ISSN 2364-2351 | A 60711 | BIOCOM.

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Life Sciences and Industry Magazine

Autumn Edition 2019 | Volume 18 | 20 €

Interview

Ovid Therapeutics CEO Jeremy Levin on orphan drugs as his company turns to Europe with the first therapy for AS.

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Biotechnology Requires a Predictable Patent System

Picture: Ovid Therapeutics Inc

JEREMY M. LEVIN, PHD, was elected Chairman of the Biotechnology Innovation Organization in 2019. He serves as the Chairman and CEO of Ovid Therapeutics Inc. Before joining Ovid, Levin served as President and CEO of Teva Pharmaceutical Industries Ltd; he was a member of the Executive Committee of Bristol-Myers Squibb, where he helped position BMS as a leader in immuno-oncology. Prior to this, Levin was Head of Global Business Development and Strategic Alliances at Novartis and served as Chairman and CEO of Cadus Pharmaceuticals, Inc.

Modern biotechnology creates new therapies and cures, reduces dependency on fossil fuels, increases crop yields, and delivers value to patients and consumers. These advances require rational policies that maintain incentives for future innovation – including in the form of intellectual property rights – while, at the same time, providing fair and equitable consumer access to innovative products. But today, the biotechnology industry faces great challenges caused by concern about pricing and access to medicines. Political and public pressure is already leading to premature and ill-conceived legislation that could reduce incentives to innovate, as it impacts return on investment and access to capital.

Just as unwise legislation may impact investments in innovation, so too are we seeing the negative effects of legal evolution in the patent system. In Europe, we are witnessing an erosion of patent term for approved drugs. In the United States, we are faced with increasingly irrational rules of patent-eligibility, which have rendered patents on new diagnostic methods largely unenforceable and are beginning to do the same for other precision medicine inventions. Patents on new therapies are now being attacked with the argument that the body's response to a synthetic drug is really just a natural physiological phenomenon, unworthy to even be considered for patenting. This is destroying any return-on-investment for such innovations and dims the prospect for a future where personalized medicine treatments can be crafted specifically for each individual.

Much of this change stems from a series of US Supreme Court decisions that have expanded judge-determined exceptions to patentable subject matter in ways that diverge sharply from European law, and that create mounting uncertainty over what is and will be patentable and not patentable. Nothing could be worse for investment in innovation. We need a patent system that provides legal certainty, not one in which the rules of patentability change unpredictably.

The US Senate is examining whether this current patent practice is hindering commercial investment due to uncertainty in its interpretations by the courts. BIO, the Biotechnology Innovation Organization, is actively taking part in this process on behalf of its more than 1,000 member companies. BIO believes that rational patent doctrine should be framed by two key principles: patient benefit and driving innovation. An intact patent system is one key to achieving this. ■

Acknowledgements: This article has been coauthored by Professor Hans Sauer, Deputy General Counsel for Intellectual Property, BIO, a legal advisor of the BIO executive committee. Prior to taking his current position at BIO in 2006, Professor Sauer was Chief Patent Counsel for MGI Pharma, Inc., and Senior Patent Counsel for Guilford Pharmaceuticals Inc. Professor Sauer has 20 years of professional in-house experience in the biotechnology industry. He did his postdoctoral fellowship at Genentech, Inc., and holds a M.S. degree from the University of Ulm in his native Germany; a PhD in Neuroscience from the University of Lund, Sweden; and a J.D. degree from Georgetown University Law Center.

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COVER STORY

IMPRINT European Biotechnology (ISSN 2364-2351) is published quarterly by: BIOCOM AG, Lützowstr. 33–36, D-10785 Berlin, Germany, Tel.: +49-30-264921-0, Fax: +49-30-264921-11, Email: service@european-biotechnology.com, Internet: www.european-biotechnology.com; Publisher: Andreas Mietzsch; Editorial Team: Thomas Gabrielczyk (Editor in Chief), Derrick Williams (Co-editor), Dr. Martin Laqua, Sandra Wirsching, Uta Mommert, Patrick Agresz; Advertising: Oliver Schnell, +49-30-2649-2145, Christian Böhm, +49-30-2649-2149, Andreas Macht, +49-30-2649-2154; Distribution: Lukas Bannert, +49-30-2649-2148; Graphic Design: Michaela Reblin; Production editor: Benjamin Röbig; Printed at: Königsdruck, Berlin; European Biotechnology Life Sciences & Industry Magazine is only regularly available through subscription at BIOCOM AG. Annual subscription fees: €80.00, Students €40.00 (subject to proof of enrolment). Prices include VAT, postage & packaging. Ordered subscriptions can be cancelled within two weeks directly at BIOCOM AG. The subscription is initially valid for one year. Subscriptions will be renewed automatically for one more year, respectively, unless they are cancelled at least six weeks before the date of expiry. Failures of delivery, which BIOCOM AG is not responsible for, do not entitle the subscriber to delivery or reimbursement of pre-paid fees. Seat of court is Berlin, Germany. As regards contents: individually named articles are published within the sole responsibility of their respective authors. Cover Photo: Collage by BIOCOM, Galina Timofeeva (background), Krowtraerc (Label), both by stock.adobe.com; Supplement: Donau Universität Krems; ® BIOCOM is a registered trademark of BIOCOM AG, Berlin, Germany.

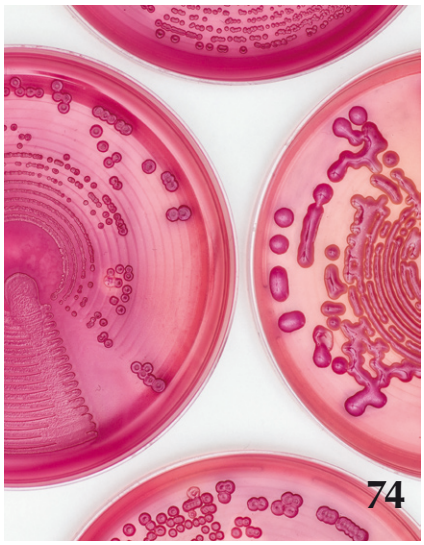
Picture: Shurong Hou, SLAS Discovery, doi: 10.1177/2472555218766842

SUSTAINABILITY

Greening finance

Sustainable financing has become the talk of the town. But are proponents just giving lip service to the idea in an era of record-breaking climate protests? Or even worse – does a cynical industry see nothing more than a new way to cash in? The verdict is still out. But at least some activities appear to be having an impact on banks, insurance providers and other finance industry players.

ANTIBIOTIC RESISTANCE



Next steps in AMR

Designers of novel antibiotics continue to struggle with inadequate returns. Experts around the globe are now trying to figure out the best way to balance push and pull incentives in an attempt to get developers interested in last-resort antibiotics again. They're being helped by a major AMR accelerator initiative in Europe.

Pictures: Cell Free Technology (above), Henrik Larsson/stock.adobe.com (left), BIOCOM AG (right), AdobeStock/viperagp (below)

SPECIAL

CROs & CDMOs

EDITORIAL

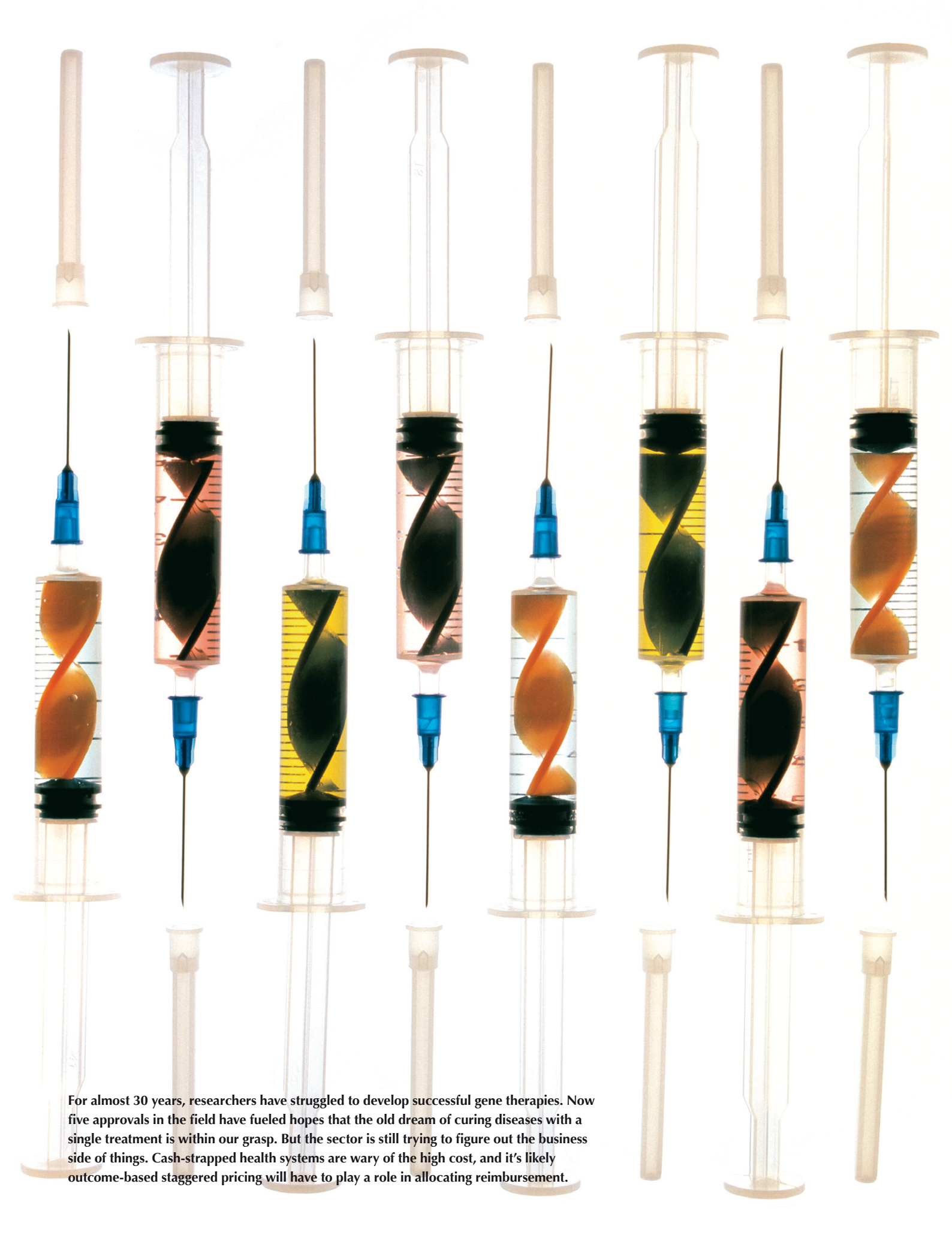
Pharma's ugly side

The pharma industry's reputation has never been spotless. It's suffered significantly in the past from malpractice, with some firms hiding safety data or promoting drugs for unapproved uses. In the last 15 years, companies have had to pay a total of over US$14bn for misbehaviour in promoting treatments, such as Vioxx, Celebrex or Avandia – a major reason why Big Pharma has lost public confidence when it comes to drug development.

Now Swiss giant Novartis AG has come under fire for hiding manipulation of preclinical data from Avexis' SMA gene therapy Zolgensma. With a list price of US$2.125m per patient, it's the most expensive therapy on the market. Responsibility for the data manipulation has been laid at the doorsteps of two former Avexis managers, and to prevent similar cases in the future, Novartis says the subsidiary's quality management process will now be absorbed into its network. However, the fact remains that Novartis started its internal investigation in March 2019. Zolgensma was approved on May 24, yet the Swiss pharma only informed the FDA about the problem on June 28.

Only credibility can provide a basis for constructive talks about the true value of super-expensive therapies like Zolgensma. But there are also other reasons why payors could demand outcome-based pricing. Read more about it in our cover story on p. 12.

Thomas Gabrielczyk
Editor-in-Chief



For almost 30 years, researchers have struggled to develop successful gene therapies. Now five approvals in the field have fueled hopes that the old dream of curing diseases with a single treatment is within our grasp. But the sector is still trying to figure out the business side of things. Cash-strapped health systems are wary of the high cost, and it's likely outcome-based staggered pricing will have to play a role in allocating reimbursement.

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Treatments – paying for performance

OUTCOME-BASED PRICING It's not easy to put a price tag on a medical cure, particularly when it comes to gene therapies. To receive what they say is an appropriate return on investment, developers are demanding up to €1.9m per patient for 'one-time' treatments. Payors are sceptical. Outcome-based pricing is one way to compromise. But what payment model would work best?

When the first gene therapy went into clinical testing in 1990, researchers were wildly optimistic about its potential impact. The chance to cure people with monogenetic defects that caused life-long maladies with a single treatment seemed just around the corner – but proved far from easy. Developers first had to learn how to construct gene vectors that wouldn't be attacked by a patient's immune system or randomly inserted into the genome, potentially causing cancer. The first gene therapy approved for the EU market only arrived in 2012. Priced at €1.1m, uniqure's Glybera promised a cure for lipoprotein lipase deficiency.

But some would say the extraordinarily high price limited patient access to the therapy. One way or the other, the adeno-associated vector carrying the intact copy of the LPL gene wasn't destined to succeed. Uptake was limited, and in 2017, uniqure and its partner Chiesi Pharmaceuticals stopped reporting long-term follow-up data to the European Medicines Agency (EMA), phasing out conditional market approval for the product.

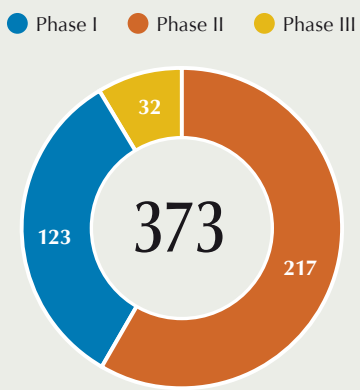
Two years later, four further genuine gene therapies with larger addressable patient populations than Glybera have received market approvals. And with more than 30 gene therapies in registration studies, Big Pharma players are in a stampede to add late-stage gene therapy programmes to pipelines. Among them:

- Roche offered US$4.3bn to acquire Spark Therapeutics, which has a portfolio that includes the US- and EU-approved retinal dystrophy gene therapy Luxturna and an impressive pipeline of further gene therapy products.

"Price is the Achilles heel of precision medicine"

- Pfizer announced it was building a US$500m manufacturing facility to produce AAV-based gene therapies
- Following the US$8.7bn takeover of Avexis, in May Swiss Novartis AG received FDA market approval for Zolgensma, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA). The Swiss pharma giant's treatment price makes it the costliest therapeutic delivery treatment ever: €2.125m per patient. It has further stimulated the debate between payors and developers on what lasting one-shot genetic cures should cost.

Number of gene therapy clinical trials (as of QI/2019)



Source: Alliance for Regenerative Medicine

"It's a single dose which seems to imply life-changing results," says Doug Henderson, Managing Director at the British patient advocacy group SMA UK. If Novartis' promise holds true, that would actually make Zolgensma much cheaper than Biogen's approved first-in-class SMA antisense drug Spinraza, which costs US$750,000 for the first year of treatment and $375,000 for each additional one. "If you look 10 years ahead and compare Spinraza versus a one-time gene therapy, it's a no-brainer what will end up being cheaper over time," stresses Henderson. To achieve the break-even point with Spinraza, a single Zolgensma treatment would need to last 3.6 years. Recently announced results from Novartis' ongoing STRIVE study demonstrate that patients treated with Zolgensma at least remained event-free for a median time of 13.6 months […]

›› **Read the full story in the printed issue.**

Pictures: Shurong Hou, SLAS Discovery, doi: 10.1177/2472555218766842 (left)

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Seeing chances in the global threat

FINANCE INDUSTRY TRANSITION Sustainable financing has become the talk of the town. But are proponents just giving lip service to the idea in an era of record-breaking climate protests? Or even worse – does a cynical industry see nothing more than a new way to cash in? The verdict is still out. But at least some activities appear to be having an impact on banks, insurance providers and other finance industry players.

"Sustainability in other industries such as chemicals and automotive was a popular topic much earlier. The financial industry was hesitant about the sustainable development of its own core business," says Kristina Jeromin, Head of Group Sustainability at Deutsche Börse, a publicly listed marketplace organiser for trading shares based in Frankfurt. "Overall, in the case of financial market products and structures, there is a need to catch up and expand in terms of pricing in all opportunities and risks," she adds. "This means that in the future, all financial products and all services in the industry should not only consider the classic financial key figures of companies, but also the entire value chain – including relevant ESG information."

Three pillars of sustainability

The acronym ESG stands for 'environmental, social and governance', and refers to the three central factors currently used to measure the sustainability and ethical impact of an investment in a company or business. The scoring concept was adopted by large index providers back in the late 1990s. While the term 'ESG' is still used widely, the impact of the underlying system proved limited. A newer sustainability scoring concept – the sustainable development goals (SDGs) – was initiated in 2015, driven by the Division for Sustainable Development Goals in the UN's Department of Economic and Social Affairs. There are 17 such goals, which together represent an urgent call for action by all countries – both developed and developing – in a global partnership.

KRISTINA JEROMIN Head of Group Sustainability Deutsche Börse, Managing Director of Green & Sustainable Finance Cluster Germany

? How can the finance industry help in the transition to a more sustainable society?

! *Politics alone won't be able to direct this transition. All stakeholders – including scientists, consumers, the producing economy and also financial market players – will have to contribute. It's the central responsibility of the finance sector to shape this transformation process together with the producing economy through smart financing.*

"Sustainable finance for me is a broad transformation of the whole financial market," explains Jeromin. "We are seeing more and more investors who want to invest in a very impact-oriented way. For example, they might want to invest specifically in a company that is targeting SDG 7 – 'Affordable and Clean Energy'." The logic is straightforward. For long-term investors like pension funds, analysing corporate sustainability leads to a better understanding of a company's quality of management and future performance potential. This in turn enables investors to identify investment opportunities that can generate long-term shareholder value. Speaking with EUROPEAN BIOTECHNOLOGY, Jeromin sums it up: "Sustainable finance is about minimising risks and making value chains transparent."

The EU takes action

The biggest challenge is to define what businesses and activities help in striving to reach a specific SDG. The EU has sought to address this by setting up a 'taxonomy' for sustainable activities. This taxonomy is part of the EU Action Plan for Sustainable Finance, which was launched in 2018 to ensure the EU complies with targets laid out in the Paris Climate Agreement […]

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Pictures: lassedesignen/stock.adobe.com (left); Deutsche Börse (right)

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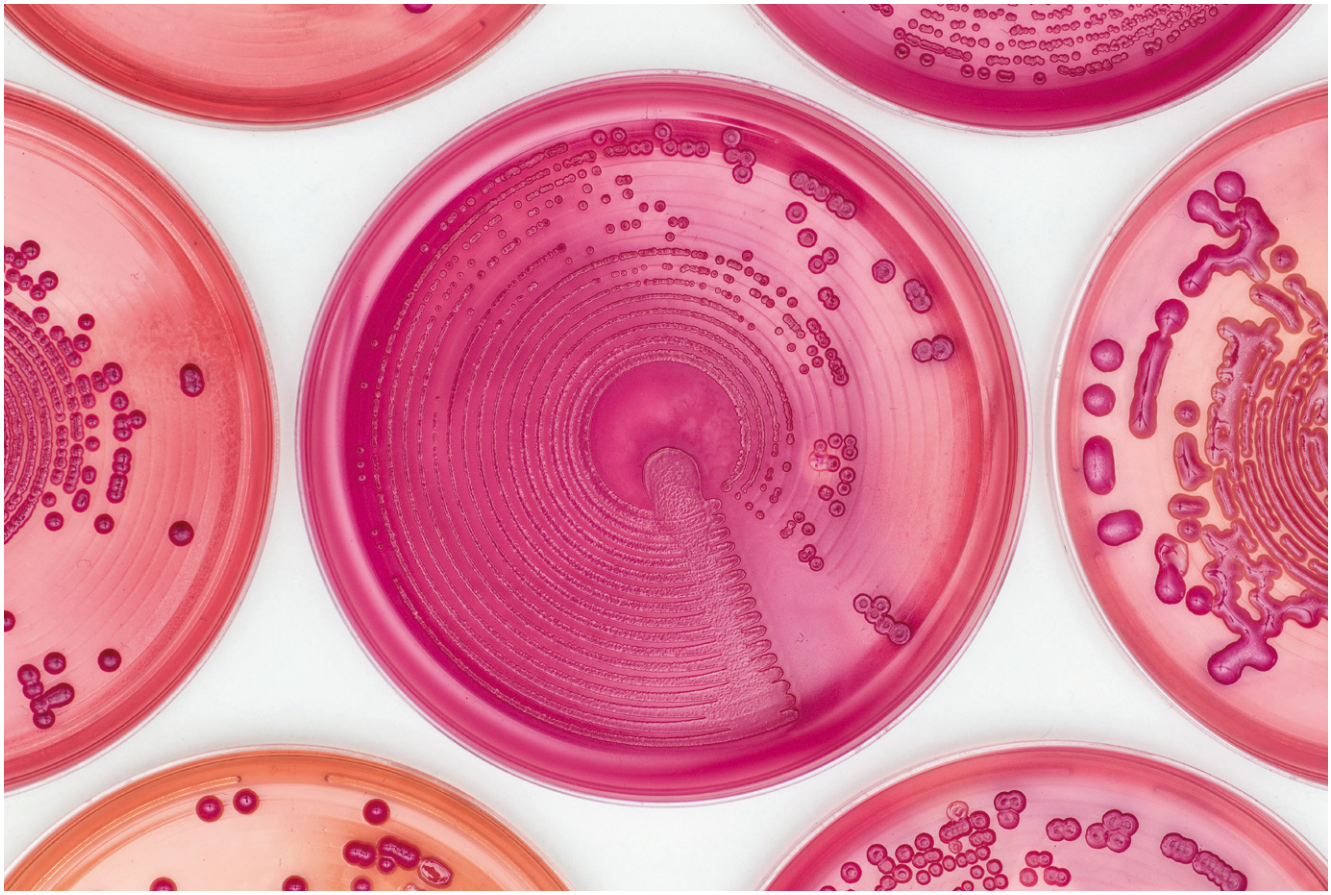

The AMR business

ANTIMICROBIAL RESISTANCE Companies active in the development of novel antibiotics struggle with uncertain market conditions, weak reimbursement schemes and low turnover once a drug is approved. Everyone is worried about becoming the next Achaogen – a company that brought a product to the market, but was forced into bankcruptcy despite that success. Experts around the globe are still trying to figure out the best way to balance push and pull incentives. Meanwhile in Europe, a major AMR accelerator initiative has kicked off.

Pictures: Daniela Beckmann

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The threat of antibiotic resistance is as great as that posed by climate change – a warning repeated by Dame Sally Davies several times this summer. In September, she stepped down as England's Chief Medical Officer after serving in the role for nine years. But by nominating her as a special envoy for AMR – a role she will take on alongside her official new job as Master of Trinity College in Cambridge – the UK has reaffirmed its desire to play a key role in high-level international fora and debates, and to keep pushing to further political commitments.

This is underpinned by the fact that NICE and NHS England are set to explore a 'de-linkage' style innovation model for antibiotic reimbursement. To that end, the NHS announced a trial in July 2019 for a subscription-style model that will pay pharmaceutical companies up front for access to effective antibiotics. The step makes the UK the only European country to be currently pushing actively for a solution to the widely discussed problem of market failure in the field of AMR.

Some recent developments in the US have provided further hope. Recently, the country's Centers for Medicare and Medicaid Services (CMS) launched policies aimed at providing incentives for hospitals to use newer, more expensive, more effective and less toxic antibiotics for the treatment of infections caused by resistant pathogens. The CMS is taking a two-pronged approach. Hospitals can now apply to receive reimbursement of 75% of a drug's cost beyond the usual diagnostic related group (DRG) reimbursement. The previous reimbursement allowed under their New Technology Add-on Payment (NTAP) programme was just 50%. "The new payment rule on antibiotics is a clear acknowledgement by Medicare that economics have stood in the way of appropriate use of new antibiotics in US hospitals," comments Kevin Outterson, Executive Director of the international accelerator CARB-X. "The Administrator of Medicare, Seema Verma, made this clear in her article in Health Affairs on 2 August, the same day the final rule was published." He also adds that "the new rule takes several helpful steps that became effective on 1 October 2019, but the most important work is left to next year's rule – to create something akin to a carve-out for QIDP antibiotics from the hospital DRG." In addition, the US Senate might release a new act called DISARM. The bill currently under consideration in the US Congress would allow 100% reimbursement for drug charges arising from treatments of resistant infections. According to Outterson, "the proposed DISARM Act has similar goals to the Medicare initiative; we need one of these as soon as possible to stabilise the market while work continues on a longer-term solution like a Market Entry Reward."

However, experts in the field remain uncertain whether these new reimbursement changes will really make a scalable difference to bottom lines at companies. At the ASM-ESCMID conference, which took place in early September in Boston, some of the 400 AMR experts were in favour of the model having at least one more pull parameter in the system. Others, however, were uncertain, saying that due to low resistance rates in US hospitals, many haven't even considered it necessary to keep stocks of novel antibiotics. In view of the hot debates surrounding various aspects of drug pricing and the expense of pharmaceuticals in the US, it's not clear yet whether policymakers there will be able to push through a bill leading to higher reimbursement for antibiotics.

Picture: CARB-X

KEVIN OUTTERSON **Executive Director, international accelerator CARB-X**

? Will the DISARM Act provide substantial support for companies active in AMR?

! *"The proposed DISARM Act has goals similar to the US Medicare initiative. We need one of these as soon as possible to stabilise the market while work continues on a longer-term solution like a Market Entry Reward."*

International campaigns and demands for a robust AMR policy

Despite the quagmire, lobbying groups are pushing hard, and one broad global coalition of AMR stakeholders has sent policymakers a sign that action is urgently needed. On 23 September, US Department of Health and Human Services (HHS) Secretary Alex Azar announced during the 74th United Nations General Assembly in New York that since its inception a year ago, the US government's Antimicrobial Resistance (AMR) Challenge has received nearly 350 commitments from 33 countries to implement specific actions to combat AMR. Global commitments have come from pharmaceutical, biotech and health insurance companies, the food industry, medical professionals, healthcare systems, government health officials, NGOs and others. The AMR Challenge "marks a historic step, and sets a promising precedent," Azar said at an event co-hosted by the Bill and Melinda Gates Foundation, the British Wellcome Trust, the American Society for Microbiology, the Antimicrobial Resistance Fighter Coalition, and the Centers for Disease Control and Prevention (CDC) Foundation. Azar also announced a second Antibiotic Resistance Threats report aimed at "giving us a clear picture of the significant work that is still needed to prevent resistant infections and stop the spread of germs."

In addition to this more general political alliance, over 70 public and private AMR stakeholders have also joined forces in the campaign "Working To Fight AMR" to specifically advocate for short-term reimbursement change and pull […]

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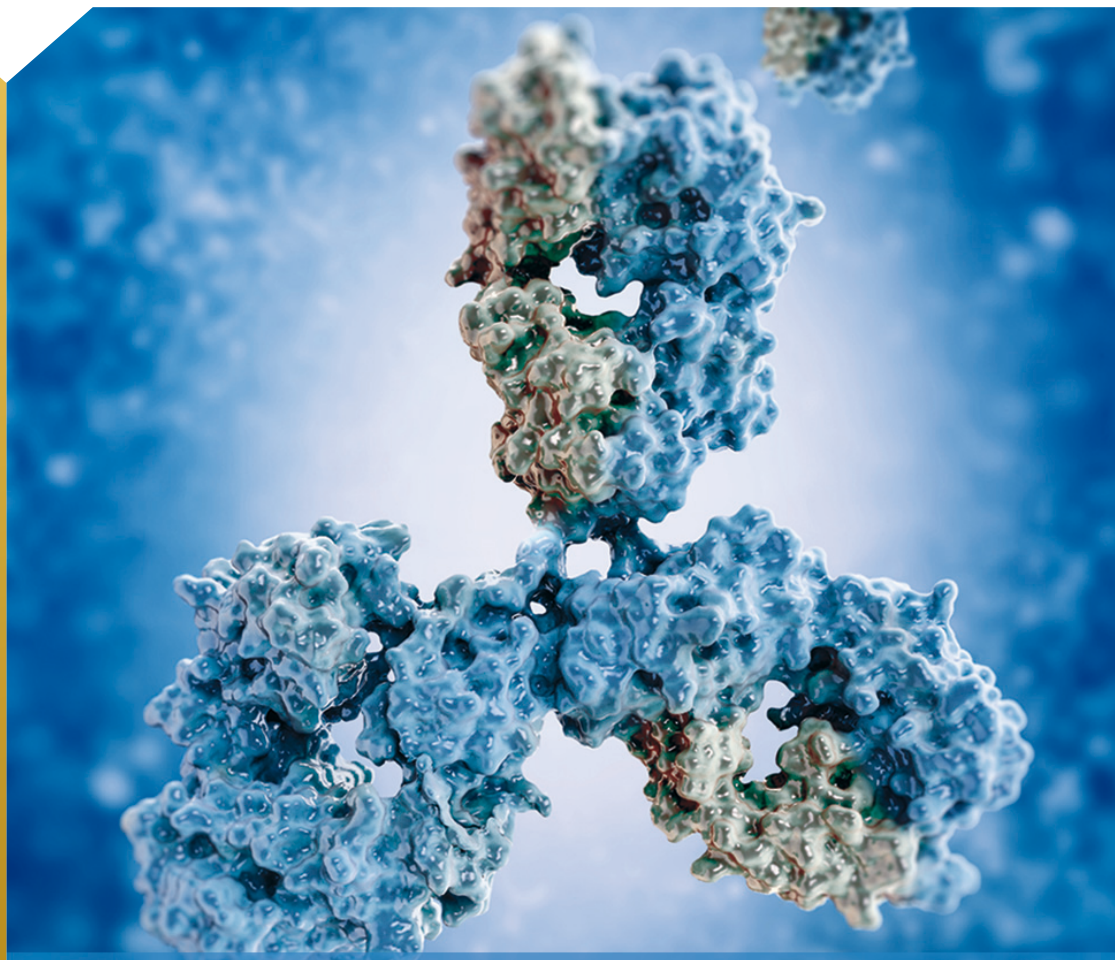

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