pharmaphorum deepdive

# Changing steps:

## Rewriting the rules of the biologics patent dance

*With several blockbuster biologics set to lose exclusivity in the US by 2030, biosimilars are preparing to make their move. But, in order to make it to market, they must first master the complex choreography of "the patent dance"*

April 2024: Market Access

*Rare diseases: the urgent need for health equity and accelerated access*

*Overcoming AMR market failure: Three start-up stories*

*Integrating market access considerations into biopharmaceutical asset investment decisions*

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# **Deep Dive:** Market Access 2024

Against a backdrop of escalating healthcare costs and resource constraints, ensuring patient access to vital medicines is an uphill battle for pharma companies. From navigating complex regulatory landscapes and reimbursement policies to overcoming market exclusivity hurdles, successfully overcoming the myriad obstacles encountered on the path to market and beyond is both a science and an art.

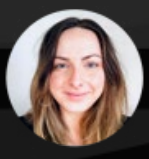
But, as this issue's contributors illustrate, the industry does not shy away from a challenge.

With multiple big-name biologics nearing the precipice of a steep patent cliff, pioneers in biosimilars are primed to take a slice of the market, bringing hope for more affordable medication options in the US. But, patients may have to wait to access those competitor products. In this issue, delve into the high-stakes patent games drugmakers play to extend exclusivity windows.

Elsewhere in this issue, Alexion discusses the urgent need for accelerated access programmes for rare disease treatments, Putnam (part of Inizio Advisory) explores common pain points and best practices in integrating market access considerations into investment decisions, and in a double feature, pharmaphorum's Jonah Comstock and Nicole Raleigh dive into the world of AMR.

Plus, we find out what is driving ongoing ADHD drug shortages and experts on the floor at Reuters Pharma US share their views on improving access to affordable therapeutics.

For all this and more, read on.



Eloise

***Eloise McLennan – editor, Deep Dive***

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# Chasing the holy grail of value-based healthcare

**Patients, healthcare professionals, payers, and other stakeholders can have vastly different views on the value of a particular product, often resulting in a struggle between prioritising access to innovation and optimising costs. Addressing the ramifications associated with misaligned incentives in the fee-for-service payment model has been a driving force in the pursuit of value-based care.**

The goal? Strike a balance – ensure patients can access medicines, maintain a sustainable healthcare system, and foster a robust pipeline of innovation that continuously improves treatment options. It's a delicate dance, where pricing signals guide innovators on where to focus their R&D efforts, shaping the overall investment in healthcare and the expected value of future innovations.

Whereas the traditional fee-for-service model reimburses healthcare providers based solely on the volume of services delivered, value-based care is all about aligning prices with the value a new medicine brings to patients, healthcare systems, and society, compared to the current standard of care. This approach rewards innovation appropriately, prioritises access to the most valuable innovations, and aligns price signals with patient and citizen priorities, maximising the expected value of innovation for a given level of investment.

## 1900s Dr Codman vs. the golden goose

**While the term "value-based care" is relatively new, its spirit can be traced back to the early 1900s and the pioneering work of Ernest A Codman, widely known as the "father of outcome management".**

Born in Massachusetts in 1869, Codman, a respected clinician and surgeon, believed that medical work was a craft that could be continuously honed and enhanced over time. As such, he made it his mission to systematically follow up with his patients after treatment, meticulously recording their outcomes. By analysing errors and linking them to outcomes, he aimed to prevent similar mistakes in the future, asserting that "every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire, 'If not, why not?'"

*Pictured: Dr Ernest Codman as a young man. Credit: Public domain, via Wikimedia Commons*

Frustrated by his colleagues' resistance to adopting his tracking measures, Codman resigned from Massachusetts General Hospital in 1911 and established the 'End Results Hospital', where he could fully embrace his pioneering, data-driven approach. At this new facility, he meticulously collected and analysed patient outcome data – a concept he had developed at MGH – and took the groundbreaking step of transparently sharing these findings with patients and publicly publishing the results. The core focus was rigorously evaluating care delivery and openly communicating outcomes, laying the foundation for what is now known as evidence-based medicine.

Unfortunately, Codman's tenacity for progress was somewhat marred by the more provocative and incendiary methods he adopted in pursuit of his goals. This side of his personality was put on full display when, while hosting a medical meeting in Boston in 1915, he unfurled a 6-foot-tall cartoon of a golden goose with its head buried in the sand, satirising what he saw as his colleagues' apathy toward healthcare reform.

Unsurprisingly, Codman's blunt delivery ruffled many feathers in the medical community, resulting in his dismissal from the Massachusetts General Hospital and Harvard Medical School faculty position. Despite initial resistance, his relentless pursuit of outcome tracking and quality improvement laid the groundwork for the value-based care movement we see today. His "End Results System" embodied the common-sense notion that hospitals should follow up on patients to determine treatment success and learn from failures, paving the way for a more accountable and data-driven approach to healthcare delivery.

# 1960s

# Medicare & Medicaid: A new way to pay

**In the mid-20th century, a seminal framework emerged that would profoundly shape the way quality of care is evaluated and understood. In 1966, Lebanese physician and healthcare administrator Avedis Donabedian first described the three elements of what would become known as the Donabedian Model in his article "Evaluating the Quality of Medical Care".**

Donabedian's model proposed that quality of care could be assessed through three interdependent dimensions: structure, process, and outcome. Structure refers to the attributes of the settings in which care is delivered, including material resources, human resources, and organisational structure. Process denotes the activities involved in delivering care, encompassing both technical and interpersonal aspects. Outcome represents the effects of care on the health status of patients and populations.

His groundbreaking work emphasised that these three dimensions should not be mistaken for attributes of quality themselves; rather, they serve as classifications for the types of information that can be obtained to infer whether the quality of care is poor, fair, or good.

*Pictured: US President Lyndon Johnson signing Medicare bill. July 1965. Credit: White House Press Office. Public domain, via Wikimedia Commons*

Over in the US, another landmark change was in motion with the with the establishment of Medicare and Medicaid in 1965. These landmark programmes, introduced under President Lyndon B Johnson's administration, aimed to provide comprehensive health insurance to the nation's elderly and low-income populations, addressing longstanding disparities in the nation's healthcare system, and paving the way for further reforms in the decades to come.

## 1970s New models emerge

**Of course, identifying the best quality treatment for patients is just one piece of the puzzle; to have an impact, a patient has to actually be able to access the medication. By the 1970s, the dilemma of balancing innovation and cost seen in pay-for-service models had become clear.**

As part of efforts to address the mounting cost of medicines, countries like the United Kingdom and the Netherlands began experimenting with alternative payment models that moved away from pure fee-for-service. The UK introduced the Resource Allocation Working Party (RAWP) formula, which adjusted capitation payments (determined by the number of patients served) to general practices based on population health needs. Meanwhile, the Netherlands explored integrated primary care models like the Transmural Care Model, which aimed to improve coordination between primary, secondary, and community-based services.

In the US, paediatrician and healthcare reformer Dr Paul Ellwood coined the term Health Maintenance Organisation (HMO). Dr Ellwood saw HMOs as non-profit organisations offering comprehensive care within a designated provider network in exchange for fixed annual payments. Dr Ellwod envisioned cost containment primarily via preventive medicine, including annual exams, screenings, and immunisations.

The Health Maintenance Organisation (HMO) Act of 1973 Based on Dr Elwood's ideas, this legislation created a Federal assistance programme supporting the establishment and expansion of HMOs operating under a capitation model.

# 1980/90 The Dartmouth Atlas

**John Wennberg was an obscure clinical investigator when he began his research at Dartmouth Medical School in the late 1960s. Having noticed a significant variation in tonsillectomy rates between two neighbouring towns, Wennberg embarked on a path that would form the basis of his research for years to come. Wennberg's research resulted in his being named the founding director of The Dartmouth Institute for Health Policy and Clinical Practice (then the Center for Evaluative and Clinical Sciences) in 1988.**


*Pictured: Political campaigning for President Bill Clinton. Credit: Public domain, via Wikimedia Commons*

Following the election of Bill Clinton in 1992, expectations of healthcare reform were growing. That year, healthcare costs had risen to $838 billion (approximately $3,000 per person), with millions of uninsured Americans unable to afford premium costs. Recognising the opportunity, Wennberg and his research team quickly got to work, using historical Medicare data to create the Dartmouth Atlas of Health Care, which meticulously mapped and analysed the variations in care delivery patterns across different regions and healthcare systems. Published in 1996, the insights gleaned from the Atlas catalysed a national dialogue on the pressing need to redirect the healthcare system towards a value-driven model, one that incentivises providers to deliver high-quality, cost-effective care tailored to individual patient needs.

Subsequent iterations of the Dartmouth Atlas of Healthcare continued to build upon Wennberg's pioneering efforts.

# 2000s A moniker for change

**The start of a new millennium ushered in a period of significant progress for value-based care, particularly in the UK.**

In 2004, the UK's National Health Service (NHS) implemented the Quality and Outcomes Framework (QOF), the world's largest healthcare pay-for-performance scheme at the time. The QOF rewarded general practitioners based on their performance across a comprehensive set of clinical and organisational indicators spanning chronic disease management, patient experience, and practice infrastructure. This value-based payment model aimed to enhance quality and outcomes in primary care. By linking a significant portion of practice income to meeting evidence-based targets, the QOF drove improvements in areas like blood pressure control and clinical data recording. However, it also faced criticisms regarding potential unintended consequences.

Two years later, the movement would be given its official title, "value-based care", a term coined by American researchers Michael Porter and Elizabeth Olmsted Teisberg in their 2006 book "Redefining Healthcare". Building on the same concepts established by pioneers, such as Codman and Wennberg, the authors set out to argue for a healthcare system that prioritised value to patients over volume of sales.

Back across the Atlantic, the National Institute for Health and Clinical Excellence (NICE) was laying the groundwork for a landmark move that would showcase key elements of Porter and Teisberg's proposal. In 2007, the organisation accepted a proposal for a new type of scheme to provide patients with access to Millennium Pharmaceutical and Janssen Cilag's previously rejected cancer drug Velcade. Under the deal, the NHS would only have to pay for patients who benefitted from Velcade (priced at around $48,000 per patient). Any money spent on individuals whose tumours did not shrink sufficiently would be refunded by Johnson & Johnson.

# 2010s Controversy and COVID-19

**The 2014 launch of revolutionary Hepatitis C drugs like Sovaldi and Harvoni brought value-based pricing discussions into the spotlight. These highly effective treatments came with eye-watering price tags – in the US, Sovaldi cost $84,000 for a 12-week regimen, while Harvoni was priced at $94,500. Amid intense public backlash, a fierce debate raged as payers and policymakers questioned whether the drugs' clinical value justified the immense budgetary impact on already strained healthcare systems.**

This furore highlighted the complex interplay between clinical value, budget impact, and affordability in value-based pricing models. While the drugs offered superior cure rates and long-term cost savings, their high upfront costs strained payer budgets and limited patient access.

One year later, debates around how to balance innovation with affordability sparked once again in the US when, in 2015, the American Society of Clinical Oncology (ASCO) introduced its Value Framework, a tool designed to provide a standardised approach to assess the value of cancer drugs based on clinical benefit, side effects, and cost. The framework quantified clinical benefits using measures such as survival rates and disease response. It then weighed this against toxicity and treatment costs to calculate a net health benefit score, which could be used to guide treatment decisions.

However, the framework faced criticism for oversimplifying the complexities of patient preferences and quality of life factors. Detractors argued that quantifying elements like personal utilities and risk tolerance was highly subjective. There were also concerns about the framework's impact on access if payers used it to restrict coverage.

Value-based care initiatives continued to proliferate globally throughout the decade. However, as healthcare systems grappled with the practical implementation of these models, bogged down by challenges – such as segmenting patient populations, establishing standardised outcome measures, deploying the necessary technology infrastructure for data collection, and facilitating the exchange of best practices at scale – it all seemed overwhelming and overly complex.

The arrival of the COVID-19 pandemic swiftly changed this stagnant status quo. Driven by necessity, healthcare systems quickly began to define centralised goals that focused on the outcomes that mattered most to patients. Navigating the urgency of such an unprecedented landscape highlighted the necessity for agile, outcome-driven healthcare delivery, breaking down silos and fostering an environment of cross-sector collaboration. By aligning around patient-centred goals, stakeholders could streamline processes, leverage collective expertise, and drive meaningful progress towards implementing value-based care models at scale.

## 2020 Post-pandemic progress

**Kicking off a new decade, albeit amid an international pandemic, 2020 marked a pivotal moment for value-based pricing initiatives across the globe. The World Health Organization (WHO) introduced pricing guidelines to enhance medicine affordability, highlighting value-based pricing as a critical strategy. Simultaneously, the Centers for Medicare & Medicaid Services (CMS) proposed a rule allowing Medicaid to adopt innovative payment models for promising, curative therapies, while ensuring long-term sustainability.**

As the momentum built, China took significant strides towards value-based pricing in 2021 when the National Health Commission (NHC) issued guidelines to standardise the evaluation process for new essential medicines at national and provincial levels.

In 2022, the UK witnessed an innovative agreement between Shionogi and NHS England, implementing a subscription payment model for Fetcroja (cefiderocol). This arrangement saw Shionogi receive a fixed payment based on the drug's assessed value to the NHS, decoupling reimbursement from usage volume.

Concurrently, Dubai's Dubai Health Authority (DHA) launched the "EJADAH" programme, restructuring healthcare around value-based principles, rather than volume-based metrics. Japan's Pharmaceutical Manufacturers Association (JPMA) also proposed a value-based pricing system for innovative drugs, with provisions against price reductions during patent protection unless clinical or scientific value changed post-market entry.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) introduced the "Equity-Based Tiered Pricing" framework, extending upon value-based pricing principles. This framework allows countries to negotiate confidential value-based prices reflecting individual value assessments, with a "best price rule", ensuring lower prices for less affluent EU nations.

More recently, in 2023, France's Social Security Finance Act established a legal framework for funding Advanced Therapy Medicinal Products (ATMPs) with a specific focus on value-based pricing, allowing for outcome-based pricing and staggered payments. Sweden's TLV also proposed updates considering high and low volumes when assessing reasonable costs for value-based pharmaceutical pricing.

It's been a long journey to get to this point. However, the progress of recent global initiatives underscores the growing recognition of value-based pricing as a means to enhance access, affordability, and sustainability, while rewarding innovation aligned with patient and system priorities.

## About the author

Eloise McLennan is the editor for pharmaphorum's Deep Dive magazine. She has been a journalist and editor in the healthcare field for more than five years and has worked at several leading publications in the UK.

Additional reporting provided by Navlin Daily.

ALEXION
AstraZeneca Rare Disease

# **Rare diseases:** the urgent need for health equity and accelerated access

**Rare diseases are complex, but the need is urgent. Alexion's Eunice Alvazzi discusses the shared responsibility in achieving access to innovation in rare diseases**

An estimated 400 million people globally are affected by rare diseases. While each condition individually may be rare, in Europe alone, there are approximately 36 million people living with a rare disease. Rare diseases are often severe, progressive and life-threatening, and the path to diagnosis can be lengthy and convoluted. The limited medical and scientific knowledge about individual rare diseases and limited access to specialist care pose unique challenges to healthcare professionals and health systems, creating considerable health inequity for rare disease patients.

Once a diagnosis has been ascertained, people living with a rare disease continue to face barriers to care; of the estimated 10,000 rare diseases, more than 90% currently have no meaningful treatment options. Even when an appropriate treatment exists, access isn't guaranteed. There are significant disparities between EU countries in how quickly patients can access innovative orphan medicines, and across the globe, people living with rare diseases face challenges navigating access in countries where there is no rare disease infrastructure and access has not previously existed for rare disease medicines.

One way to begin to address these disparities is to ensure that there is strong data and evidence demonstrating the clinical and economic value of the medicine for rare disease patients and the health care system.

# Traditional value assessments fuel health inequity

**National healthcare systems and value assessment processes for rare diseases need to evolve to address the disparities – and, therefore, inequities – in how quickly patients can access innovative rare disease medicines.**

To overcome access challenges, the complexities of rare diseases must be taken into consideration. For example, while the UK Rare Disease Framework established in 2021 emphasises the importance of enhancing access for patients with rare diseases, progress in patient access has been limited due to a lack of updates to the value assessment framework for rare diseases medicines.

One of the factors driving inequity is that traditional value assessments do not comprehensively capture the full impact on the quality of life for people living with complex rare conditions and their carers. An openness to embracing novel approaches and actively involving patients is required to accelerate access to rare disease medicines.

# Developing compelling evidence on the burden of rare disease

**Rare diseases impose a high social and economic burden for patients and their families, health care systems and society overall, yet demonstrating this can be difficult and there is a scarcity of cost of illness (COI) studies. The main issue to address in the COI analysis of rare diseases is the lack of primary and/or aggregated data, making it challenging to estimate the economic burden.**

For example, evidence may be limited to only the patient and fail to account for the broader impact on the quality of life of parents caring for a gravely ill or disabled child throughout their life – or adequately represent the financial burden of rare diseases on families and wider society.

Markers of disease progression may also be unidentified or unmapped, making arguments for time-critical intervention difficult to evidence.

Many agencies responsible for assessing the quality and efficacy of medical treatments are now actively seeking inclusion of patient-reported outcomes data in health technology assessment (HTA) submissions, including burden of disease data that could better inform decision-making by presenting a more complete picture of the impact of a rare disease. Thus, it is especially important for industry and clinical trial investigators to actively seek out and respond to patient feedback on meaningful outcomes and incorporate novel clinical trial endpoints that can be used to develop cost-effectiveness arguments.

## Increasing patient participation in evidence development

**With rare diseases being inherently unique and not well understood, conducting clinical research in these areas is often complex, particularly with small patient population sizes. Establishing meaningful clinical endpoints also may be problematic due to the nature of evidence that it is possible and ethical to produce.**

Successful approaches often involve working closely with regulatory decision makers at an early stage to define and establish novel outcome measures that patients have identified as uniquely meaningful to them. Collecting real-world evidence from registries can also provide new and complementary information for regulatory submissions, as well as generating the long-term data required as part of post-marketing surveillance.

Additionally, new digital technologies are increasingly being employed to generate compelling outcome data and include the patient voice. For example, Alexion was one of the first companies to use video evidence of patients in regulatory submissions to demonstrate the impact of an outcome measure for a rare metabolic disease – an approach that is now considered standard practice.

# Partnering to improve access to medicines

**Given the acknowledged challenges in accelerating access to innovation in rare disease, as a global rare disease community, we must together champion equitable access for all. It is incumbent on all stakeholders working in this complex area to proactively identify and work to remove access barriers at local and regional levels and to build the capabilities of healthcare systems across the world to best serve the significant unmet needs of people living with rare diseases.**

Achieving access to medicines is at one end of the journey – but creating a favourable environment for innovation to flourish is the essential starting point. The European Orphan Medicinal Products (OMP) regulation was introduced to address the lack of R&D and subsequent lack of treatments for rare diseases. After two decades, it is appropriate to review the framework, but the proposed update of the OMP regulation could unravel the innovation incentives that the original regulation helped create. The rare disease community needs policies that encourage steps forward, not back.

The best possible chance of improving access to innovation for rare disease patients is through partnership. As an industry, we must continue to invest in innovations and forge new collaborations to improve accessibility to treatments and solve affordability challenges together with payers. We must proactively engage in dialogue with access decision makers, sharing our perspectives, identifying the challenges and then problem solving and forging unified commitments together. People living with a rare disease deserve health equity – and it is our shared responsibility to make this happen today and for future generations.

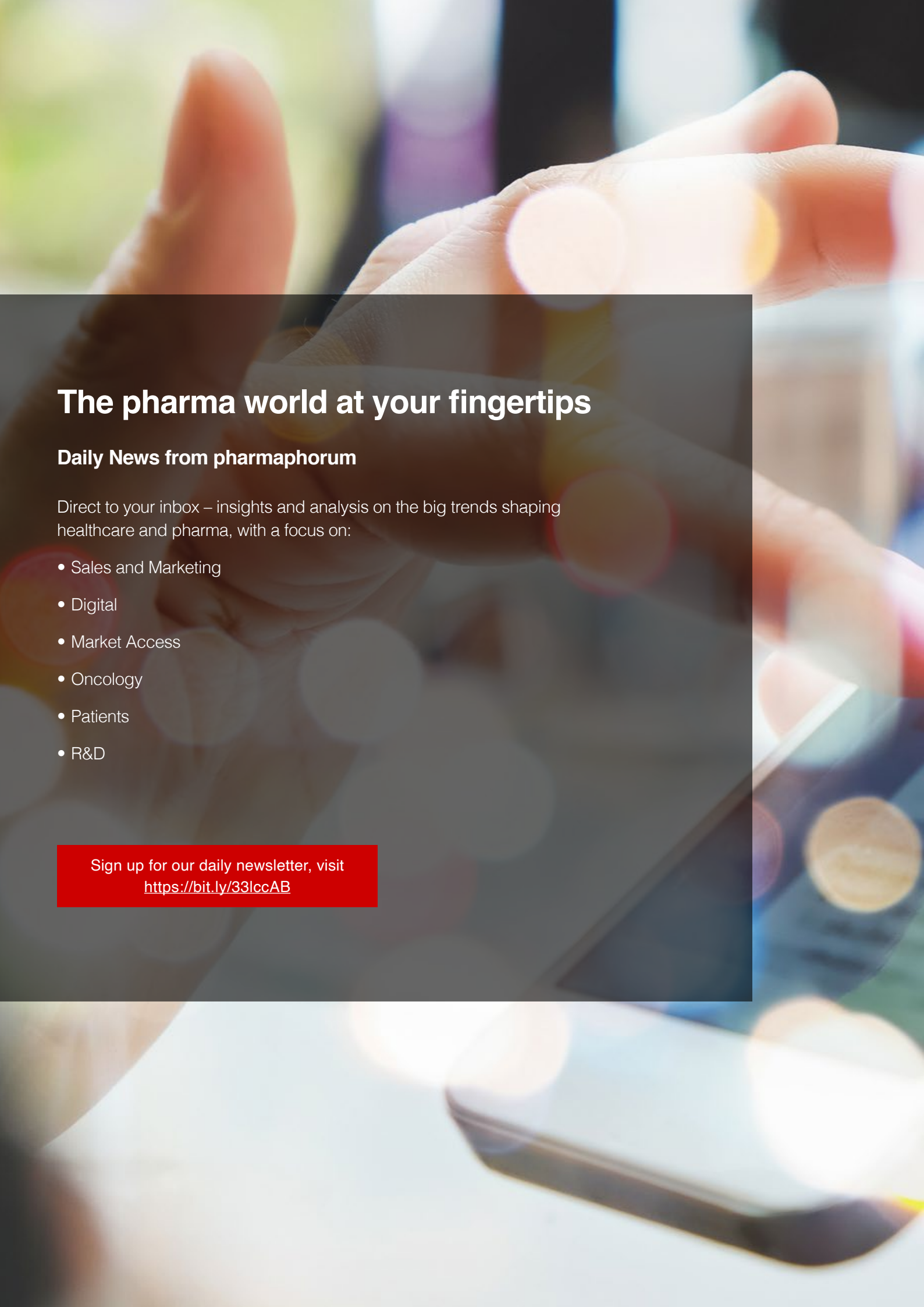
## About the author

Eunice Alvazzi is the global head of haematology, nephrology, and neurology value and pricing at Alexion, AstraZeneca Rare Disease, a global biopharmaceutical company focused on developing life-changing therapies for people living with rare diseases. She is passionate about advancing patient access for rare disease patients.

# About Alexion

Alexion, AstraZeneca Rare Disease, is the group within AstraZeneca focused on rare diseases, created following the 2021 acquisition of Alexion Pharmaceuticals, Inc. As a leader in rare diseases for more than 30 years, Alexion is focused on serving patients and families affected by rare diseases and devastating conditions through the discovery, development, and commercialisation of life-changing medicines.

Alexion focuses its research efforts on novel molecules and targets in the complement cascade and its development efforts on haematology, nephrology, neurology, metabolic disorders, cardiology, and ophthalmology. Headquartered in Boston, Massachusetts, Alexion has offices around the globe and serves patients in more than 50 countries. For more information, please visit www.alexion.com.



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# The biosimilars dance:
## How drugmakers game the US patent system

**When the primary patent on a blockbuster drug expires, affordable generic or biosimilar competition is expected to balance the market, offering relief to patients who could not afford the high price tag associated with the brand-name drug.**

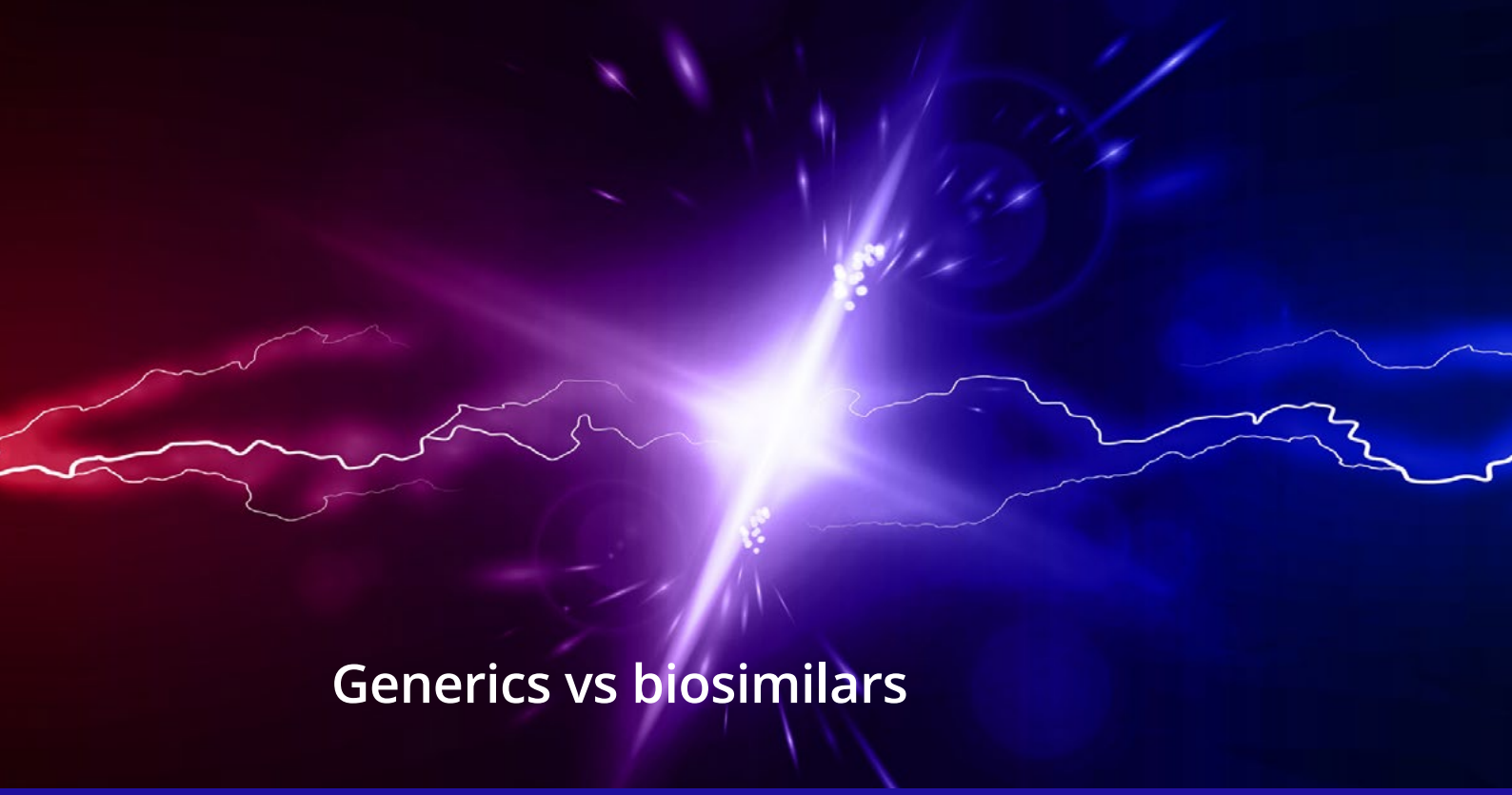
However, in reality, this is not always the case.

Major pharma companies use an extensive array of legal manoeuvres to keep competition at bay for years, if not decades, after the first licensure expires. These “patent games” come in many forms, each contributing to the stunted growth seen in the US biosimilars market, compared to its international counterparts.

According to The Initiative for Medicines, Access & Knowledge (I-MAK), three drugs – Humira, Eliquis, and Enbrel – launched in Europe an average of 7.7 years before their belated US entries, costing American patients an estimated $167 billion during that competition gap.

While generics manufacturers are well prepared to navigate the challenges involved in getting copycat drugs from approval to patients, in the growing biologics space, the path to market is far more complicated for biosimilars.

As more blockbuster biologics start facing patent expirations, Pharma’s efforts to protect their exclusive pricing power are coming under heightened scrutiny.



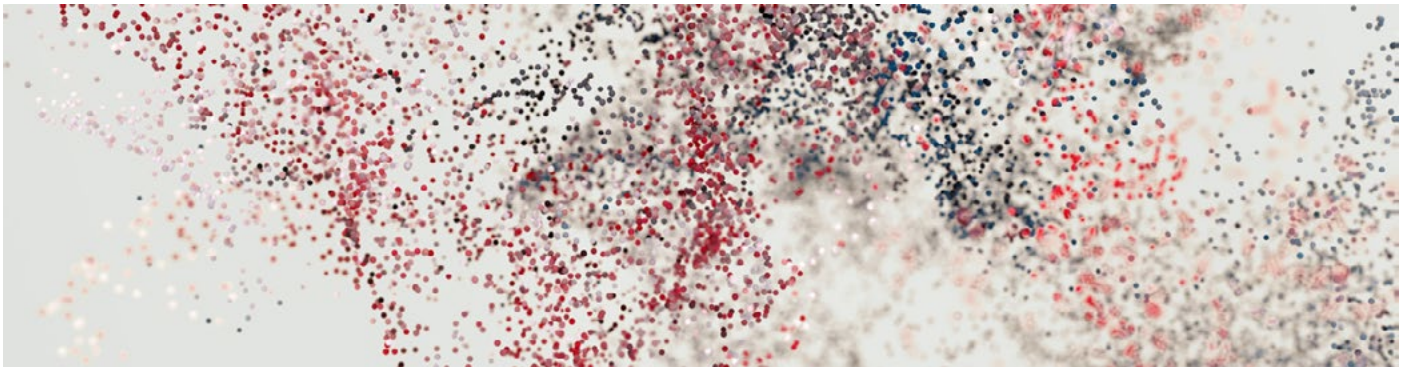
# Generics vs biosimilars

**When the first biosimilar therapeutic launched in the US back in 2015, the news was heralded as the start of a tectonic shift in pharma. Albeit the decision came almost a decade after the European Medicines Agency approved the first biosimilar in Europe, the news of a "generic" copy of Amgen's cancer drug Neupogen (filgrastim) paved the way for an entire class of costly drugs to enter the US market.**

Yet, despite being touted as cost-effective alternatives to biologic drugs, biosimilars have faced significant challenges in gaining market share in subsequent years. According to Goldberg Distinguished Professor of Law, and Director of the Center for Innovation at the UC Law San Francisco, Professor Robin Feldman, a decade after the Biosimilars Act, only 18 biosimilars corresponding to seven biologic drugs had entered the US market as of 2020. Even by 2023, just 27 biosimilars for 11 biologics had launched.

UK leader of Pharma and Life Sciences at PwC, Stephen Aherne, highlights that biologics, including advanced therapies like cell and gene therapies, now make up nearly 50% of the drug development pipeline. In fact, many of today's blockbuster drugs, including Merck's Keytruda and BMS' Opdivo, are biologics. However, whereas generic drugs for small molecule therapeutics are a ubiquitous part of the industry, for biologics, the emergence of non-brand name options has been dramatically slower.

There are many reasons for this disparity. Primarily, there are stringent regulatory requirements for biosimilars. Unlike small molecules, which are clinically like-for-like replicas of a brand-name drug, biosimilars (once known as bio-generics) cannot be exact replicas due to their large, intricate molecular structure and manufacturing variations. "They are never exactly the same," explains Aherne.



Consequently, biosimilars must demonstrate that their product is "highly similar without meaningful clinical differences," says Feldman; however this requires clinical trials and development, which, according to Pfizer, "may take five to nine years and cost more than $100 million, not including regulatory fees." Compare these numbers to generics, which take approximately two years to develop and cost between $1-2 million, and you begin to see the problem.

Further complicating biosimilar adoption is the "interchangeable" subcategory requiring switching studies to prove alternating use doesn't diminish efficacy or increase risk.

"With US generics, the pharmacist can substitute for a prescription that has the brand without contacting the doctor," explains Feldman. "With biosimilars, the pharmacist can only substitute without contacting the doctor for the subcategory of interchangeables. Even then, only if there's a state law permitting it."

At the time of writing, only seven US biosimilars have achieved this holy grail of interchangeable status.

Ultimately, Feldman laments the "deeply disappointing" market penetration and price reductions for biosimilars, describing it as "more of a trickle than a waterfall."

# The biologics patent dance

**In the US, biologics are granted a 12-year period of exclusivity from the date of first licensure. On paper, that sounds like a long time. This exclusivity is crucial, as it compensates for the extensive costs and risks associated with the development of biologics; however, when you account for the time needed to develop the drug after the initial discovery, which can be upwards of 10 years, by the time the product reaches patients, the exclusivity period can be nearing its end.**

But as many pharma companies have discovered, there are ways to game the system to extend exclusivity beyond a product's initial protection term. Key strategies include "evergreening", which Feldman defines as "artificially extending the period of monopoly from the core patent rights", and "patent thicketing", which involves accumulating secondary patents to artificially extend the monopoly period of time on aspects such as dosage forms, manufacturing methods, or minor molecular modifications, elements that can make a big difference in biologics.

In the biologics space, companies have been known to file for hundreds of patents on a biologic drug, with large swathes of such patents filed after the drug has been approved. I-MAK argued in a 2023 report titled "Overpatented, Overpriced", that patenting activity today "extends well beyond the time-limited monopoly intended by the Constitution", with drugmakers filing more than 140 patent applications on average per drug.

"Patent thickets can also serve to deter potential competitors from even developing a competing version of a patent product if they feel the patent barriers are too difficult to navigate. In both cases, competition is affected and consumers end up paying higher prices for longer during the branded drugmaker's extended market monopoly," explains I-MAK founder and CEO, Tahir Amin.

Even if a company can afford the costs and resources needed to develop and market a biosimilar, it first must navigate a minefield of dispute resolution in a process known as the patent dance.

"At the heart of the biosimilar entry process is the patent dance," says Feldman. "With the patent dance, the brand and the biosimilar follow an intricate structured set of steps to exchange information about patent rights that the brand could assert against the biosimilar.

"If a biosimilar company wants to enter the market, it has to answer four simple questions. What's the drug? How do you make it? What patents apply? When do those patents expire?" Feldman explains. "These should be relatively simple to answer under the current system. They're not."

The challenge is that the brand does not have to publish patent information until after a biosimilar has requested approval, and it doesn't have to submit information unless the parties reach certain stages in the processes. As a result, Feldman explains, companies face an information desert where, "the biosimilar company has to enter in the dark, in terms of patent rights."

# Cushioning the fall

**From a business perspective, it makes a lot of sense for pharma companies to employ aggressive legal tactics to extend exclusivity for as long as possible, as they ultimately face significant revenue declines once biosimilar competition enters the market. AbbVie, maker of the blockbuster biologic Humira and infamous patent chaser, provides a stark example. Although Humira sales reached $20.6 billion in 2021, its revenue dropped by 36.2% in Q3 2023 as its exclusivity erosion accelerated.**

Industry analysts expect company-wide revenue to decline for at least a year due to Humira biosimilar competition. Executives have even walked back earlier predictions of growth returning in 2024, indicating sales may remain sluggish. As Aherne explains, "Typically, whether it's a patent expiry date, or the data exclusivity, or the market exclusivity period, it allows for competition in the space…the more competitors… it's going to typically drive the price down."

The impact of biosimilar entry can be severe but more gradual compared to small molecule generics. Take Pfizer's cholesterol-lowering drug Lipitor, for example. Once heralded as the pinnacle example of a blockbuster drug, Lipitor held the top-selling drug spot for many years. That was until 2012 when Pfizers' revenue fell from $68 billion to $59 billion after generics launched for the statin. In contrast, AbbVie is forecasted to retain over one-third of its 2022 US Humira sales in 2024 and over $2 billion through 2030, according to Evaluate Pharma.


This underscores why branded firms vigorously pursue patenting tactics to delay competition. As I-MAK states, "Humira's patent thicket fostered a legal environment perfect for pay-for-delay" settlements with biosimilar makers. Despite its primary Humira patent expiring in 2016, AbbVie continued aggressive patenting, accumulating a thicket of at least 166 granted patents, according to Amin.

"Notably, two-thirds of AbbVie's total US revenue earned on Humira since the drug was approved, was made in the additional seven years of monopoly after its main patent expired," he explains.

While financially rewarding for AbbVie, garnering an estimated $100 billion post-patent expiry, such practices directly oppose societal interests of affordable access that Feldman highlights.

"This is certainly manipulation of the existing systems. However, pharmaceutical companies are profit-making," she says." If a CEO of a pharmaceutical company were to stand before the board and say, 'I'm going to lower prices, because it's the right thing to do,' one would see a new CEO shortly."

## As patent cliffs loom, all eyes on Big Pharma

**With blockbusters such as Keytruda and Opdivo facing patent expirations before 2030, scrutiny on pharma's exclusivity games will likely intensify, particularly in the run up to the US presidential election in November. But how can we begin to unravel the tangled web created by the current system to encourage innovation in biosimilars?**

"Markets thrive on information," says Feldman. "For a robust biosimilar market, brand companies have to put their rights into a public data set and update changes over time."

Acknowledging that this would likely be rejected by brand companies due to the sheer number of patents in existence, Feldman offers an alternative, which would require designating a restricted patent list for biosimilar challenges at approval. This "one-and-done" approach would enhance transparency, she says.

Ultimately, she argues that regulatory reforms are essential to balance innovation incentives with affordable access. "It's society's job, it's government's job to make sure company incentives align with ours," Feldman states. "If not, the result is skyrocketing prices and difficulty accessing medications."

In recent years, attempts to curb the costly and time-consuming switching study requirements for biosimilars to achieve interchangeability have tried, and failed, to make an impact. Most notably Republican Senator Mike Lee's proposed original (and subsequently amended) Red Tape Elimination Act, which did not pass Congress. However under the combined spotlight of a presidential election and a rapidly approaching patent cliff, we are likely to see further proposals to change the system in the near future.

Whatever the outcome, the decisions made over the coming years will set a precedent for the future of biosimilars. And for the millions of patients priced out of potentially life-saving treatments by patenting gambits, the stakes are very high.

## About the author

Eloise McLennan is the editor for pharmaphorum's Deep Dive magazine. She has been a journalist and editor in the healthcare field for more than five years and has worked at several leading publications in the UK.

Additional reporting provided by Navlin Daily.

# **The UK vs. superbugs:** Combatting AMR on the homefront

**AMR, or antimicrobial resistance, is never far from the conversation these days. According to the World Health Organization (WHO), the growing resistance to the world's existing antibiotics is one of the largest threats facing public health, with 1.27 million deaths attributed to bacterial AMR worldwide in 2019 alone – more than HIV and malaria combined.**

While academics might have developed a means to reinvent the old, today, the industry faces a weak pipeline for new antibiotics, as there is no commercial payoff to act as an incentive for the resource-intensive development of AMR drugs. Though smaller companies are exploring new treatment possibilities with the likes of CRISPR technology, for example, others are turning to AI to better identify the appropriate antibiotics for the appropriate bacterial infections.

In February this year, Deep Dive headed up to Liverpool, UK, for the BioInfect Conference on AMR. Held at the top of The Spine for the first time, the location of Liverpool's Royal College of Physicians, as well as the Pandemic Institute, the day sought to bring to light – via discourse and insights from scientists and politicians, researchers and practicing clinicians – the state of affairs when it comes to AMR in the United Kingdom and beyond.

# Life sciences in the North West

**The BioInfect agenda – an event now in its 10th year – covered a range of topics, kicking off with a welcome address from Mayor of the Liverpool City Region, Steve Rotherham, sharing investment plans for the life sciences sector, before the official launch of the Liverpool City Region Investment Zone in Health and Life Sciences.**

Liverpool is a "cultural powerhouse," he said. With the right level of funding, £42 billion can be generated in gross-value-added (GVA) when pulling together all the "wonderful projects", he said, to become a "scientific superpower".

However, achieving this status will require an expansion in laboratory capacity facilities, an expansion that Rotherham argued Liverpool is primed to accommodate – "There are a dearth of labs throughout the UK, so why not Liverpool City?" he posited. To follow, Professor Janet Hemingway CBE, director of iiCON and a senior technical advisor on neglected tropical diseases for the Bill and Melinda Gates Foundation, announced the launch of the Liverpool City Region Investment Zone in Health and Life Sciences and spoke further about opportunities for the North West: a "levelling up".

What relevance to AMR, though?

The majority of the UK Government's £80 million investment will go into infrastructure, and tax free zones, boosting economy in Liverpool, Runcorn, St Helens Magull, and Prescot, plus Freeport. Much of this building will surround The Spine. Therein, streamlining organoids with Cat 3 robotics, AI, and machine learning. At this level, the area will be set apart from Europe.

This, of course, means more jobs, more talent, and iiCON itself, in its mere three plus years of existence, has created over 360 jobs in that time. A consortium led by the School of Tropical Medicine, bridging the gap in the infection innovation ecosystem between industry, academia, and the NHS – remember those academics seeking industry's uptake of their latest research into antibiotics – iiCON's portfolio programme is now worth >£250 million, with contracts with 345 companies to assist in product development. Indeed, 36 new products have been brought to market in three years (that is a product for every month of existence), and over five billion units of those products are in patients, in populations, in the US, Canada, and Europe.

At the time of BioInfect, LifeArc was a new iiCON partner, offering a humanised antibody platform for infection therapeutics. The other organisation that had joined iiCON was CELT (the Centre for Long-acting Therapeutics), which aims to broaden the understanding of long-acting medicines. However, iiCON is not just interested in the clinical side and developing new antibiotics, but in tackling AMR itself, and "looking at surfaces".

# State of AMR on national levels

**To address these points, an opening panel chaired by Beverley Isherwood, strategy leader & PACE programme director at the Medicines Discovery Catapult, discussed the state of AMR in different nations. Panellists included: Nicholas Feasey; Sir James Black, chair of Infection Medicine at the University of St Andrews; Nichola Jones, teaching fellow at the University of Leeds; Pia Thommes, VP of anti-infectives at Evotec; and Seamus O'Brien, director of research & development at the Global Antibiotic Research & Development Partnership (GARDP).**

Opening the discussion, the panel cut straight to the point: AMR deaths are escalating.

It's been almost a decade since the O'Neill Report was published in 2016. This review on Antimicrobial Resistance (AMR), commissioned in July 2014 by the UK Prime Minister, saw economist Jim O'Neill tasked with analysing the global problem of rising drug resistance and proposing concrete actions to tackle it internationally. Jointly supported by the UK Government and Wellcome Trust, it was established as a two-year, time-limited process, engaging widely with international stakeholders to understand and propose solutions to the problem of drug-resistant infections from an economic and social perspective.

Commenting on the main successes since the report's publication, Feasey, highlighted that the burden of AMR remains huge, and to quantify the size of the problem is an important contribution, so as to place AMR in context with other health problems. He noted the Christopher J Murray paper (PDF) and, on the O'Neill Report, O'Brien commented that it focused minds on the risk of market failure, very much in the pharma sector, kickstarting incentive and initiatives. It was, he said, propositional, talking about certain models that could be looked at, but that there were significant gaps in the data.

Jones, who works primarily in Nepal and Bangladesh, meanwhile, stated that policymakers have an impetus for change, positioned in those countries where AMR is seen on par with other health issues in those settings. Thommes is also an optimist, noting Roche's research on new antibiotics, and that many attendees of BioInfect in the audience had new entities, drugs, and approaches to AMR.

Progress, in short, has been made.

O'Brien agreed, stating that the regulatory framework for development of antibiotics has improved, but only in limited indications, and not approved beyond major industries and countries. Indeed, whilst national action plans have been helpful, they have followed a very templated approach. Feasey, who has been working in East Africa, where neonatal sepsis is common, concurred that focus needs to be where the greatest problem of burden falls: the unsexy but important health systems innovations, which need to be driven by the countries from the ground up.

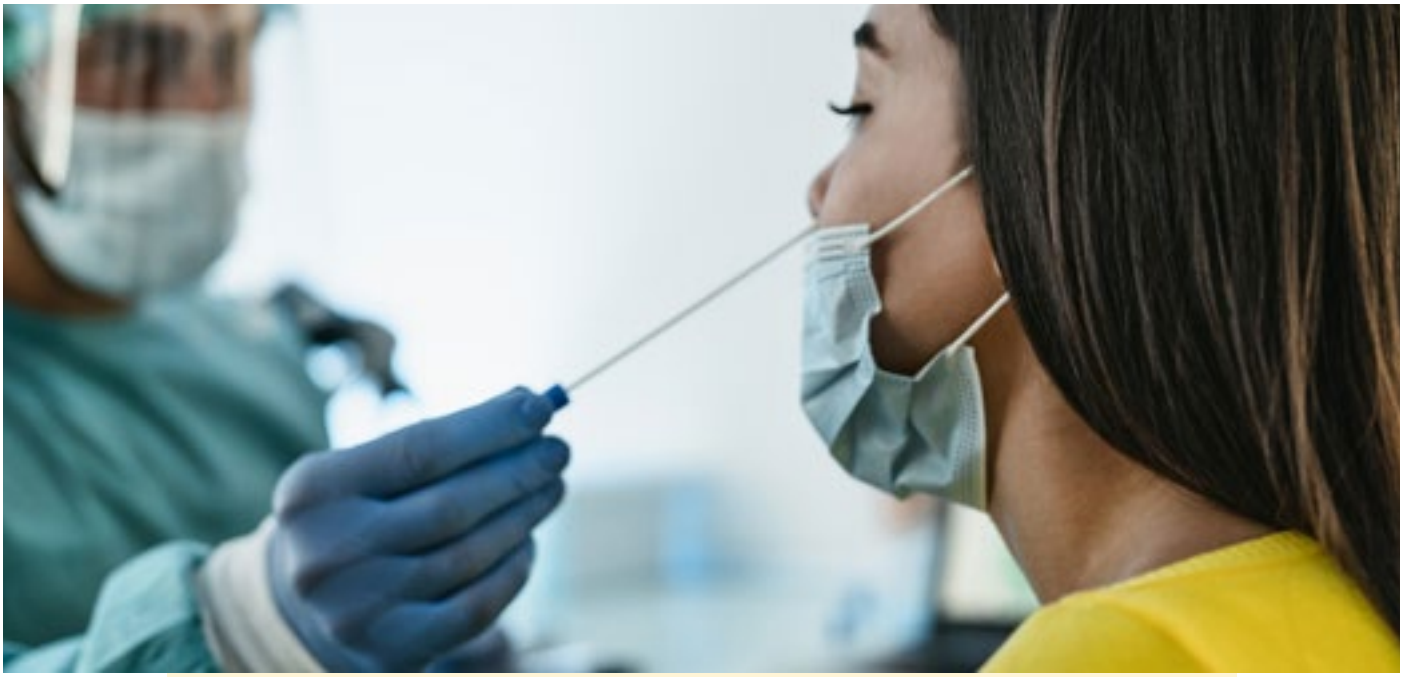
# A connected commitment to AMR research

**As AMR returns to the limelight in New York this September, at a high-level meeting during the 2024 UN General Assembly, there will be new opportunities for countries to commit to clear and bold new targets and practical steps for tackling the issue. One audience member asked what the panellists hope to see achieved by then and the commitments to be made after that.**

Feasey said there's an emerging narrative on accountability allied to that and that it would be a shame if LMICs are held accountable for AMR if no funds are invested in them. In 2018, he said, someone compared AMR to HIV/AIDs and that the missing piece of the puzzle was, it was agreed, money. Therefore, what he would like to see is action from the Global North to invest in the problem where the need is.

However, Thommes – on tangible solutions – posited a point of care rapid diagnostic, rather than antibiotics. Jones, from the perspective of demand, urged funding of better surveillance, but from a community citizen-scientist perspective, mentioning that the access route differs by seasons, for example, in some countries. So, there is also the supply chain issue. And O'Brien completely agreed: it's about sustainable solutions and future proofing. One approach GARDP has been discussing with partners is an integrated access programme, he said.

AMR is a cross-cutting thing that aligns with a number of sustainable development goals, agreed Feasey. There is a need for protection, prevention, and control. On surveillance, the UK Government, he said, has invested half a billion in Fleming Fund. Jones noted the UK's individualised perspective on health, rather than a community approach. To which, O'Brien mentioned the gonorrhoea community and that it's clear for such a population that AMR impacts their choices: it is a community of direct understanding of the impact of AMR.



While there were lessons learned from population responses to testing during the COVID-19 pandemic, O'Brien reiterated the need for more data on antibiotic use in certain countries. But, he said, he's excited to see how AI and ML can use AMR datasets for predictions and decisions; small datasets looking at efficacy and safety of antibiotics for resistance to particular phenotypes and genotypes. The missing piece, Feasey caveated, is coordination between primary and secondary care data. The global AMR hub data set is a 50/40 split in terms of funding versus discovery – and it needs to be better joined up, he said. A compartmentalised and fragmented approach is not best going forwards.

O'Brien suggested that what is needed is a greater connection of the FDA and the EMA, together with national agencies and pathways to enable faster discussion and registration with member states. Another attendee raised the topic of tuberculosis, which hasn't seen a new antibiotic developed since 2013 (though O'Brien commented here that some antibiotics are in existence which are not being approved for use). Indeed, Thommes added that innovation in TB is being driven by the Bill and Melinda Gates Foundation, bringing together companies working in that area.

Thommes commented that a One World approach is needed, and that – despite the day's ethos of the BioInfect event – the bubble of the North West of the UK cannot solve this issue alone. Solutions can come from there, but need to be applied in the right context in order to work for humankind.

## About the author

**Nicole Raleigh, Web Editor**

Nicole Raleigh is pharmaphorum's web editor. Transitioning to the healthcare sector in the last few years, she is an experienced media and communications professional who has worked in print and digital for over 18 years.

# **Overcoming AMR market failure:** Three start-up stories

**Slowly but surely, the world's antibiotics are becoming less effective as disease-causing bacteria evolve into drug-resistant "superbugs". The crisis is inevitable, but there's little short-term financial incentive to develop new antibiotics: Drug companies would have to spend significant money to develop the drugs, and they might never recoup it, since the price point for antibiotics is so low and the existing drugs still work – until they don't.**

This isn't a hypothetical problem. The last five years have seen a number of small biotechs try to make it in this space only to declare bankruptcy, their novel drugs fading into obscurity. Big pharma, meanwhile, mostly avoids the space for similar reasons.

Where the free market fails, governments and non-profits step in, and this is where the bulk of AMR work is being done. The pharma-supported billion-dollar AMR Action Fund and the CARB-X accelerator dominate non-profit investment.

In the US, government investment is coming from the National Institute of Allergy and Infectious Diseases (NIAID, a division of the National Institutes of Health), while the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense are interested in new antibiotics for battlefield medicine. Elsewhere in the world, the governments of Germany and the UK are some of those taking the threat most seriously, with the UK putting into action a plan to change the way the NHS pays for antibiotics.

But entrepreneurs are a tenacious bunch. Tell them something will never pay, and at least a few of them will try to prove you wrong. Deep Dive talked with the leaders of three start-ups tackling antimicrobial resistance in their own ways.

# **Revagenix:** The resurgent phoenix

**One of the cautionary tales of biotechs trying to develop new antibiotics is Acheogen. In 2019, it got an antibiotic approved by the FDA to treat carbapenem-resistant Enterobacteriaceae, a lethal superbug that can emerge in intensive care units and kill around half the people it infects. Less than a year later, it was declaring bankruptcy, having made less than a million dollars in six months on the market.**

But that's not necessarily the end of the story for Acheogen, or its pipeline. Founder Ryan Cirz was able to buy some of the company's assets and hire a chunk of the team. Under the name Revagenix, they're trying to take up the company's mantle.

"We grabbed the pipeline, but we don't work on a lot of it because a lot of it we can't make sense of what to do from a non-scientific standpoint," he said. "Some things we think we know maybe what to do."

Of the three companies Deep Dive spoke to for this piece, only Revagenix is actually working on novel antibiotics. And though Cirz didn't want to go into too much detail about their strategy, he laid out the broad strokes.

"We're really focused on broad-spectrum antibiotics that include coverage for multiple gram-negative priority pathogens, as many as we can get, although sometimes there are limits with chemistry," he said. "Sometimes gram-positive pathogens come along for the ride, depending on the chemistry. We're trying hard just to be committed to working on molecules that can meaningfully affect things like mortality. But we're also realistic that you can't necessarily study or develop the drug for that because some of those highest on the need settings are the least economically viable."

For the moment, the company relies on government and non-profit funding sources to pursue its mission of creating new antibiotics for unmet needs. They're supported by NAIAD and the Department of Defense, among others, along with the occasional private investor.

"We meet investors really one at a time and eventually find somebody that listens to what we're thinking, and then honestly watches us for a little while and sees, 'Hey, they're actually doing the things they said.' With our government partnerships, we have that time to not always be desperately fundraising. We effectively have to go one by one meeting people, and that's how we raise money."

Cirz says he hopes governments will find a way to solve the investment problems, but he's not hopeful. Even approaches like the UK's subscription model are fundamentally flawed, he believes, because they create new adverse incentives.

"The company is going to want to sell zero products because every $1 drug I sell, I take a dollar of straight cash away," he said. "But that dollar did not make me a dollar. That dollar made me 50 cents. Now I have someone using drugs. Now I've got to make more. I've got to report pharmacovigilance for the first five years to the FDA. I got to do all this work. They're creating an incentive where people are going to beg for no one to use the thing, even the company, and just take the check."

He hopes stories like Acheogen's will wake the world up to the scope of the problem.

"It's so much like climate change, unfortunately. When it's too late, you'll know," he said.

## **LimmaTech:** The stalwart partner

**Making novel antibiotics isn't the only way to combat antimicrobial resistance. With many of the superbugs on the WHO and CDC watch lists, it's possible to identify at-risk populations who could then be vaccinated against the bug. No infection in the first place means no antibiotics, and no opportunity for the superbugs to adapt any further.**

“The less antibiotics you are giving, the less you increase the antibiotic resistencies because people are not taking them,” said Franz-Werner Haas, the CEO of LimmaTech. “So it’s not mutually exclusive to have an antibiotic or a vaccine. Vaccine protects and keeps you away from the disease, certainly, but also the antibiotics. So it’s symbiotic somehow, additive. And that’s where we are at LimmaTech. We are working in this field of vaccines in order to protect from microbial infections.”

LimmaTech is looking at several high-risk infections that crop up in predictable populations: gonorrhoea, which tends to surface in sex workers, the gay population, and healthcare workers who serve these communities; shigella, which targets whole communities in the developing world; and staph aureus, a hospital-acquired infection, where people can be vaccinated before high-risk procedures.

Today, most vaccines are designed to fight viruses, not bacteria. But biologic drugs provide a platform that can be used for bacterial vaccines. LimmaTech uses an e. coli-based bioconjugate platform licensed from GSK to develop its vaccines.

LimmaTech, which was built from the unacquired assets of GlycoVaxyn when that company was purchased by GSK, relies heavily on its partnerships with GSK and another company, AppVac, to sustain itself as it develops its pipeline. But Haas thinks there’s enough opportunity here to support the company in the long run.

“How many companies are working in this very, I think, still underestimated field of antimicrobial resistance, and then to tackle it via vaccines?” he said. “There is a huge interest, and it is a niche. The hard news is it is a niche. The positive news is it is a niche. There are not that many companies working in this field, but there is a very high unmet medical need.”

But more than the potential for a payout, Haas believes the industry needs to be mobilising to meet the threat of AMR head-on, in whatever ways it can.

“If no antibiotics are working because of this resistance, we are back in a Stone Age where just before Fleming discovered penicillin,” Haas said. “That is really why the people call it a silent pandemic.”

# **Lumen:** The novel innovator

**The heart of the problem with making a profit in the antibiotic business is the disconnect between the cost of the drugs and the revenue they can be expected to bring in. Much of the effort by government and non-profit actors is aimed at increasing that revenue potential. But what if you could dramatically reduce the cost of manufacturing?**

Seattle, Washington-based Lumen Bioscience has an innovative approach to drugs that the company hopes will hit that sweet spot. Like LimmaTech, they're focusing on prevention rather than treatment, but they also have a unique approach to the drugs themselves.

"We can price the product. That's our trick," Brian Finrow, Lumen's CEO, told Deep Dive. "That's our hack, the prevention versus treatment distinction. We make a product that is safe enough and cheap enough to use preventatively. Antibiotics are cheap enough, but not safe enough. Conventional biologics are safe enough, but not cheap enough. We got the good box in that two by two grid, and that means we can sell it at a price that saves the system money on net and still makes us a reasonable return. Neat trick, right?"

At the heart of the "trick" is a little organism called spirulina. You might have seen it in the grocery store where it's sold as a dietary supplement. A single-cell photosynthetic microbe, spirulina, can be easily cultivated as a crop. Less easily, Lumen has found a way to engineer strains of spirulina to deliver therapeutic proteins, vastly reducing the price of creating biological drugs. In addition, because the pill is essentially a foodstuff, it has a very favourable safety profile, even at high doses.

On the AMR threat list, Lumen Bioscience is targeting Clostridioides difficile (C. diff), which the CDC puts on a short list of urgent threats when it comes to AMR. They are trialling it to prevent recurrence of C. diff in patients being treated with antibiotics.

"Antibiotics are a very broad spectrum, and so they kill off your microbiome," Finrow explained. "That's actually what opens up the opportunity for C. diff to recolonise. But the biologics have this attribute scientists call specificity, which means you can make them like a scalpel. They only go after the bad bugs and none of the others. Because they're absorbed, in addition, you don't have to worry about all the liver toxicity and other issues of antibiotics. They're safer and much more specific. That's why we can give them to you during the preventative phase, allowing your normal bacteria to regrow without risking another case of C diff."

Not all of Lumen's products are AMR-related. In fact, Finrow says, the company doesn't brand itself as being in the AMR space precisely because of the stigma around profitability.

"Even if, as in our case, there's a really compelling business case, it doesn't matter because you can't do research without funding," he said. "The fact that everyone disagrees with us in the investor world that there's a business case, it's just it's too bad. We get painted with a broad brush."

Instead, they seek VC funding for other programmes, work with the US Department of Defense, CARB-X, and the Gates Foundation on their various AMR programmes, and hope that their strategy proves itself out in the long run.

"Preventive drugs, we think, are where we can operate," he said. "We can't solve all of the AMR crisis single-handedly. We're not trying to. There are plenty of them that are systemic, and we don't have a way to go after those. But for areas where we can operate, that's our shot at proving all of the VCs wrong."

## About the author

Jonah Comstock is a veteran health tech and digital health reporter. In addition to covering the industry for nearly a decade through articles and podcasts, he is also an oft-seen face at digital health events and on digital health Twitter.

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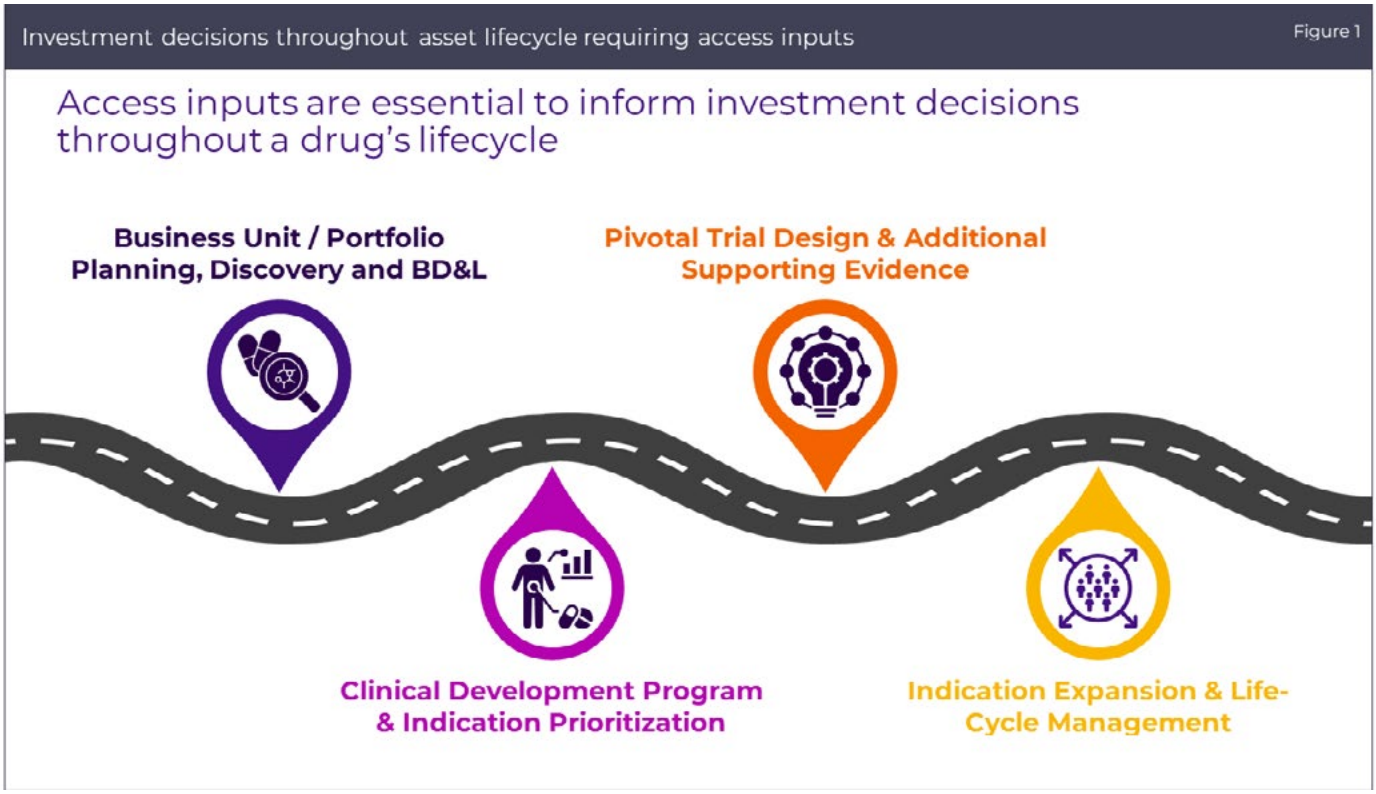
# **Integrating market access considerations into biopharmaceutical asset investment decisions:** Common pain points and best practices

**The biopharmaceutical industry operates at the intersection of health innovation and market viability, where the significance of integrating market access insights into investment decisions cannot be overstated. From the inception of a new therapy to clinical development and pivotal trial designs, market access analyses provide a critical lens through which the commercial trajectory of a product is evaluated. This approach ensures not only the development of clinically effective products but also their market success by aligning them with payer expectations and healthcare systems' needs. As the industry faces growing complexities, the ability to navigate these with informed access integration becomes imperative for reaching patients effectively.**

In our work with clients, we have experienced several common organisational pain points in integrating market access into investment decision-making, and we have identified and replicated best practices for mitigating these challenges.

Investment decisions throughout asset lifecycle requiring access inputs

Figure 1




# Common pain points in integrating access voices into investment decisions

**The path to integrating market access considerations into pharmaceutical asset investment decisions is fraught with challenges that can hinder effective decision-making:**

## Inefficient and unclear objectives:

Market access teams may find themselves navigating without a clear direction, working towards objectives that are not only vague but also inconsistently applied across different stages of the process. The focus often shifts between assessing static Target Product Profiles (TPPs) and trying to develop a singular "reimbursable" TPP, without considering the dynamic nature of market access environments and the multitude of potential pathways a drug development process could take.

In contrast, clients who seek to focus on early identification of risk and rewards trade-offs associated with different investment options, rather than static assessment or development of a TPP, are much more likely to facilitate dynamic decision-making that adapts with evolving information.

## Cross-functional communication challenges:

Effective collaboration is hindered by the absence of a shared language and understanding between cross-functional teams. This gap in communication can lead to key market access considerations being lost in translation among teams unfamiliar with access-specific terminologies and concepts.

Successful integration of access considerations requires establishing a common language and replicable frameworks to bridge this divide, facilitating clearer insights and mutual understanding that facilitate the integration of market access insights and enhance decision-making confidence.

## Blurred cross-functional input responsibilities:

Successful, informed investment decision-making requires a variety of critical, cross-functional inputs. There is often ambiguity surrounding the roles and responsibilities of different teams involved in providing inputs to the decision-making process. This lack of clarity can result in duplicated and misaligned efforts and a general inefficiency in progressing towards strategic goals. Clarifying these roles and establishing clear lines of responsibility and coordination among teams can streamline processes and ensure that market access considerations are effectively integrated and leveraged.

### Overemphasis on barriers vs. opportunities:

Market access teams are frequently tasked with assessing the challenges and barriers to achieving patient access at a price that supports the investment hypothesis, leading to a predominant focus on identifying and communicating the hurdles that may be faced in gaining market entry, sustainable pricing, and patient accessibility. This focus can tend to overshadow the vigorous investigation of pathways to maximise the pricing and access opportunity. Encouraging a balanced perspective that equally weighs the realistic identification of barriers and the creative and opportunistic exploration of potential positive drivers can yield a more balanced view of an asset's prospects and an early stimulus to developing a holistic and proactive pricing and market access strategy.

## Best practices to address key pain points

**Each of these pain points underscores best practice opportunities for market access leaders to frame and organise their role and maximise their influence and impact on asset investment decision-making across the asset lifecycle. By implementing these best practices, leaders can ensure that the market access lens is applied rigorously and improve the efficiency and effectiveness of their organisation's investment decision processes, ultimately benefiting both the business and the patients it serves.**

**Key best practices include the following:**

## Streamlining objectives to focus on trade-offs:

**Profile a range of options and scenarios:** Instead of focusing on a singular TPP or trying to identify a singular "reimbursable" TPP, systematically consider a variety of potential paths, their implications and feasibility.

**Identify risks and reward trade-offs:** Leverage the systematic scenario approach to identify trade-offs to inform decision-making under uncertainty, encouraging a dynamic approach to decision-making that adapts as new information becomes available.

## Creating common language and replicable frameworks:

**Establish replicable frameworks:** Develop frameworks that educate cross-functional stakeholders and provide a consistent and replicable approach they can digest.

**Use simple and intuitive language:** Ensure that the frameworks and language used facilitate mutual understanding and productive dialogue, remembering non-access stakeholders are often unfamiliar with market access vocabulary, that key market access terms often have multiple meanings dependent upon stakeholder context.

## Clearly defining the market access role:

**Clarify roles, responsibilities, and decision-making authority:** Ensure every team knows their specific contributions to the process, and very clearly identify the boundaries of input that the market access team will provide.

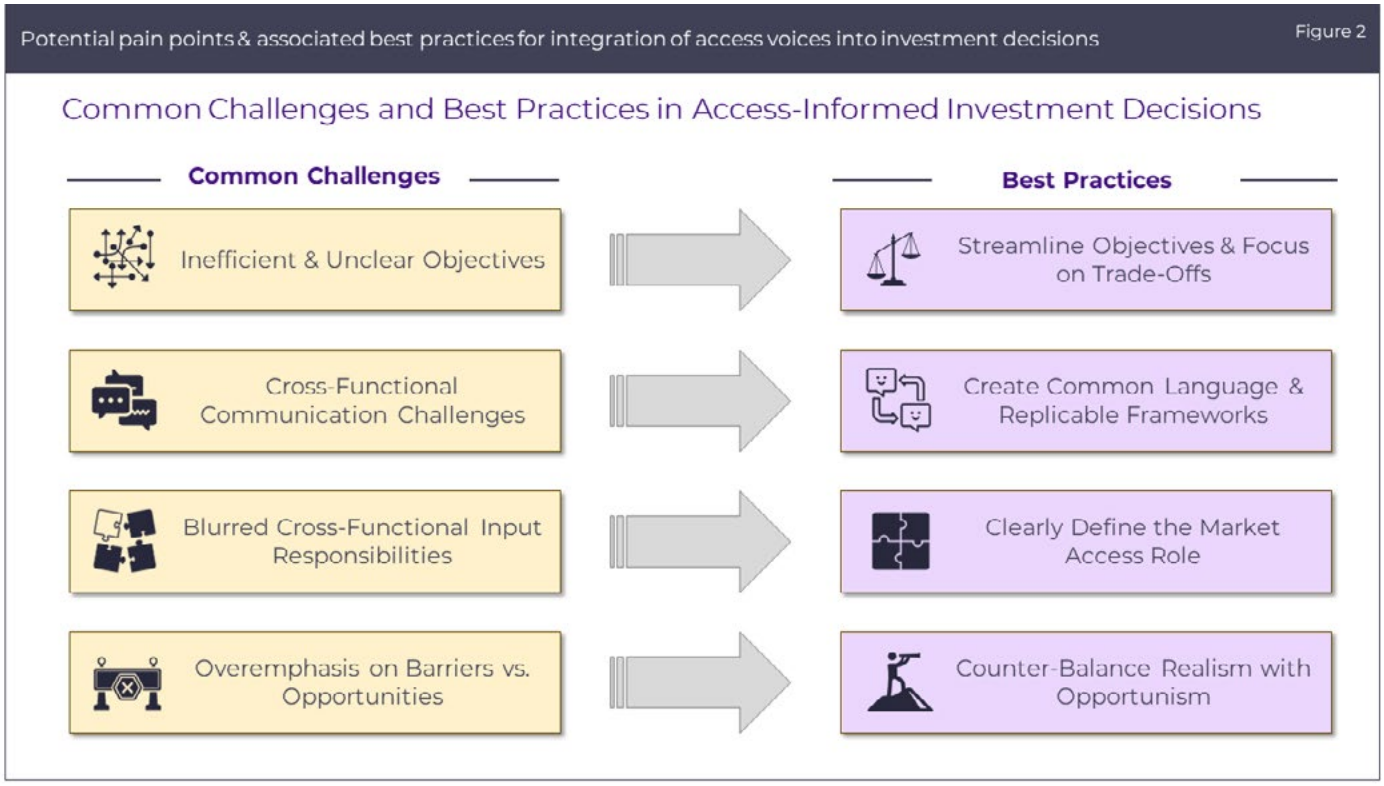
**Ensure cohesive vision:** Clearly define the specifics of dependencies and intersectionality between market access inputs with assumptions and inputs that are the responsibility of other cross-functional teams.

## Counter-balancing realism with opportunism:

**Adopt a solution-oriented mindset:** Balance the roles of realist and optimist, looking beyond known or forecasted challenges to identify pathways and opportunities for pricing and access optimisation.

Potential pain points & associated best practices for integration of access voices into investment decisions

Figure 2




## Conclusion

Integrating pricing and access functions into asset investment decisions is crucial for developing pharmaceutical assets that are not only innovative, but that are accessible to appropriate patients and realise an adequate return on investment. By recognising and addressing the common pain points through established best practices, organisations can pave the way for innovations to achieve their true potential, reaching those who need them most, and providing a return that supports and encourages further innovation and progress. As the healthcare landscape continues to evolve, and biopharmaceutical innovations grow more complex and more narrowly targeted, the strategic and timely integration of market access considerations into investment decision-making will only grow in importance. It will be upon market access leaders to ensure efficient and effective engagement to maximise their impact in the decision-making process.

# About Putnam

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Putnam, an Inizio Advisory company, is a leading scientific and strategic consulting partner that helps the global life science community make confident decisions, build value, and bring life-changing innovations to clinicians and patients. For more than 30 years, our rigorous, bespoke approach and globally diverse team have delivered unrivalled depth across therapeutic areas, business functions, geographic markets, healthcare sectors, and technology platforms to maximise the human impact and commercial success of client innovations.

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# About the authors

**Eric Auger,** *Partner, VPA Practice Lead*

Eric Auger leads Putnam's Value, Pricing & Access global practice, which consists of over 250 market access strategy, HEOR and RWE professionals across 10 global offices. Prior to Putnam joining Inizio, Auger was Putnam's Partnership Chair, coordinating firm strategy and governance.

With over 27 years with Putnam, he has built deep expertise in market access strategy and supporting clients in navigating challenging payer, healthcare system, and competitive environments. Auger has supported clients across a wide range of therapeutic areas, modalities, and healthcare system sectors, with much of his work helping clients to pioneer new areas. Prior to Putnam, he started his consulting career at Bain and Company, and completed degrees in Economic and International Relations from Providence College and Boston University.

**Joanne Evason,** *Partner*

Joanne Evason leads the European Value, Pricing & Access practice at Putnam, with 18 years' experience in pricing and access.

The focus of her work is advising biopharmaceutical clients from early phase asset planning, through to launch, and how to navigate complex payer and healthcare systems to ensure optimal patient access.

Prior to joining Putnam, Evason gained experience in developing and implementing Real World Evidence studies to support a broad range of applications, including evidence generation planning/implementation and innovative contracting. Evason also has experience leading global cross-functional teams including medical, HEOR, commercial, access and R&D, across a broad range of therapeutic areas, including rare diseases, oncology, immunology, biomarker and companion diagnostic strategies.

She has direct experience working as a payer within the UK market and remains close to key payer groups across European markets, supporting the evolution of key policies to enable patient access. She has strong links with NICE and NHS England and works with pan-European groups such as EUCOPE and EUnetHTA.

**Hugo Hayes,** *Manager*

Hugo Hayes' work focuses on the Value, Pricing & Access strategy practice area, specialising in generation of pricing and contracting strategies for pharmaceutical and biotech clients across both US and international markets.

He has extensive experience in developing access strategies for therapies in both inpatient and outpatient settings, at all stages of the product lifecycle. Recent projects have covered a range of therapeutic areas including inflammation and immunology, rare diseases, and vaccines. Hayes joined the Putnam London office at its inception in 2020.

Prior to joining Putnam, he worked for Monitor Deloitte, focusing on healthcare strategy across a broad range of public and private sector clients. Hayes holds a BA in Philosophy, Politics and Economics from the University of Oxford.

**Jean Sellier,** *Senior Consultant*

Jean Sellier is a member of the Value, Pricing & Access practice at Putnam. Specialising in Global Pricing & Access Projects and Commercial Opportunity Assessments, Sellier focuses on evidence generation planning to navigate intricate payer systems, as well as indication prioritisation and sequencing for early-phase assets.

Prior to joining Putnam, Sellier gained experience at DRG Consulting working across Commercial and Global Pricing & Access Projects. He also has direct experience working for the Pharmaceutical industry through his role at Norgine, a European specialist pharmaceutical company, where he supported the Business Development & Licensing team to perform commercial due diligence."

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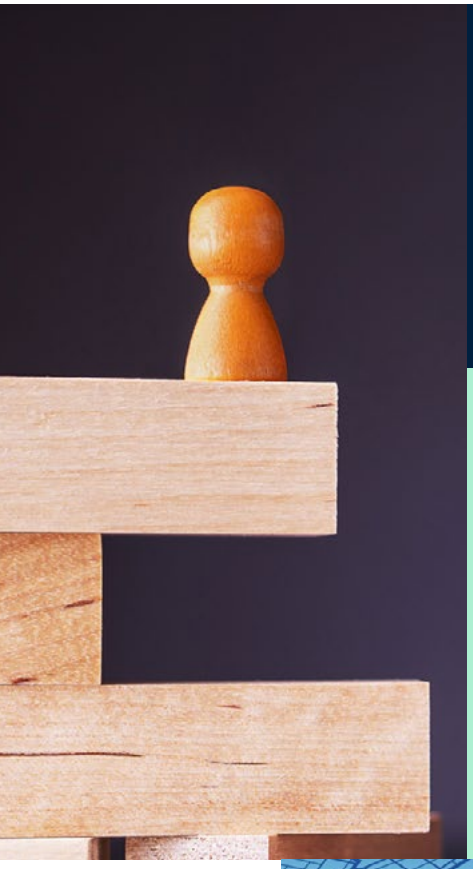
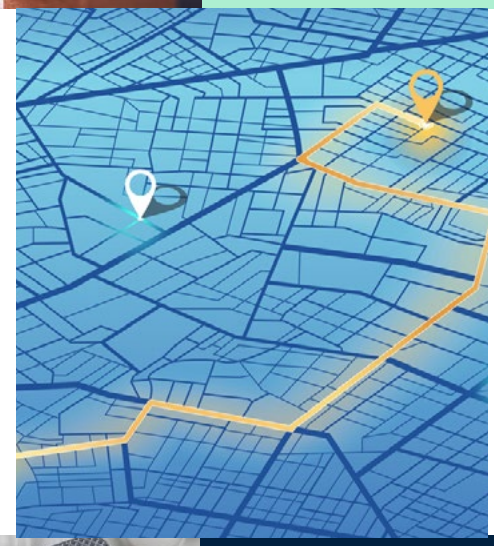


# Mind the gap: What is causing the ongoing ADHD drug shortage?

**Since late 2022, medications for Attention Deficit/ Hyperactivity Disorder, or ADHD, have been in a shortage in the United States and the UK. What began as a paucity of long acting medications, specifically Adderall in the US and Methylphenidate prolonged-release capsules in the UK, has snowballed into an ongoing shortage of nearly every ADHD medication as patients scramble to access prescriptions they can fill.**



It's only one of many drug shortages currently affecting patients – as of writing, the FDA is tracking more than 300 – many of which involve life-saving and life-sustaining medications. But the ADHD medication shortage is notable for its persistence, its unique affect on patients, and the ambiguity around causes and potential solutions.

# The impact of missing medications

**ADHD affects as many as 10% of children in the United States and about 2.5% of adults, both in the US and globally. That number could be higher as adults, particularly women, often go undiagnosed.**

In those patients, medication allows them to focus and perform in work and school and to avoid accidents that can be caused by distraction or lack of executive function. If not life-sustaining, it's at least quality of life sustaining.

"The consequences of not being on your medication are very much like the consequences of not being able to get glasses for a couple of months," Dr David Goodman, an assistant professor in the Department of Psychiatry and Behavioural Sciences at Johns Hopkins School of Medicine, told Deep Dive. "Imagine that you have blurred vision and you wear glasses, and then somebody steps on your glasses and you can't get your glasses for two months. How well are you going to function? You'll muddle through, but you're clearly not going to function."

In adults, this can mean everything from strain on relationships to a loss of work productivity to lack of focus at a critical moment leading to a car crash.

"I've had a patient who lost their job because they weren't on their medication," Goodman said. "They had a fairly high demanding job. [Their employer] couldn't tolerate the error rate, and they weren't very understanding about what was going on."

For children, still the largest population of ADHD patients, lack of medication can lead to disruptions in school and an increased burden on parents and teachers.

"It requires a lot of time on the part of parents to oversee them, make sure they're sitting down and doing their homework. It requires more attention by the parents in the morning to help get them organised and out to school, out to the bus, out to the car," Goodman says. "It's generally exhausting for the parents who are involved with the child who previously was medicated and they were enjoying the relationship. And now they're left with this unmedicated child who has a lot of needs and demands on the parents' time."

As the shortage stretches into its second year, it could have a meaningful effect on kids' grades, test scores, and futures.

# The challenges of filling prescriptions

**Furthermore, there are several aspects of ADHD that make shortage conditions particularly challenging.**

ADHD medications are powerful stimulants, which means they are heavily regulated. In the United States they can only be prescribed in a 30-day supply and they require prior authorisation for those supplies to be refilled. There are two types of medication options: short release, such as Ritalin, which provide a brief burst of focus for just a few hours; and extended release drugs like Adderall or Lisdexamfetamine (Vyvanse), which can last between eight to 12 hours depending on how quickly the patients body processes the medication. These longer-lasting options tend to be favoured by prescribing physicians and patients.

Strategies for maintaining access to medication include calling multiple pharmacies in the hopes of finding one with the medication in stock, or calling one's doctor to ask for a different drug, dosage, or formulation – each of which requires a new prior authorisation.

Ironically, that process requires exactly the mental capacity that many patients rely on their medication for.

So why are treatments in short supply for a condition that's so common? Well, no one knows for certain, or those who do aren't telling.

"I think one of the most frustrating parts is all of the secrecy that happens with the pharma companies," Erin Fox, a PharmD and professor at University of Utah who also works with the American Society of Health System Pharmacists as an expert on shortages, told Deep Dive. "The drug companies are actually not required to publicly give a reason for why they're having a shortage."

They do have to report reasons to the FDA, but the FDA's explanations have been limited—they blamed intermittent manufacturing delays at Teva, but that seems insufficient to explain a shortage that's well into its second year.

In fact, there are a number of plausible hypotheses for the shortage, and the likelihood is that it's some combination of them.

# Manufacturing delays and quotas

**When the shortage first began, authorities pinned it on "ongoing intermittent manufacturing delays" at a Teva plant, possibly related to labour shortages caused by the COVID-19 pandemic.**

But that explanation doesn't seem sufficient to explain a shortage of this duration, Fox says.

Manufacturers have reported that they don't have sufficient raw materials to make more drugs. Because ADHD drugs are schedule 2 drugs, those materials are doled out by the Drug Enforcement Agency (DEA) in the US via a quota system. But there's a catch – DEA and FDA say the manufacturers aren't even utilising the quota they have.

"We also hear from companies that they don't have enough quota, the raw materials, to make the products," Fox said. "But then we have the DEA who is in charge of the quota, coming out and saying you have plenty, you just haven't chosen to make enough drug. We had the very unusual situation of FDA and DEA together writing a letter telling these drug companies, 'Make more drug.'"

NBC news dug into this he said-she said, but the best they could do was speculate that some manufacturers may be sitting on unused quota, something they wouldn't be required to share.

"There's a lot of finger-pointing between the pharmaceutical manufacturers, the providers for the basic elements to make the medication, and then the distributors and the insurance companies," Goodman said. "Everybody's got fingers pointed at everybody else."

In the UK, supply chains are partly to blame, with a report in The Guardian suggesting that a number of NHS drug shortages, including the stimulant shortage, can be traced back to the effects of Brexit – both on the importation of drugs and the red tape associated with the UK's standing up internal approval processes rather than using the European Medicines Agency.

# Increased demand

**Another explanation, also partially fuelled by COVID-19, is that the industry simply wasn't ready for an increase in demand for ADHD medications, stemming from an influx of adult ADHD diagnoses.**

Goodman said the number of adult ADHD diagnoses has been steadily increasing in recent years, likely owing to a combination of a decrease in stigma among patients, especially millennials and Gen Z, and growing professional consensus among providers about the reality and seriousness of adult ADHD.

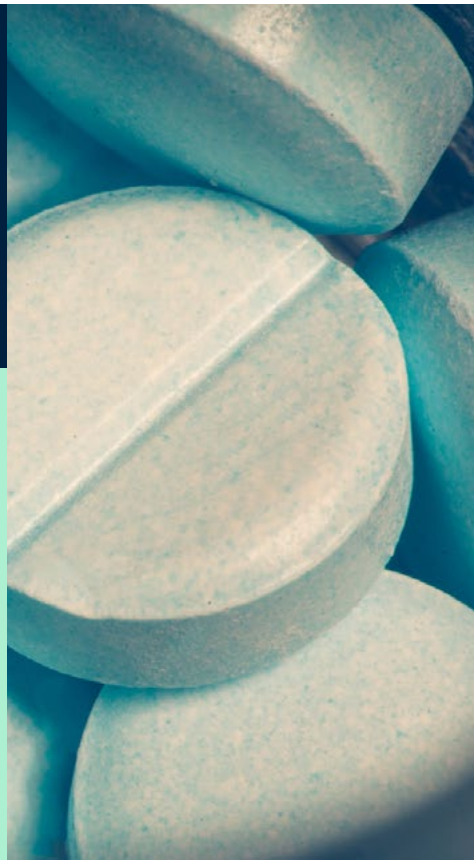
The pandemic may have accelerated this trend in a couple of ways. For one thing, pandemic-era telehealth rules made it easier to obtain an ADHD prescription. For another, adults with undiagnosed or untreated ADHD who were able to function without medication in an office environment may have found themselves in need of more assistance in the new, distracting world of work from home.

"If you're in a structured environment and you're held accountable to that, the structure allows you to perform at a higher level," Goodman said. "If you have to sit at home, structure yourself, and be self-disciplined and initiate tasks, it becomes more challenging. For a lot of ADHD individuals, being at home wasn't a very good way of conducting their work."

Fox says there's one problem with the demand explanation.

"I think If there's any bright spot to the pandemic, it was telehealth and giving people more access, which I think is great," she said. "I think on the demand side, if demand was truly driving this, then it seems like DEA would increase the quota, but they haven't."

# Unintended side effects of the opioid settlement



**Finally, there's one more unexpected cause behind the shortage in the US: The legal settlement between the US government and the opioid manufacturers. In addition to manufacturers needing to order quotas of raw materials from the DEA, the settlement requires wholesalers like McKesson and Cardinal to limit the amount of controlled substances, including ADHD medications, they give to pharmacies.**

That supply is calculated according to a formula that's not made public, leaving pharmacies unable to get the drugs they order and not sure why.

"This whole system is really incentivized to not have any extra on the shelves," Fox said. "Basically, as a pharmacy, you have to prove that you are out or you don't have enough to fill your prescriptions, but that automatically means that patients are going without getting a prescription. This entire settlement is designed to almost make sure that patients are going without treatments."

Unlike legislation, a legal settlement, even one involving the government, can't really be addressed by lobbying and its terms aren't even publicly available, Fox says.

# Solving the shortage

**Everyone from government bodies to manufacturers says they are working to solve the shortage, and Fox says there are signs that it's getting better.**

The end of the pandemic telehealth allowances in November could lead to a decrease in demand that helps alleviate the shortage if it hasn't been solved by then. But it's unlikely to have a full effect because newly diagnosed or prescribed adults won't stop taking medications that work for them just because they now have to go into a doctor's office to get them.

The FDA approved new generics last year, which could also help ease the difficulties. And the DEA announced changes to its quota process late last year that could also help.

Meanwhile, patients are increasingly vocal about the need for a solution.

"I think the public shaming is usually where we sometimes see action," Fox said. "But I think that's where we're at. I think we're at the public shaming part of this."

## About the author

Jonah Comstock is a veteran health tech and digital health reporter. In addition to covering the industry for nearly a decade through articles and podcasts, he is also an oft-seen face at digital health events and on digital health Twitter.

# Heard on the pipeline: Access to medications

**Solving the challenge of access to medication has fuelled many a debate among healthcare stakeholders over the years. Yet, while discussions have been plentiful, even fruitful, patients around the world still struggle to access treatments.**

When pharmaphorum editor-in-chief, Jonah Comstock hit the floor of Reuters Pharma US, in Philadelphia last month, it seemed an ideal opportunity to find out what is stalling progress in this space. And so, he put one question to industry experts attending the event.

## "What systemic changes are needed to ensure that medications become more accessible and affordable worldwide?"

## Mindy McGrath

***Senior executive and health industry advisor at Vynamic, an Inizio company***

I think our system here in the United States is a very complex system. There are many players within the system – intermediaries, if you will. One thing we're not doing enough of is talking about the role of the pharmacy benefit manager and that rebating model, which seems very opaque to many in the industry.

I don't think we've had a really good national conversation on the intention of pricing in the United States. There is so much value in pharmaceuticals and yet I don't think as an industry we've done a great job of really articulating and positioning that correctly. And as a result it becomes part of the headline news on a regular basis.

Headline news can be really dangerous because underneath of all of that there is a level of complexity that in many ways doesn't reside with pharmaceutical companies. It really resides with the intermediaries that play a role in the US healthcare system.

So how do you solve that? You know I'm not big on legislating all over the place but I do think at some point we need to have a very robust conversation about how payment actually occurs through the system and what types of incentives exist. And, candidly, transparency. There are just too many areas in the healthcare system that are not transparent enough, so nobody can really make good decisions on how you actually get to the root cause of this issue.

*Watch our full interview with McGrath here.*

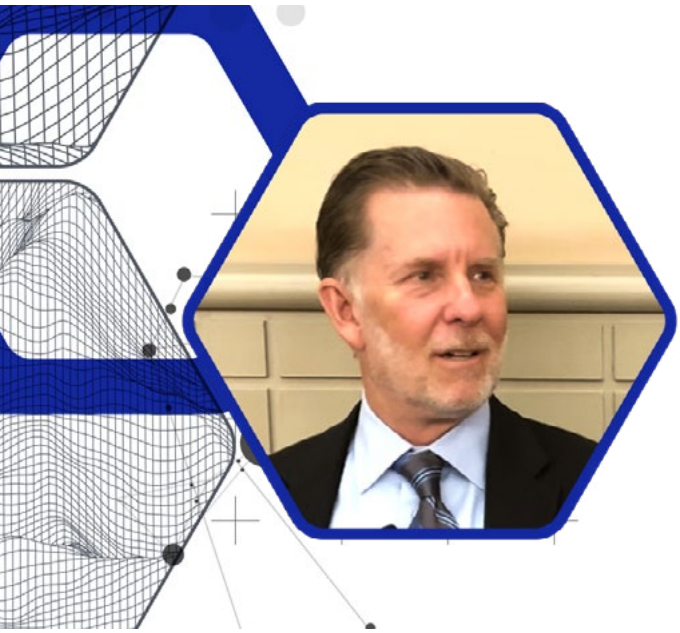
## Lung-I Cheng

***VP cell and gene therapy, Cencora***

I think drug pricing is part of the equation. It's a very important piece. But I feel that the question is more around how do we make healthcare more accessible, right? There's the drug, but it's the most cost effective medical intervention that you can get, prescription drugs.

There are many other elements where we can find efficiencies. As we think about the health system here in the US and outside the US, what can we do better to make sure that there's more of an effort to decrease the fragmentation and hopefully therefore improve access to better care?

*Watch our full interview with Cheng here.*



## Mark Morgan

***President and head of US operations, UCB Pharma***

I think there's got to be a combination of reasonable legislative solutions and all of the stakeholders – easy to say, hard to do – stepping up to the plate. Because for payers, they most often look at it as unit price. Manufacturers often think more about the patients. If we can stop talking past each other and figure out how we can advocate for solutions together, that may be pie in the sky but I think that's where the opportunity is.

Even the recent legislation, there's a lot that as a manufacturer we don't agree with, there are pieces of it we do agree with it, and yet in the big picture there's an opportunity to kind of refine a body of legislation like that so it can work for us societally.

## Amy Niles

***Chief mission officer, Patient Access Network Foundation***

You know we're focused at PAN on the United States. I mean there are lots of issues globally but here in the United States and there are lots of systemic ways that we can improve access to care. If we look at the Medicare reforms that, for example, the Part D cap of $2000 that goes into effect on the 1st of January, that's great news for Medicare beneficiaries.

But what about everyone else who doesn't have Medicare insurance? They have high deductibles, they have high costs. So I think from a systemic perspective, we would love to see those costs applied to a broader population.

I think systemically we need to, and this is going to take time and it's a challenge, but we need to look at the total cost of care. So prescription medications is really important, but that's just one piece of the pie and we know that the patients we serve are struggling with really high premiums and they pay a co-pay every time they go to a healthcare professional.

All of this adds up and it becomes quite unaffordable for many Americans. So those are just a couple of ways that I think all of us need to think more broadly.

## Meruno Perugini

***President, pharmaceutical division, Nestlé Health Sciences***

Regulators are looking for a way to make it more affordable for some communities. The Inflation Reduction Act (IRA) is coming our way as a matter of fact and is going to be looking after I guess the Medicare Part D population.

I really believe that the affordability is more and more a component for each of us. Now that cannot be sorted out only by the manufacturer, because the reality is that also health insurance plays a big role in this country together with the government for some of the channels.

I was pretty impressed with some of the discussion on value-based agreements — paying the right price for the value that that the product brings and I believe that that's very exciting.

One hope that for the future is to go beyond the pharmaceuticals and really looking at the healthcare system overall, right? Pharmaceuticals represent one part, and not the most significant part as a matter of fact, of the healthcare system and the cost of the healthcare system in the US. And I really believe that there is opportunity of getting together and evolving it.

## About the author

Jonah Comstock is a veteran health tech and digital health reporter. In addition to covering the industry for nearly a decade through articles and podcasts, he is also an oft-seen face at digital health events and on digital health Twitter.

# Around the world in pharma events

## Stay up to date with key industry meetings and conferences in 2023/24


### Americas

**American Society of Gene & Cell Therapy Annual Meeting**
07-11 May
Baltimore, US

**ASCO 2024**
31 May – 4 June
Chicago, US

**BIO 2024**
03-06 June
San Diego, US

**PCC Canada 2024**
04-05 June
Toronto, Canada

### Middle East/Africa

**PrecisionMed Exhibition & Summit**
8-10 May
Dubai, UAE

**Pharmaconex**
08-10 September
Cairo, Egypt

**41st IASP World Conference on Science Parks and Areas of Innovation**
24-27 September
Nairobi, Kenya

**Africa Health 2024**
22-24 October
Cape Town, South Africa

### Europe

London Biotechnology Show
08-09 May
London, UK

NEXT Pharma
14-15 May
Dubrovnik, Croatia

2nd Pharma Omnichannel HCP Engagement Conference
23-24 May
Lisbon, Portugal
Event details

European Congress on Biotechnology (ECB2024)
30th June – 3rd July
Rotterdam, The Netherlands

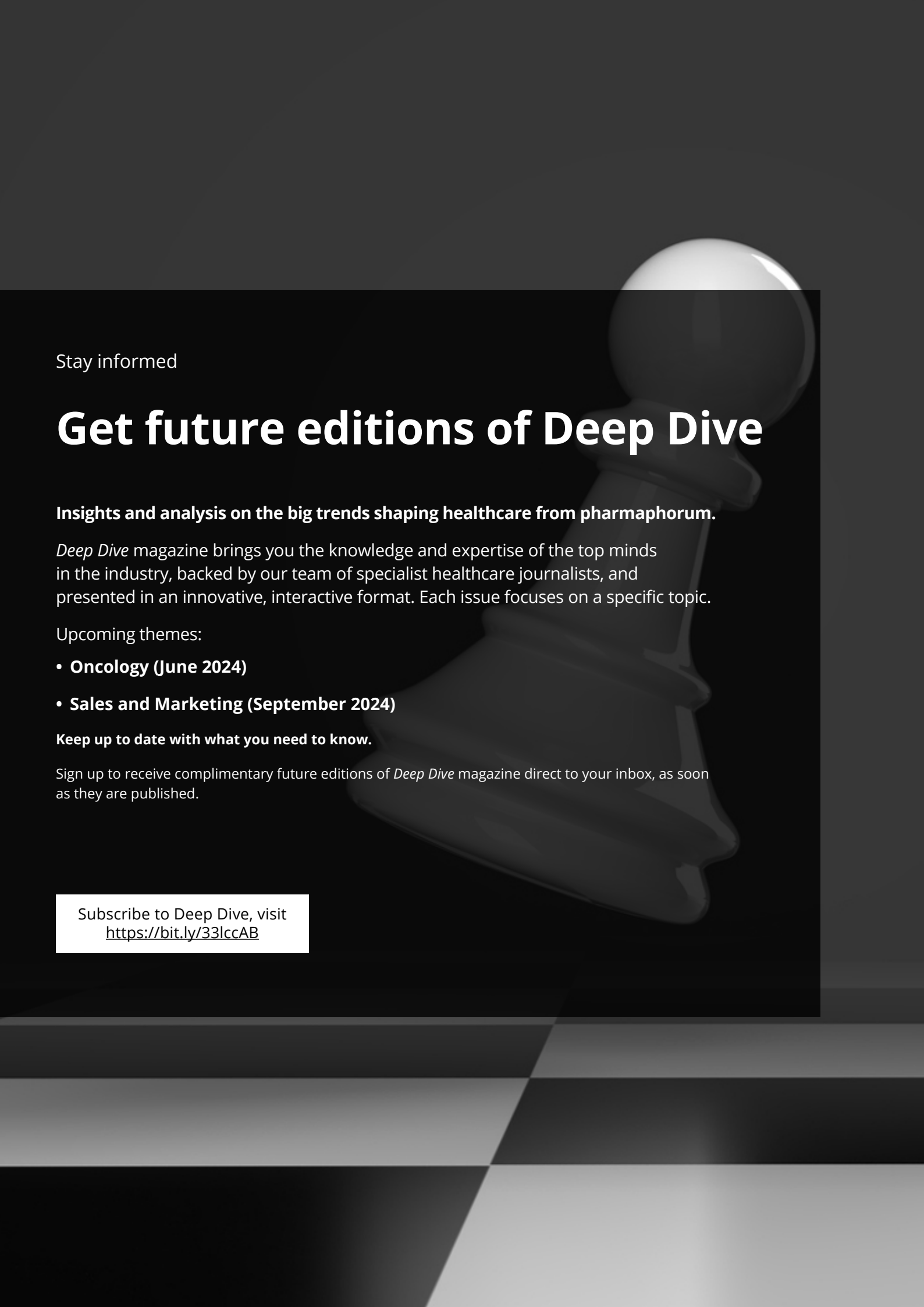
### Asia Pacific

**ICPPS 2024**
14-17 June
Seoul, South Korea

**CPHI China**
19-21 June
Shanghai, China

**BIO Asia-Taiwan**
25-18 July
Taipei, Taiwan

**Biotechnology and Bioengineering Congress**
23-24 September
Singapore, Singapore



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*Deep Dive* magazine brings you the knowledge and expertise of the top minds in the industry, backed by our team of specialist healthcare journalists, and presented in an innovative, interactive format. Each issue focuses on a specific topic.

Upcoming themes:

- **Oncology (June 2024)**
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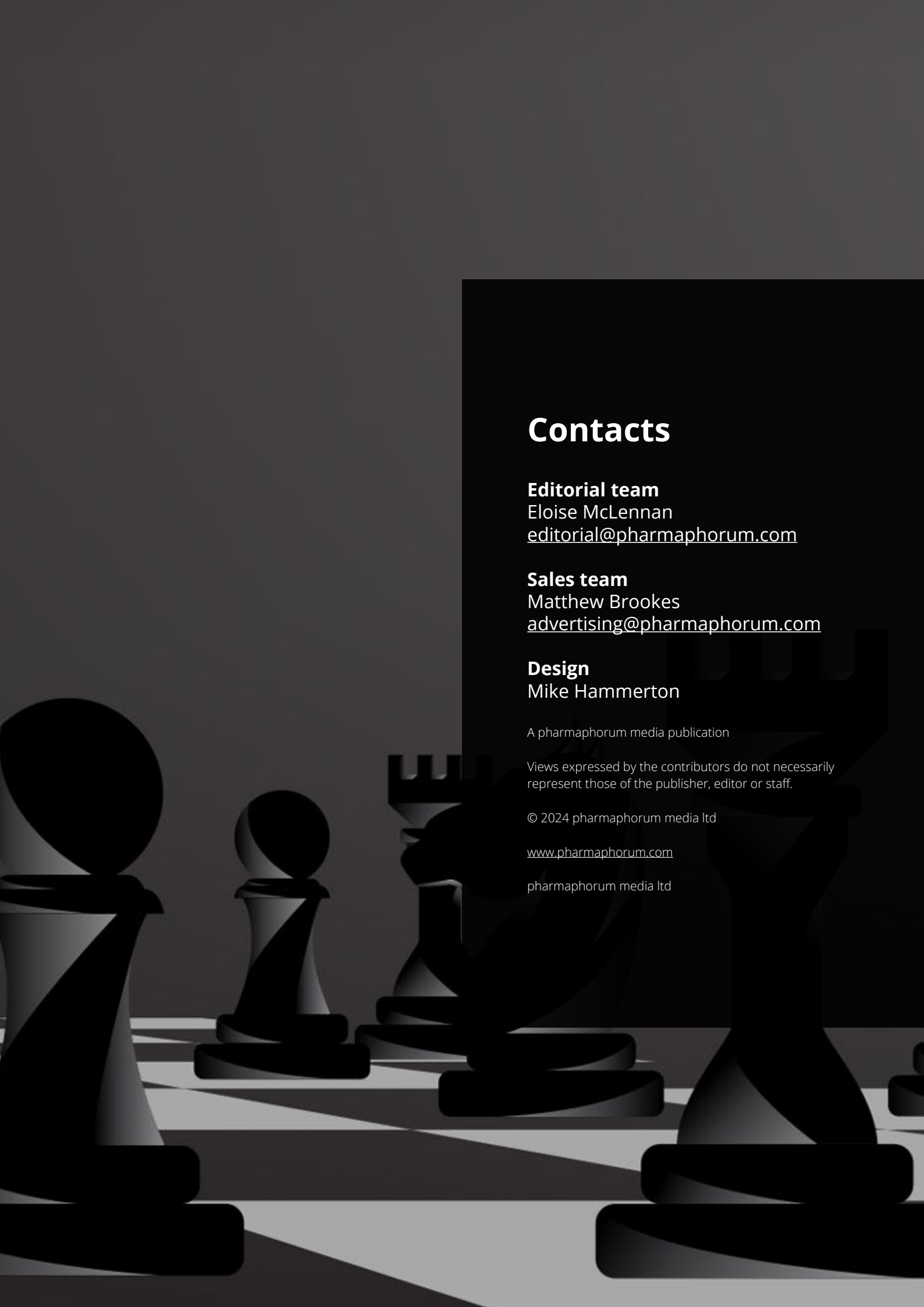

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