and Biogen is responsible for GMP manufacturing activities beyond the first clinical trial for each of those products. Sangamo's compounds were developed using its zinc finger protein transcription factors (ZFP-TF) genome regulation platform. The ZFP-TF are delivered via adeno-associated virus (AAV) to modulate the DNA involved in neurological diseases and thus selectively repress or activate the expression of specific genes to achieve a desired therapeutic effect. The parties seek to create the first disease-modifying treatments for patients with neurodegenerative diseases such as AD and PD. Just last month Biogen paid $75M up front for **Pfizer Inc.**'s Phase I casein kinase 1 inhibitor PF05251749 for patients with AD and PD. Under that deal Biogen could shell out another $635M in development and commercial milestones, plus an estimated 7-12% in royalties. In a recent conference call, Biogen announced that it is actively engaging with the FDA on its Phase III AD therapy aducanumab and seeks to complete the regulatory filing in the near future.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
TRUTINO BIOSCIENCES

Boehringer Ingelheim GmbH and **Trutino Biosciences** penned a collaboration surrounding the latter's *On-Demand Cytokine* (*ODC*) platform. (Feb.)

Compared to traditional cytokine treatments, Trutino's *ODC* platform masks the activity of systemically delivered cytokines, keeping them inactive in the body until they reach the tumor site, where they are fully activated. BI gets access to *ODC* to generate and develop up to three new cancer immunotherapies, to which it will have global rights. The deal includes undisclosed up-front money in addition to development, regulatory, and sales milestones, and royalties. The 2018 start-up is responsible for generating and preclinically validating new *ODC* molecules, after which BI will take over late preclinical testing through the remainder of development. The goal of the collaboration is to develop both single-agent cytokine therapeutics as well as therapies in combination with BI's existing cancer vaccine, oncolytic virus, T cell engager, and myeloid-targeting programs.

EQUINOX SCIENCE LLC
EYEPOINT PHARMACEUTICALS INC.

Equinox Science LLC licensed **EyePoint Pharmaceuticals Inc.** exclusive rights to develop and commercialize vorolanib worldwide (excluding China, Macau, Hong Kong, and Taiwan). (Feb.)

EyePoint will pay Equinox $1M up front, up to $50M in milestones based on development (completion of a Phase II trial) and regulatory (tied to activities in the

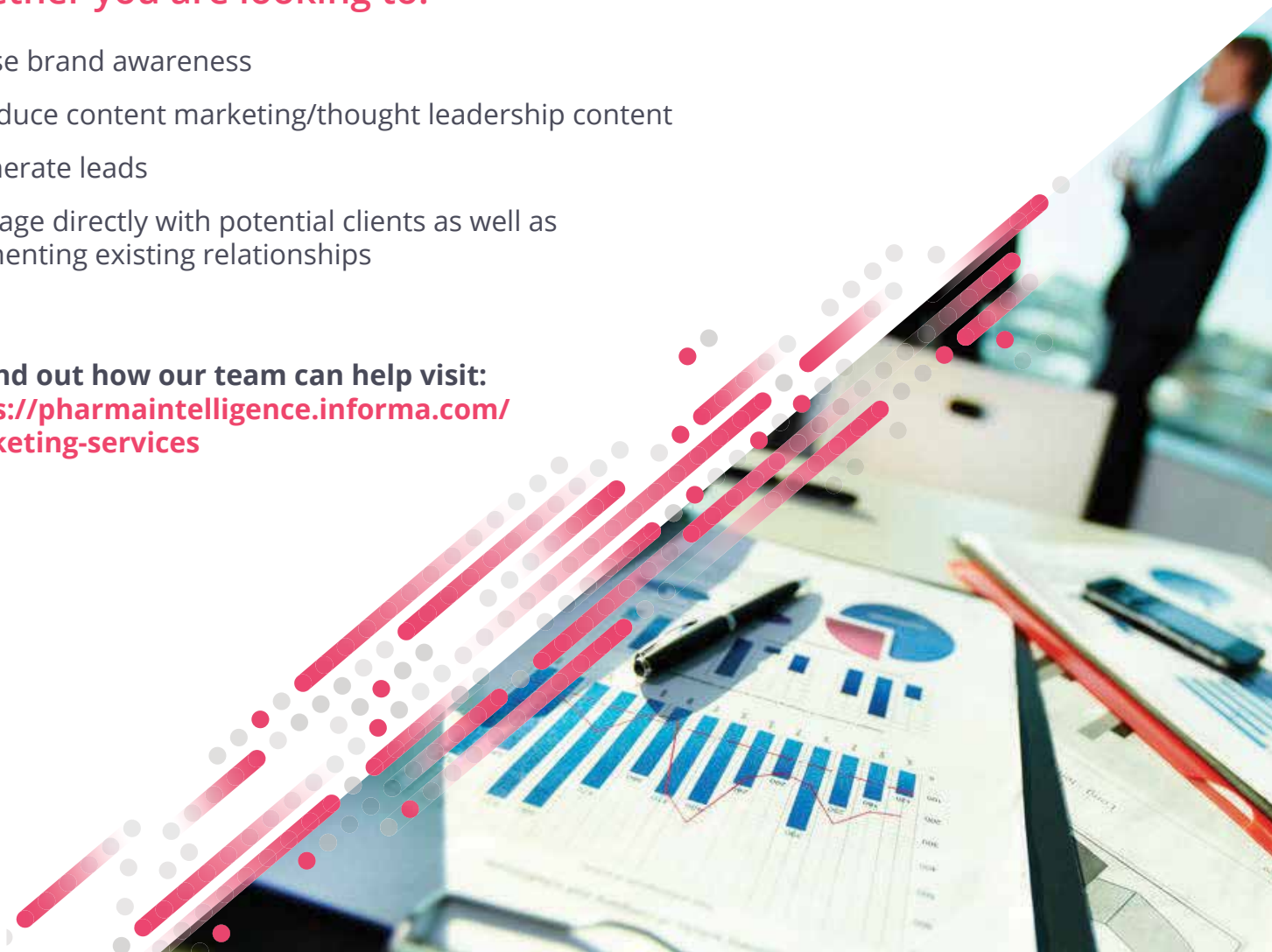
Pharma Intelligence
Informa

Are you looking to reach and do business with senior decision makers in pharma and medtech?

We offer a range of marketing opportunities whether you are looking to:

- Raise brand awareness
- Produce content marketing/thought leadership content
- Generate leads
- Engage directly with potential clients as well as cementing existing relationships

To find out how our team can help visit:
https://pharmaintelligence.informa.com/marketing-services



Generics Bulletin

Informa Pharma Intelligence

Generics Bulletin – the industry-leading source for unparalleled coverage of generics, biosimilars and value-added medicines.

Login to the online version of Generics Bulletin and start benefitting from a powerful platform that enables you to:

- Access news and content online via any internet device, 24/7
- Stay in tune with news and events as they happen
- Jump straight to the content that matters to you including commercial developments, policy and regulation updates, and the latest on generic drugs, biosimilars and value-added medicines
- Customize your homepage to your areas of interest, saving time and letting you dig deeper into critical topics
- Get breaking news and relevant new content delivered straight to your inbox with customizable emails and alerts
- Save searches or bookmark content so you can easily return to it later and share it
- Access training videos, user-guides, and pre-scheduled training sessions to help you get the most from Generics Bulletin online.

PLUS: Get answers to your toughest business questions and Generics Bulletin content queries with the Ask-the-Analyst service, included in your subscription.

Visit: https://generics.pharmaintelligence.informa.com/ to register for online access and to find out more.

US, UK, or EU) achievements, plus sales royalties ranging in the high-single to low-double digits (*Strategic Transactions* estimates 7-29%). Vorolanib (EYP1901) incorporates EyePoint's bioerodible *Durasert* sustained-release intravitreal drug delivery technology. The tyrosine kinase inhibitor is currently in preclinical studies for wet age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion. A Phase I trial is expected to commence in 2020, with top-line results anticipated in H2 2021.

FIVE PRIME THERAPEUTICS INC.
SEATTLE GENETICS INC.

Five Prime Therapeutics Inc. granted **Seattle Genetics Inc.** exclusive global rights to develop and sell antibody-drug conjugate therapies for cancer with antibodies developed by Five Prime. (Feb.)

The monoclonal antibodies licensed to Seattle Genetics are directed towards a single undisclosed target. Five Prime gets $5M up front, up to $525M in development, regulatory, and sales milestones ($295M each for the first two projects), and royalties in the mid-single digits (*Strategic Transactions* estimates 4-7%). Five Prime adds Seattle Genetics to a strong list of partners benefiting from the company's expertise in the antibody space, including **BMS**, **bluebird bio**, **ADC Therapeutics**, **GSK**, and **UCB**. Seattle Genetics' antibody pipeline includes blood cancer candidate brentuximab vedotin (with partner **Takeda**, enfortumab vedotin for solid tumors with **Astellas** and **Merck**, the breast cancer therapy tucatinib (NDA submitted).

GLAXOSMITHKLINE PLC
IMMATICS BIOTECHNOLOGIES GMBH

Immatics Biotechnologies GmbH and **GlaxoSmithKline PLC** are teaming up to discover, research, and develop next-generation T-cell receptor (TCR) therapies for solid tumors. (Feb.)

The initial focus of the collaboration will be autologous T-cell therapies but the firms may eventually look to develop allogeneic cell therapies using Immatics' *ACTallo* approach. Immatics will utilize its *XCEPTOR* TCR discovery and engineering platform to identify TCRs which will be directed against two targets discovered and validated by its *XPRESIDENT* technology. GSK will pay Immatics $50M (€45M) up front for the two initial programs and up to $550M in development, regulatory, and commercial milestones for each, plus sales royalties. GSK can opt to select additional targets and would shell out additional option payments, milestones, and royalties. Under the collaboration, Immatics is responsible for the development and validation of the TCR therapies up to clinical candidate designation, after which time GSK will take over additional global development, manufacturing, and commercialization. At GSK's request Immatics can choose to co-develop one or more programs. In August 2019, Immatics signed a similar deal with **Celgene** for adoptive cell therapies for cancer.

NESTLE SA
Nestle Health Science SA
VALBIOTIS

In a long-term collaboration, **Valbiotis** licensed **Nestle Health Science SA** exclusive worldwide rights to develop and commercialize TOTUM-63 for prediabetics at risk for Type 2 diabetes. (Feb.)

In exchange for the rights, Nestle will pay Valbiotis $5.2M (CHF5M) up front, up to $68.4M in development and sales milestones, plus tiered sales royalties. Valbiotis will use the money to fund the latest phase of clinical development until health claims are obtained in the US and Europe. (Commercialization may happen prior to obtaining those health claims.) The parties will create a joint steering committee to oversee clinical development, regulatory activities, supply, and commercialization. Valbiotis will supply Nestle with TOTUM-63. Phase I/II TOTUM-63 is a patented combination of 5 plant extracts designed to reduce the risk of developing Type 2 Diabetes in prediabetics. It has demonstrated its ability to reduce fasting and two-hour blood sugar levels. The key global markets for TOTUM-63 include Europe, the US, Russia, China, Japan, Brazil, and Australia.

VIR BIOTECHNOLOGY INC.
WUXI PHARMATECH INC.
WuXi Biologics

WuXi Biologics and **Vir Biotechnology Inc.** are teaming up in the development of human monoclonal antibodies for treating coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (Feb.)

Vir has isolated antibodies from SARS patients and identified several mAbs that bind to SARS-CoV-2. Both firms will conduct clinical development, manufacturing, and commercialization of the antibodies. WuXi will perform cell-line development, process and formulation development, and initial manufacturing for clinical trials. Upon approval, WuXi gets rights to commercialize the therapies in China, Macau, Hong Kong, and Taiwan, while Vir has commercialization rights in all other global markets. There is a dire need for a therapy to address the global COVID-19 threat.

FINANCINGS

ADMA BIOLOGICS INC.

ADMA Biologics Inc. (developing plasma-derived biologics for immune deficiencies and infectious diseases) netted $88.9M via an upsized follow-on public offering of 27M common shares (including full exercise of the overallotment) at $3.50 each. The company will use the proceeds to obtain raw materials needed for manufacturing its primary humoral immunodeficiency products *Asceniv* and *Bivigam*, for ongoing commercialization of both products, to expand the manufacturing capacity of one of its facilities, for R&D activities, and to expand our plasma collection facility network. (Feb.)

Investment Banks/Advisors: Jefferies & Co. Inc.; Morgan Stanley & Co.; Oppenheimer & Co. Inc.

ADVERUM BIOTECHNOLOGIES INC.

Adverum Biotechnologies Inc. (gene therapies for ocular and rare diseases) netted $141.2M through a follow-on public offering of 10.9M common shares (including full exercise of the overallotment) at $13.75. The company will use some of the proceeds for ongoing development of its gene therapy pipeline and AAV vector discovery platform. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; LifeSci Capital LLC; SVB Leerink

APPLIED GENETIC TECHNOLOGIES CORP.

Applied Genetic Technologies Corp. (adeno-associated virus (AAV)-based gene therapies for rare diseases) netted $30.55M in a follow-on public offering of 6.5M common shares at $5 each. The company plans to use the funds to complete Phase I/II trials of its X-linked retinitis pigmentosa (XLRP) and achromatopsia (ACHM) programs, to initiate a pivotal trial for the XLRP program, and to advance its optogenetics program. (Feb.)

Investment Banks/Advisors: HC Wainwright & Co.; Janney Montgomery Scott Inc.; Roth Capital Partners; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

AVROBIO INC.

Gene therapy firm **AVROBIO Inc.** netted $94M through a follow-on public offering of 4.35M common shares at $23 each. The company will use some of the funds for ongoing development of its programs for Fabry disease, cystinosis, Gaucher disease, and Pompe disease; additional R&D activities; and manufacturing activities. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Guggenheim Partners LLC; Morgan Stanley & Co.; Nomura Securities International Inc.; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

BEAM THERAPEUTICS INC.

Beam Therapeutics Inc. (precision genetic medicines based on a proprietary base editing technology) netted $192.5M through its initial public offering of 12.2M common shares (including the overallotment) at $17. The company originally filed to sell 6.25M shares at a range of $15-17. (Feb.)

Investment Banks/Advisors: Barclays Bank PLC; JP Morgan Chase & Co.; Jefferies & Co. Inc.; Wedbush PacGrow Life Sciences

CATALENT INC.

Life sciences service provider **Catalent Inc.** (drug delivery and manufacturing of pharmaceuticals, biologics, and consumer health products)--through its subsidiary **Catalent Pharma Solutions Inc**.--raised €825M ($903.4M) through the sale of 2.375% senior unsecured notes due 2028. The offering was originally expected to be worth significantly lower, €450M. Catalent will use some of the proceeds to redeem in full its euro-denominated 4.750% senior notes due 2024 and to repay existing loans. Just weeks ago the company brought in $493.9M through a FOPO to support its recent acquisition of **MaSTherCell**. (Feb.)

CATALENT INC.

Catalent Inc. (integrated services, drug delivery systems, and contract manufacturing and development for pharmaceutical, biologics, and consumer markets) netted $493.9M by selling 8.4M shares at $58.58. Catalent will spend approximately $330M of the proceeds on its concurrent acquisition of fellow cell therapy CDMO **MaSTherCell Global**, and the rest will be used to pay down $100M in debt. (Feb.)

Investment Banks/Advisors: JP Morgan & Co.; UBS Investment Bank

CATALYST BIOSCIENCES INC.

Catalyst Biosciences Inc. (treatments for rare diseases and complement-mediated disorders) netted $32.4M through a public offering of 5.3M common shares (including the overallotment) at $6.50. Some of the funds will support development and manufacturing activities for Phase II projects MarzAA (marzeptacog alfa; hemophilia and bleeding disorders) and DalcA (dalcinonacog alfa, hemophilia B). (Feb.)

Investment Banks/Advisors: Chardan Capital Markets; LifeSci Capital LLC; Raymond James & Associates Inc.

COLLEGIUM PHARMACEUTICAL INC.

Collegium Pharmaceutical Inc. received a total of $339.4M in committed debt financing to support in part its concurrent $375M purchase of US rights to oral opioid analgesic *Nucynta* (tapentadol) from its 2017 partner **Assertio Therapeutics Inc.** It secured a $200M term loan facility from BioPharma Credit PLC. The four-year loan will bear interest at a rate based upon LIBOR, plus 7.5% per annum. The company also publicly sold $143.75M ($139.4M net), including the overallotment, in 2.625% convertible senior notes due 2026. (Feb.)

Investment Banks/Advisors: Jefferies & Co. Inc.

DECIPHERA PHARMACEUTICALS INC.

Deciphera Pharmaceuticals Inc. (kinase inhibitor therapies for cancer) netted $164.5M through the public sale of 3.18M common shares at $55. Proceeds will support continued development of candidates including ripretinib (Phase III for gastrointestinal stromal tumors and Phase I for systemic mastocytosis and other solid tumors), DCC3014 (Phase I for solid tumors and tenosynovial giant cell tumors), rebastinib (Phase I/II for solid tumors), and DCC3116 (preclinical ULK kinase inhibitor). (Feb.)

Investment Banks/Advisors: Guggenheim Partners LLC; JP Morgan Chase & Co.; Jefferies & Co. Inc.; SunTrust Banks Inc.

EYEPOINT PHARMACEUTICALS INC.

EyePoint Pharmaceuticals Inc. netted $20.4M in a follow-on public offering of 15M common shares at $1.45 each. The company will use the proceeds for ongoing commercialization of *Dexycu* (dexamethasone intraocular suspension) for postoperative inflammation and *Yutiq* (fluocinolone acetonide intravitreal implant) for chronic non-infectious uveitis affecting the posterior segment of the eye. Additional funds will be used for ongoing R&D activities including EYP1901. (Feb.)

Investment Banks/Advisors: Guggenheim Partners LLC; Laidlaw & Co.

MODERNA INC.

Moderna Inc. (messenger RNA therapies and vaccines) netted $478.75M through a follow-on offering of 26.3M common shares at $19 each. (Feb.)

Investment Banks/Advisors: Barclays Bank PLC; Chardan Capital Markets; Goldman Sachs & Co.; Morgan Stanley & Co.; Needham & Co. Inc.; ODDO BHF; Oppenheimer & Co. Inc.; Roth Capital Partners

ORPHAZYME AS

Orphazyme AS (developing treatments for orphan neuromuscular protein-misfolding diseases) grossed DKK745M ($109.6M) through the directed issue and private placement of 7M shares (consisting of 4M new shares and 3M existing shares) at DKK106 apiece (a 9% discount). The company will use the proceeds to fund US and European regulatory submissions (anticipated in 1H 2020 and 2H 2020, respectively) for arimoclomol in Niemann-Pick disease Type C and prepare for its commercial launch expected in 2021. The funds will also support completion of arimoclomol trials in amyotrophic lateral sclerosis (Phase III) and sporadic inclusion body myositis (Phase II/III)--sNDA filings for both indications are expected in 2H 2020--and preparation of regulatory filings in Europe. Orphazyme is also developing arimoclomol for Gaucher disease (Phase II). (Feb.)

Investment Banks/Advisors: Danske Bank AS; Guggenheim Partners LLC

PPD INC.

PPD Inc., a PE-owned contract research organization (CRO), netted $1.5B in its initial public offering of 60M shares at $27, the high end of its anticipated $24-27 range. (Feb.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Barclays Bank PLC; Citigroup Inc.; Credit Suisse Group; Deutsche Bank AG; Evercore Partners; Goldman Sachs & Co.; HSBC; JP Morgan & Co.; Jefferies & Co. Inc.; Mizuho Bank Ltd.; Morgan Stanley & Co.; Robert W. Baird & Co. Inc.; UBS Securities LLC; William Blair & Co.

RAPT THERAPEUTICS INC.

RAPT Therapeutics Inc. (small-molecule therapies for cancer and inflammatory diseases) netted $70.5M through a public offering of 2.5M common shares at $30. Funds will support continued development of CCR4 antagonists FLX475 for solid tumors and RPT193 for inflammatory diseases. (Feb.)

Investment Banks/Advisors: BMO Financial Group; Cantor Fitzgerald & Co.; UBS Investment Bank; Wells Fargo Securities LLC

REDHILL BIOPHARMA LTD.

GI disease drug developer **RedHill Biopharma Ltd.** entered into a $115M non-dilutive royalty-backed term loan agreement with **HealthCare Royalty Partners** (HCR). (Feb.)

REVANCE THERAPEUTICS INC.

Revance Therapeutics Inc. closed a private placement of $250M (net $242M) aggregate principal amount (increased from $200M) of its 1.75% convertible senior notes due 2027. (Feb.)

REVOLUTION MEDICINES INC.

Revolution Medicines Inc. (oncology) netted $254.5M through its initial public offering of 16.1M common shares (including the overallotment) at $17. The company originally filed to sell 10M shares at a range of $14-16. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Guggenheim Partners LLC; JP Morgan Chase & Co.; SVB Leerink

SCHRODINGER INC.

Schrodinger Inc. netted $216M in an initial public offering of 13.7M shares (including the overallotment) at $17; it originally planned to sell 10M shares at a $14-16 range. (Feb.)

Investment Banks/Advisors: BMO Financial Group; Bank of America Merrill Lynch; Jefferies & Co. Inc.; Morgan Stanley & Co.

THERAVANCE BIOPHARMA INC.

Theravance Biopharma Inc. (developing organ-selected medicines) netted $139.6M through a follow-on offering of 5.5M ordinary shares at $27 each. (Feb.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Cowen & Co. LLC; Credit Suisse Group; JP Morgan & Co.; Morgan Stanley & Co.; Needham & Co. Inc.

Pink Sheet & Scrip

MARKETING SOLUTIONS

How long will it take your sales team to reach 42,000 senior decision makers in pharma companies globally?

Let us demonstrate how we can do this and show you ROI now!

BRANDING | THOUGHT LEADERSHIP | LEAD GENERATION

CHRISTOPHER KEELING
Phone: +44 203 377 3183
Email: christopher.keeling@informa.com

Pink Sheet
Informa Pharma Intelligence

Scrip
Informa Pharma Intelligence

VALNEVA SE

Valneva SE announced a debt financing with Deerfield Management and OrbiMed. The company gets an initial $60M in debt (with interest at a fixed high-single-digit rate) and can draw down another $25M in the next 12 months. Amortization payments will start in three years, and the loan will mature in six years. Valneva will use the proceeds to repay its existing loan from the European Investment Bank and to continue advancing its lead program in Lyme disease and chikungunya virus. (Feb.)

Investment Banks/Advisors: Guggenheim Partners LLC

XERIS PHARMACEUTICALS INC.

Xeris Pharmaceuticals Inc. netted $35.1M through a follow-on public offering of 9M common shares at $4.15 each. The company will use some of the funds to support commercialization activities of *Gvoke* for delivery of ready-to-use glucagon, and for R&D activities of its pipeline. (Feb.)

Investment Banks/Advisors: Jefferies & Co. Inc.; Mizuho Bank Ltd.; Piper Jaffray & Co.; RBC Capital Markets

ZIOPHARM ONCOLOGY INC.

Ziopharm Oncology Inc. netted $85M through a public offering of 27.8M common shares at $3.25. Proceeds are earmarked for continued development of the company's lead projects, which include TCR-T targeting neoantigens for solid tumors and an adenovirus-based virotherapy combined with a gene delivery system for brain cancer. (Feb.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; HC Wainwright & Co.; Jefferies & Co. Inc.; Laidlaw & Co.; Lake Street Capital Markets

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

FINANCINGS

TWIST BIOSCIENCE CORP.

Twist Bioscience Inc. netted $140.5M through an upsized public offering of 5.3M common shares (including the overallotment) at $28. (The company originally planned to sell $100M.) Twist developed a silicon-based high-throughput DNA synthesis platform and will use the offering proceeds to further invest in the company's R&D organization (including pharmaceutical biologics drug discovery and DNA data storage) and in commercialization efforts supporting NGS, drug discovery, and global expansion. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Evercore Partners; JP Morgan Chase & Co.; Robert W. Baird & Co. Inc.

In Vivo
Informa Pharma Intelligence

EDITORS
Lucie Ellis
Executive Editor

Ben Comer
Pharma Editor

Ashley Yeo
Medtech Editor

Amanda Micklus
Principal Analyst

Andrea Charles
Custom Content Editor

Regina Paleski
Contributing Editor

DIRECTOR, MEDTRACK & STRATEGIC TRANSACTIONS CONTENT
Patricia Giglio

DEALS ANALYSTS
Beth Detuzzi, Deanna Kamienski
Maureen Riordan

HEAD OF PUBLICATION DESIGN
Gayle Rembold Furbert

SENIOR DESIGNER
Janet Haniak

DESIGNERS
Debi Robinson, Jean Marie Smith,
Paul Wilkinson

HEAD OF EDITORIAL OPS (PHARMA)
Karen Coleman

ADVERTISING
Christopher Keeling

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

MANAGING DIRECTOR
Phil Jarvis

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

CUSTOMER SERVICE
clientservices@pharma.informa.com

IN VIVO: [ISSN 2160-9861] is published monthly, except for the combined July/August issue, by Informa Business Intelligence, Inc., 605 Third Avenue, Floor 20-22, New York, NY 10158.

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

Office of publication, The Sheridan Group, 66 Peter Parley Row, Berlin, CT 06037.
Postmaster: Send address changes to Informa Business Intelligence, 605 Third Avenue, Floor 20-22, New York, NY 10158.