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JO SHORTHOUSE, EXECUTIVE EDITOR, IN VIVO

As the biopharma and medtech industries return to some form of normality after the Covid-19 pandemic, challenges hanging over from that time are coming to the fore and will emerge more forcibly in 2023.

While combined pharmaceutical revenues for the companies in Scrip 100 grew 20.5% in fiscal year 2021 to reach $1.1tn, buoyed by sales of vaccines against the virus, the challenges of the industry are not over yet.

Ramifications from the US Inflation Reduction Act, signed into law by President Biden in August 2022, mean that the Department of Health and Human Sciences have the authority to negotiate prices in Medicare for the first time, with the initial drugs up for debate in September 2023.

Couple this with the macro-economic climate of high inflation and a closed IPO window that could cause some smaller companies to face tough decisions about the viability of their businesses, as well as geopolitical uncertainty in the East, and there may be a gathering storm for the biopharma industry in 2023.

While some important changes are being made, such as diversity issues gaining momentum in clinical trials, and the new normal levels of clinical trials resuming, the global pharma and medtech industries may have to endure some gloomy weather before its post-pandemic potential can fully shine.

Look through Outlook 2023 for exclusive interviews and features on topics that reach across the life sciences. Outlook 2023 also includes industry league tables for Scrip 100, Medtech 100 and *Generics Bulletin's* Top 50.

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OUTLOOK

Pharma Outlook 2023: The Rollercoaster Shows No Signs Of Slowing Down

What will 2023 bring as the industry faces one of the toughest periods in the past decade? *In Vivo* asked three industry experts for their views.

BY **JO SHORTHOUSE,** EXECUTIVE EDITOR, EUROPE

The biopharma train is riding into unfamiliar territory. An era shift to high-cost capital from low-cost capital, macro-economic considerations from the intense and unpredictable geopolitical situation in eastern Europe, worldwide inflation, and a continued flirt with global recession could push companies off course, while the swirling myriad of industry issues such as the competition for talent, the politicization of drug pricing in the US, leveling up diversity in clinical trials, and increasing pressure to prove commitment to ESG (Environmental, Social and Governance) issues could make the horizon difficult to see with the required clarity.

And how could we forget the patent cliff? Over the course of the next six years, the patent cliff looms ever closer, with 33 of the biggest selling therapies losing exclusivity. That is a lot of blockbuster drugs in a short period of time.

Fast Ride To The Patent Cliff

In 2023, the market exclusivity for Humira, Januvia/Janumet and Stelara, generators of 2021 US revenues of $17.30bn, $1.77bn, and $5.94bn, respectively, will be lost to its manufacturers. The following year, five drugs lose patent exclusivity, including Bristol Myers Squibb Company's Sprycel and Novartis AG's Gilenya.

In the recent past, high patent exposures have triggered merger activity: BMS's Celgene Corporation buy in 2019 ahead of its Eliquis patent loss, for example, and AbbVie Inc.'s acquisition of Allergan, Inc. in 2020, several years ahead of its 2023 Humira exclusivity loss. Most of the companies facing the highest cliffs, such as BMS, Pfizer Inc. and Merck & Co., Inc., have a high capacity for M&A.

Fred Hassan, chairman of Caret Group and ex-CEO of Schering Plough and Pharmacia, who lobbied for the Part D drug benefit for US seniors as chairman of the industry organization, the Pharmaceutical Research and Manufacturers of America (PhRMA), believes that the removal of the "government non-interference" clause in that original 2003 legislation, in the recent Inflation Reduction Act (IRA) will accelerate cost reduction-driven industry consolidation.

Indeed, Pfizer had an acquisitive year in 2022, with its $6.7bn Arena Pharmaceuticals, Inc. buy, the $11.6bn deal to buy Biohaven Pharmaceutical Holding Company Ltd., the $525m ReViral Ltd. buy in April, and its most recent Global Blood Therapeutics, Inc. acquisition for $4.8bn.

With Pfizer active in the M&A market, dipping into its COVID-19 coffers from sales of its Comirnaty vaccine and the antiviral Paxlovid (nirmatrelvir), which are set to sell $32bn and $22bn, respectively, this year, other companies should be following the Big Pharma's lead.

However, this year it seems most companies have favored bolt-on acquisitions rather than large-scale M&A, as was the case in 2021. By the end of the Q3 2022, total M&A deal value reached $50.7bn compared with $118.1bn for the same period in 2021. Indeed, while Pfizer seems to have spent big in 2022, it emerged that Sanofi was the most active dealmaker, inking 20 deals, while Johnson & Johnson secured 16.

These and many other companies chose to make partnerships in 2022, with the French pharma firm inking seven deals in the first three quarters of 2022 with a reported value of more than $1bn a piece.

Big Pharma is taking its time to pounce on good deals, to find the right asset at the right price. Inherent to this dynamic is good data and value. "They are taking their time, and that's understandable," Antoine Papiernik, chairman and managing partner at European venture capital firm Sofinnova Partners told *In Vivo*. "First and foremost, its data driven. Big Pharma is interested in deals, but the data must be there. Secondly, buying a company that is worth less than its cash is not as easy as it looks," he said.

Acquiring a company worth negative technology value, as many small and mid-size biotechs were in 2022, is a high-risk and high-reward activity. While this is a strategy that many Big Pharma companies opt for on a regular basis, the barriers to this are monetary as well as psychological. "Buying a company like this is complicated because you have to offer something close to the underlying value. And if that underlying value is worth $500m, and the company's worth $100m on the stock exchange, it's very difficult for a pharma company to buy a company at a multiple of its market cap that is above 2x," Papiernik explained. "The boards don't want to be seen overpaying, even though the value would be $500m. And they would find it difficult to pay five times the market cap. They would rather the company be worth $500m and buy it at $500m."

The fiduciary duty of the board, to obtain the best value for the shareholders, is difficult to follow when the large disconnect in decreased valuations is prevalent. However, if we fast forward 12 months, when there is likely to more good data and the VIX Index (the measure of expected volatility in the US stock market) is more stable, prices may come back to a mean average to reflect the true value of companies. This is when the industry will start to make more transactions, said Papiernik.

"When deals happen, premiums are often going to be good because people are looking for quality assets. People are still willing to pay because they have the money, but it must be a quality asset," Hassan told *In Vivo*.

He believes the current US administration's "sceptical view" of large mergers, which will continue for the next two years, is also reflected in the pharma industry's attitude to dealmaking, dampening enthusiasm for larger horizontal deals. "Nobody wants to get trapped in a very long review period, as you lose a lot of value. The US government has not been very successful with its legal challenges, but the delay in getting the deal done influences the valuations, this is not very conducive for big mergers, or even medium-sized mergers," he said.

Political Twists And Turns

And it is not only financial influence coming from the US government. The November mid-term elections brought to the fore the economic and cultural wars felt in the world's largest pharma market which created a more moderate result than many expected. With the US Congress divided after the mid-term elections, pharmaceutical companies that want to weaken the IRA, signed into law by President Joe Biden in August, will have to wait a while longer.

With Congressional Democrats passing major legislation to control drug prices in Medicare in August, the US Health and Human Services Department is authorized to 'negotiate' drug prices in Medicare for the first time and will be releasing an initial list of drugs up for debate in September 2023.

At the time, PhRMA president and CEO Stephen J Ubl released a statement that read: "The President signed into law a partisan set of policies that will lead to fewer new treatments and doesn't do nearly enough to address the real affordability problems facing patients at the pharmacy. We will explore every opportunity to mitigate the harmful impacts from the unprecedented government price setting system being put in place by this law. We will continue to advocate for policies that give patients better and more affordable access to lifesaving treatments and for a system that supports innovation."

Now, with the Democrats in charge of the Senate, and the Republicans running the House of Representatives in January 2023, the pharmaceutical industry will have to regroup to impact the new law.

"The list prices in the US are probably the highest in the world, but they are [simply] 'list prices.' If you hear presentations from companies, they actually follow the net price they are able to realize after rebates and discounts. Biopharma has struggled to get net price increases over the last five years, because the rebates keep going up. Drug costs as a percent of total health care costs for the US, which are at 14%, are well within the 9% to 20% band of similar ratios among other advanced economies. But these are complicated things to explain to voters," said Hassan.

While he admits that some patients, the "relatively small minority of enrolees in Medicare," that do get hit with very

high drug bills on a cost-sharing basis in any single year may feel financial "toxicity," the majority of the enrolees in insurance plans do not see such large out-of-pockets. For those who get individually impacted, more needs to be done on a selective basis. "This across-the-board conversation about price controls is not a good idea," Hassan said.

"Price controls are not the reason that societies innovate and prosper. I think it is hard to know what this particular legislation is going to do because there are still the PBMs, the market price controllers. On top of this, there are some dysfunctionalities in the legislation, which may or may not get fixed," he said. One "dysfunctionality" Hassan points to is that small-molecule drugs become subject to government price interference in Medicare beginning nine years after approval, while single-source biologics are given 13 years. "IRA is meant to be cost-cutting legislation, yet inexplicably, here it incentivizes the typically more expensive biologics over small molecules, this is the kind of thing that often happens when you push through a partisan legislation via the narrow reconciliation pathway," he said.

"IRA is meant to be cost-cutting legislation, yet inexplicably, here it incentivizes the typically more expensive biologics over small molecules, so this is the kind of thing that often happens when you push through a partisan legislation via the narrow reconciliation pathway."

Fred Hassan, Caret Group

Non-visible decisions on R&D projects are already being made as a result of the IRA. Some decisions are also becoming visible. Alkermes plc, for example, has spun off its oncology drugs unit, which is based on the biologics nemvaleukin alfa, an interleukin-2 drug, and two additional cytokine therapeutics. "The Inflation Reduction Act … fundamentally [shifted] the relative economic value of biologic medicines in cancer," chairman and CEO Richard Pops said during the company's earnings call on 2 November.

Meanwhile many have come forward to criticize the law, saying it is particularly destructive to the development of small molecule drugs.

Hassan has individual concerns about the lost opportunity in CNS which is characterized by small molecules that can cross the blood-brain barrier, as opposed to large biotech molecules which typically have a difficult time doing this.

The next decade should be the years in which brain science flourishes, he said, because researchers have learned so much about targeting therapies for diseases such as Alzheimer's, Parkinson's, epilepsy, anxiety and depression. These distressing diseases missed the biotech revolution in the last three decades and also the oncology-led precision medicine revolution in the past decade. A nine-year exclusivity period is not enough to learn much about a drug, he continued. He recalls his time at Wyeth. The company introduced the first of the SNRI-class antidepressant, Effexor (venlafaxine), in 1993. Originally the drug was administered twice a day, but some years later, this was improved to a more targeted delivery beyond the stomach and as a once-a-day form. Beyond its improved adherence benefit, this form also reduced the side effects of nausea and changes to blood pressure. This enabled the company to bring in the anxiety indication on top of the depression indication. Effexor became a blockbuster several years after the drug launched. "That cycle of innovation is not easy to accommodate if you only have a nine-year window, and you can see why this would affect people's investment decisions," he said. Generic venlafaxine has been available since around 2008, and in 2020 it was the 43rd most prescribed drug around the globe.

Round And Round We Go

In 2021, investment in the life sciences sector, and biotech specifically, reached an all-time high. According to figures from McKinsey, venture capital firms invested in 2,200 biotech start-ups in 2016, and by 2021, that number had grown to 3,100. Biotech companies raised more than $34bn globally in 2021, more than doubling the 2020 total of $16bn.

2022, however, spoilt biotech's party. Companies endured a post-pandemic market correction, coupled with macro-economic pressures of inflation and rising interest rates, causing one of the worst years in many decades as market values sank below cash.

For those companies that went public in 2020 and 2021, the impact has been "brutal", said Robert Tansley, partner at Cambridge Innovation Capital. "There are a lot of companies suffering, but also there are a lot of companies who are trading under their cash."

The biopharmaceutical stock performance has caused valuations to fall sharply throughout 2022. At the time of writing (December 2022), the Nasdaq Biotechnology Index is down by year-on-year 11.9%. Falling valuations have made the path harder for companies to raise capital, both for privately and publicly held firms.

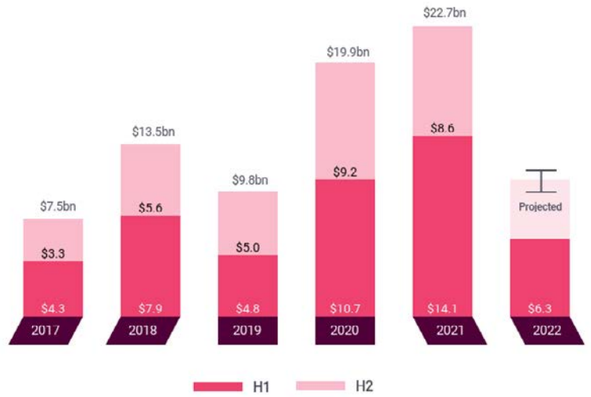
With limited fundraising options, those companies that need to extend their cash runways have restructured and actioned layoffs to protect shareholder value. Companies such as Mereo Biopharma have laid out plans to articulate how their cash will continue to fund lead assets.

Some biotech companies that need cash now may not even survive, Sofinnova's Papiernik told *In Vivo*. "There are two types of biotech companies, those that have two to three years of cash have a real chance to get to the other side of the chasm without too much trouble and meet milestones. If you need money today, you could be in trouble. Even if you have a great company, if that company is in trouble, it may go under if its current investors don't support it," he said.

At the time of writing, Acrivon Therapeutics, Inc.'s $99.4m IPO was only the 20th listing of 2022, while a record-breaking 2021 saw 107 biopharma listings.

The fall in valuations has caused companies to stay away from the public markets, but while these markets continue to confound, there have been some large follow-on financings on NASDAQ.

Exhibit 1: Cell And Gene Therapy Investment By Year



Source: Alliance for Regenerative Medicine

"Many of the founders or the entrepreneurs are not happy at the prospect of selling equity at discounted valuations, they're also concerned about the effect on the existing investors if they sell into the market with a discounted valuation," Hassan told *In Vivo*. "IPOs are going to remain pretty shut, there will be a few IPOs of companies which are higher quality with good assets, but much fewer, like this year. And I think it's likely to remain like that through 2023."

Because the IPO window is shut, and is likely to remain so throughout next year, the impact on those later-stage private companies that cannot list is significant. The US investment bank, Raymond James, estimates that between 50 to 70 companies have filed S-1 forms but cannot list; these companies represent a large number of later-stage companies that will have to do an extra round of private investment.

Private investors now need to back their portfolio companies for longer than they predicted, said CIC's Tansley. "But some large investors who can invest in both public and private are looking at the public markets and, given that valuations have come down so dramatically, are finding a lot of bargains," he explained. Where the investment syndicates are strong, they are doing internal rounds to bridge until at least 2024, and maybe even longer. Where an external investor is brought in, there have been decreases in valuation. The most recent report from the US banking firm, Wilson Sonsini, suggests that there has been around a 30% to 50% reduction in the late-stage valuations when an external investor was brought in.

LARGEST IPOS OF 2022

Jiangsu Asieris	1	$373m (STAR Market in China)
HilleVax	2	$213.9m
Third Harmonic	3	$198.1m
CinCor	4	$180m
Amylyx Pharmaceuticals	5	$176.7m (Upsized IPO)
Prime Medicine	6	$162.8m
Arcellx	7	$142.3m
Lepu Bio	8	$103.9m (HKEX Market in Hong Kong)
PepGen	9	$100.4m
Jiangsu Recbio	10	$97.6m (HKEX Market in Hong Kong)

Leveling Out

Market volatility looks set to continue pharma's rollercoaster ride into 2023. Cell and gene therapy, however, is a market that is expected to have an exciting news flow in 2023, and venture capital remains the bedrock of funding for the sector. In 2023, there are expected to be 14 US, and three European regulatory decisions made. Among those are bluebird bio's lovo-cel gene therapy for sickle cell disease, BioMarin Pharmaceutical Inc.'s Roctavian gene therapy for hemophilia A, and Orchard Therapeutics Limited's Libmeldy gene therapy for metachromatic leukodystrophy. Just over a decade after CRISPR was first discovered, the first CRISPR technology may reach the market, with Vertex Pharmaceuticals Incorporated/CRISPR Therapeutics AG's CTX001 gene editing therapy for sickle cell disease and beta thalassemia on the cards for US, EU and UK regulatory approval.

Venture capital was at 40% of full-year 2021 levels through the first half of 2022, according to figures from the Alliance for Regenerative Medicine (ARM). This indicates

continued investor excitement about scientific breakthroughs and new treatment possibilities, despite investment headwinds, it says.

In 2022, sector financing reverted to pre-pandemic levels from the records set in 2020 and 2021 (*see Exhibit 1*). While it was a difficult environment for public financing, ARM expects total 2022 investment to land somewhere between $9.8bn and $13.5bn, the sector's performances from 2019 and 2018, respectively.

Despite ongoing investment confidence, regenerative medicine remains a subset of the pharmaceutical industry that is hindered by market access issues and commercialization challenges, especially in Europe. Bluebird bio exited Europe in 2021, after failing to achieve "value recognition" for its gene therapy product Zynteglo for beta thalassemia. In another example, in September 2022 Insmed stopped supplies of Arikayce after failing to agree a price with the German National Association of Statutory Health Insurance Funds (GKV). Indeed, according to ARM, seven of the 23 advanced therapy medicinal products (ATMPs) approved in the EU have been withdrawn from that market.

In the US, the latest wave of modernization efforts has been spearheaded by the director for the FDA's Center for Biologics Evaluation and Research, Peter Marks, and these should start to take effect in 2023. Approvals aside, the wave of ATMPs potentially coming to market in the next few years may be hindered by payment systems that are not equipped to allow patients the access to drugs that are desperately needed by the rare disease population.

The Big Dipper

Questioned on this theme by *In Vivo*, all three interviewees stated that fundraising would be the biggest challenge for the next 12 months. "We've seen four or five years of record amounts of money, I think we'll see a significant decrease in 2023," said Tansley. "Those funds which have raised in the last two or three years will be well placed. And often in difficult times, that's when the best returns are had. Those looking to raise may have to temper those ambitions. Fundraising for venture intervention is going to be tough next year."

Sofinnova Partners has 100 portfolio companies and has completed 10 deals and 23 refinancings in the last 12 months. It has been a very active fundraising environment caused by venture investors raising a lot of money over the last two years, said Papiernik. "The coffers are relatively full which has created a 'positive inertia' to the system. People have money and will defend the company when they can." In his view, there is no reason for this situation to change, and 2023 will be no different unless the IPO starts going up, a situation which seems unrealistic. This "harsh environment" will remain the same for the 2023, he said.

There will be a prolonged period of caution until the IPO window opens again, concurred Tansley. "Until we see an uplift in the in the public markets, the later-stage investors will focus on the public markets rather than private," he said.

But, as far as sectors are concerned, the biopharma industry is well positioned as the predominant part of the health care sector. And health care is well positioned compared to the other 10 S&P sectors, said Hassan. "It is a defensive sector, and there is a need for better health care. Populations are getting older. And innovation is helping improve the valuations in the market. I still see health care as a pretty good sector," he concluded.

> **"Those funds which have raised in the last two or three years will be well placed. And often in difficult times, that's when the best returns are had. Those looking to raise may have to temper those ambitions. Fundraising for venture intervention is going to be tough next year."**
>
> Robert Tansley,
> Cambridge Innovation Capital

Outlook 2023: The Irresistible Forces Shaping Medtech Markets And Industry

Market Access Complexities For Medtechs Grow Year On Year But The Essential Success Factors Remain Unchanged

The integration of smart connected care, broadening of diagnosis and therapy into new settings and improvement of chronic disease outcomes will continue to shape the market for devices and diagnostics companies for years to come. But there is also a maze of short-term macroeconomic issues for medtechs to work through.

BY **ASHLEY YEO,** EXECUTIVE EDITOR, EUROPE

After three years of COVID-induced disruptions of varying levels of severity, as it stood in fall 2022, the hope was that 2023 could – should – be a period of more stable market conditions for medtechs.

With COVID, it seems nothing is certain. New US COVID-19 infection rates were still doggedly above a quarter of a million a week late in the year (CDC's COVID Data Tracker). UK cases were fluctuating as the year tailed out, amid talk of a new spike at year end. China's zero tolerance policy indicated that lockdowns, mass testing, quarantine and travel restrictions would remain in place for the foreseeable future.

The Chinese situation was singled out by incoming Philips Healthcare president and chief executive Roy Jakobs, appointed to the post on 15 October to succeed the long-standing Frans van Houten. He warned of continued uncertainties related to COVID-19 measures in China.

Philips Healthcare had more than its share of headwinds in 2022, relating not just to the COVID aftermath but more pertinently to its respiratory products recalls. In 11 years in charge, van Houten shaped the Dutch company to be a transparent model of integrity and responsibility, but the rising Respironics issues found it moving into unaccustomed, uncomfortable territory.

The industry will be watching Jakobs' crisis management credentials and recovery skills in 2023. Faced with a poor Q3 2022, in which only the company's personal health business saw growth, the CEO made his first big decision in deciding to cut around 4,000 jobs. Philips was the industry's fourth largest company by revenues in 2020, but lost ground in 2021 and 2022.

The company is not alone regarding the other challenges for the industry, and Jakobs shared the view of the medtech sector generally that a worsening macro-economic environment and prolonged operational and supply issues are to come in 2023.

Forbes (24 October) wrote that there was no playbook for the economic situation ahead. The list of challenges for medtechs is long.

The global supply chain will be negatively impacted, primarily through a lack of availability of raw materials and electronic components.

These problems are not germane to medtech alone, and other industries' demands for the same goods are piling more pressure on the medtech sector, prompting a more competitive supply environment and higher costs.

Inflation, higher than it has been for several decades, will have impacts up and down medtech P&Ls. Inflationary effects were immediately seen in medtech raw materials, such as cobalt, chrome and titanium components used in orthopedics and lithium batteries for pacemakers.

The cost of labor has increased, and inputs like electricity, especially relating to manufactured goods coming out of Europe are also rising.

Transportation capacity has been affected by port closures and delays associated with the pandemic, leading to longer lead times in receiving raw materials and distributing finished products from manufacturing plants.

The costs of getting medtech products to the hospital have increased. EY life sciences partner Jon Babitt notes that freight inflation in 2022 was up over 60% over the previous year, and was impacting capital equipment severely.

Medtechs are seeing their cost of sales rise, while gross margins decrease. With lingering uncertainty over the duration and extent of COVID-19, they cannot gauge how long or deeply their supply chains will be constrained.

The scenario is also tough for provider organizations whose budgets are coming under increasing scrutiny and pressure, with knock-on effects on procurement and capital spending. Under-strain providers will expect medtechs to step up to provide more workflow solutions.

Medtech companies are eyeing both tougher regulatory agendas and more systems to cope with, and also a broadening and deepening "ESG agenda." Alongside, industry players are monitoring their potential and place in the digital health care environment, mindful of the need to remain competitive as the market evolves.

Supply Chain In Debate

The supply chain headwinds of 2022 are expected to continue into 2023, prompting increased operational supply chain costs for medtechs. Siemens Healthineers CEO Bernd Montag at the company's 9 November results webcast called out cost increases due to the inflationary environment, elevated procurement costs, logistics constraints and product shortages.

> **"Leadership is needed from all angles."**
>
> Ian Milimo, UNDP

If there were positives from the COVID-19 pandemic, one was that it forced the industry to successfully turn to pragmatic and speedy health care delivery solutions. Another was that a debate was started around how local populations can remain protected during the commonly-referred-to "next pandemic."

In this context, supply chain resilience, much in debate in 2022, is now seen as national duty not just a corporate preoccupation. Smaller markets are eager to address it too, in the wake of COVID. Incoming director of the UK's Medtech Directorate told an industry meeting in mid-November: "I've never known the supply chain to be as vulnerable as it is now."

Another view is that "the pandemic showed that global value chains do not always work." That was how University of the West of England (Bristol) professor of innovation Wendy Philips saw the issue, in an address to Westminster Health Forum delegates in October 2022.

A reconfiguration of supply chains can increase supply chain resilience and allow for more manufacturing at the point of care, she said, suggesting redistributed manufacturing (RDM) as an alternative to the model preferred by global medtechs. For her, "scale-out" rather than scale-up should be the goal in future.

This sense was also evident in a medtech industry study commissioned by German industry association Spectaris and compiled by legal firm H&Z Management Consulting.

In the study, released during the 2022 Medica exhibition and conference event, in Düsseldorf, Germany, the authors tellingly stated that "the old truths of Lean & Co no longer apply" in the medtech sector in its current state of evolution.

While the decades-old mantra has been that success in supply chain management precisely requires the lean approach to value creation, the consensus among some 400 manufacturers (based in Germany, Austria and Switzerland) is that this notion has been overturned. Optimized procurement costs are now a priority for only 21% of those companies participating in the H&Z survey, while 68% said securing supply was most important.

In the wake of the pandemic, the building up of safety stocks has been a measure implemented by 88% of the companies surveyed.

China Market Access Issues

China is also investing heavily in national resilience infrastructures. The Healthy China 2030 initiative within China's 14th Five Year Plan puts an emphasis on prevention, strengthening the national public health network and providing "health care for all."

The Chinese government also wants to ensure that by the end of the period 2030-35 there will be many more domestically originated, high-end medical equipment companies active on the global medtech market and featuring in the list of the top 100 companies by revenues.

A range of local measures, including state-based (so-called volume-based) procurement, are making it harder for western companies to compete in China. Some global medtechs now describe this as their number one market access issue.

With the balance of power shifting among the markets, finding ways to work with or around Chinese market access barriers has become a major concern. Industry commentators stress how important it is that foreign companies quickly find a role for themselves in China as it evolves its industrial policy.

They must monitor the market and how the competition is changing. Accordingly, it may be that western businesses learn to derive commercial benefit by actively contributing to the build-up of technology know-how in China. They can also engage in supply chain resilience locally by onshoring greater parts of their value chain.

Industry Growth Drivers

The deepening market access complexities have not altered the contention that medical technology remains a steadily growing industry in the medium and long term.

The growth drivers for industry are continuing medical progress, the aging population and global population growth. That is how Carl-Zeiss Meditec describes the future. The

German company predicts that the number of patients suffering from age-related illnesses will rise continuously, and thus so will demand for high-quality health care.

The mid-2022 global economic downturn was spurred by COVID and Russia's invasion of Ukraine, which initially led to shortages of certain medtech raw materials sourced locally. The wider industry rapidly managed to secure alternative sources for most of their raw materials needs.

The one lingering concern was about supplies of neon gas, which is used in microchip production and of which Ukraine is a major supplier. Supplies of microchips were already under pressure in the wake of COVID and associated logistics problems.

Regulatory Hurdles An Ever-Present Fixture

Increasingly stringent regulation and the multiplicity of regional regulatory requirements are adding to the complexity and cost of doing business globally.

The EU's transition from directives to regulations and the tougher requirements for manufacturers accessing the EU market has been the biggest talking point overall for the global industry since the Medical Device and In Vitro Diagnostic Regulations (EU 2017/745 and EU 2017/746) came into effect five years ago.

COVID briefly displaced it, and the Environmental, Social and Governance (ESG) agenda has rapidly risen to challenge companies to comply quickly and comprehensively. ESG is now on every medtech's radar, and genuine compliance will become a moral and ethical duty for manufacturers.

Nevertheless, pre-market regulation remains the most significant long-standing issue for medtechs.

"The time is now to put patients properly at the center, enabled by technology."

Joseph Smith, BD

The UK is mid-way through developing its post-Brexit standalone regulatory system. In late 2022, the UK Medicines and Healthcare products Regulatory Agency (MHRA) gave in to pressure and said it would extend the mid-2023 deadline for accepting CE-marked products in Great Britain by a year until mid-2024.

Global companies are known to be frustrated by the proliferation of national systems that might not converge with systems already in place.

Switzerland has taken what it sees as a pragmatic stance following the non-renewal of its mutual recognition agreement (MRA) with the EU. It recognizes EU-approved products indefinitely. In addition, its parliament voted in November 2022 to admit US FDA-approved innovations onto the national market.

Switzerland would become the first European country to accept both CE-marked and FDA-approved medtech. Countries outside Europe, such as Singapore, Australia and Israel can do this freely, but European companies locked into the CE-marking cannot.

The UK has similar, thus-far unshaped ambitions, but the success of Switzerland in being a de facto globally harmonized European country in terms of medtech regulations would likely reverberate among fellow European markets that privately would also like access to US innovations – on the strength that the US approves more quicky and has in the past three to four years become the global medtech launch market.

The consensus is that MDR will slow down local patients' access to medtech innovations. Both the MDR, postponed for a year, and the IVD Regulation (subject to 11th hour transition arrangements for certain categories of diagnostics) will lead to products disappearing from the market.

Even the extended deadlines cannot be met by most of industry and there is not enough conformity assessment body capacity to cope with high volumes of file auditing demands, especially given that existing products must be recertified by May 2024 against the new regulations.

In late 2022, the European industry requested that products with certificates issued under the Medical Devices Directive be subject to risk-dependent transitions, just as happened in January 2022 for diagnostics under the IVDR.

Sustainability Top Of The To-Do List

Compliance with ESG needs has become a necessary distraction for the medtech industry.

The drive to develop a circular economy for medtech products has compelled manufacturers to develop in-house responses to initiatives like NHS England's net zero carbon targets for 2040 and 2045. Compliance is not regulated as such, but businesses that fail to meeting the requirements will eventually not be allowed to trade with the UK provider.

UNDP's Green Procurement Drive

Meeting ESG demands, driving continued business growth is the balance medtechs must strike. The climate change doomsday scenario message was reinforced by United Nations Development Programme (UNDP) officer Ian Milimo.

Istanbul-based Milimo, a UNDP program specialist, was a keynote speaker at CMS's global life sciences and healthcare forum (Brussels, September 2022). Milimo said the climate crisis was creating new health crises, and called on health care companies to engage in sustainable procurement.

UNDP's Sustainable Health in Procurement Project (SHiPP), soon to be renewed for 2023-28, aims to reduce environmental harm caused by the manufacture, use and disposal of medical products.

The project aims to develop sustainable health procurement practices in 10 lower-and middle-income countries that have a combined health care purchasing power of $5bn-$6bn annually. The goal is to line up practices with UNDP's Sustainable Procurement in the Health Sector (SPHS) initiative to "green" the global health sector.

New health challenges are emerging from rising temperatures and the climate crisis, such as increased incidence of cardiovascular disease, chronic obstructive pulmonary disease (COPD) and asthma, waterborne diseases and heat-related deaths.

"The potential of agile methods is not yet leveraged, yet other industries show how it can be done."

Spectaris and H&Z Management Consultancy

"Leadership is needed from all angles," said Milimo – from politicians, businesses and lawyers – to develop the necessary laws to protect the environment. The UNDP has issued a business call to action (BCTA) to encourage "partnerships for sustainability."

"We are no longer talking about climate change, but climate crisis," he said.

The E In ESG: Leading Companies Respond

Medtech industry leader Medtronic set a goal of achieving carbon neutral operations by 2030. It plans to cut packaging waste by 25% for certain high-volume products by 2025, compared with a 2021 baseline. By 2027, the Dublin, Ireland company will have reduced paper instructions for use (IFUs) by 35%.

Johnson & Johnson also supports a move from printed to electronic IFUs. The New Brunswick, New Jersey company also says that plastic pouches on European product deliveries will be eliminated.

The company is also working on molecular recycling techniques to enable the use of recycled plastic. Current recycling processes make recycled plastic unacceptable for use in medical devices, says the company, whose renewable and energy efficient programs are saving 48,000 tons of CO_2 annually.

Abbott Laboratories targets a 30% reduction in absolute Scope 1 and 2 carbon emissions (2018 baseline) by the end of 2030.

The S In ESG

The societal agenda in ESG is no less daunting a challenge. In Europe, countries leading the way on legislative programs include France, with its Loi de Vigilance, and Norway, whose transparency law came into effect in July 2022.

Germany's supply chain duty of care act (Lieferketten-Sorgfaltspflichtengesetz – LkSG) was due to come into force during the fourth quarter of 2022. Legal firm CMS has been advising on the legal aspects, said CMS Hamburg's Christoph Schröder, speaking at the CMS forum.

Elsewhere, a UN treaty is in early discussions, and the European Commission has proposed a Corporate Sustainability Due Diligence Directive (CSDDD), laying down companies' obligations on human rights and avoiding environmental adverse impacts.

Keeping abreast of these regulations implies a high compliance burden for medtech companies. However, they must comply in all countries where they have subsidiaries, said CMS. Equally, customers might actively request that their suppliers fall into line with new local rules.

Shooting For The Stars On Digital Readiness?

Digital maturity in health care has been a promise for many years, but a reality take on the pace of progress towards the digital transformation was provided by ZS principal Brian Chapman.

"It can be tempting to shoot for the stars to include AI, and virtual and other capabilities," said Chapman, who is a member of *In Vivo*'s editorial board. But in conversation with the PatientPop portal, he said digital transformation in medtech and health care to date had been somewhat less ambitious. It currently extends to:

- Tools that bring insights (wearables and patient-reported outcomes). Automated collection of PROs and home diagnostic testing are currently delivering value to patients and carers;
- Significantly improving decision making by going beyond readily-available electronic medical records; and
- Back-office process improvements, for billing, coding and referrals – ostensibly mundane applications, but equally, in digital health care, "this is probably the thing that is closest to real today," Chapman said.

Three Irresistible Forces In Health Care

This Medtech Outlook for 2023 might sound like it has been written in a minor key, but medtechs are aware of near-term market difficulties ahead. Equally, there are always compelling arguments in favor of medtech in the medium and long term.

EY's John Babitt reminded *In Vivo* that medtech is a space fueled by innovation, at present especially by robotics and digital surgery, liquid biopsy and non-imaging diagnostics, and remote monitoring technologies that facilitate care outside of the chronic or acute care hospital settings.

Similarly pragmatic is BD's chief scientific officer Joseph Smith. Addressing APACMed's 2022 Medtech Forum in Singapore, Smith agreed that smart connected care was one of the three irresistible forces that are shaping health care in the 2020s.

The transition to patient care settings outside the hospital is another, and the third is applying both of these to tackle the burdensome issue of chronic disease.

"We see the value of technology driving better insights and better automaticity of care, which improves everything from speed to diagnosis, to better pharmacy management at hospitals to improvement in bedside patient care," he said.

Moving care to the patient is now more or less expected. The care of chronic patients will be transformed by connected diagnostics for a broader range of conditions and connected monitoring that collects more than just vital signs information.

"The time is now to put patients properly at the center, enabled by technology," said Smith to the APACMed audience. "I do think we are at a special moment in history."

SCRIP 100 ■

Decentralized Clinical Trials: Driving Economic Value In Clinical Development

The advantages of decentralized clinical trials (DCTs) are well recognized. COVID-19 showed that the DCT model was not only viable but practicable as a means of overcoming physical constraints on patient access to trial sites. Additional benefits are increasingly in evidence, such as speed, efficiency, patient convenience and diversity, improved recruitment/retention or data enrichment.

Nonetheless, clinical trials are expensive, and the attrition rate can be brutal. Trial sponsors want to know that, if they take DCTs on board, their bottom line is going to benefit too. Making a case for the economic merits of DCTs, though, can be challenging. The baseline costs of DCTs may not ultimately look that different from those of a conventional trial.

A better argument can be made for outcomes, but those may be hard to pin down, especially at the stage of deciding how a clinical trial is going to roll out. The inherent complexity of clinical trials also complicates generalized claims of economic value. No two studies are quite alike, given variables such as study design, duration, therapy area, patient population or disease prevalence.

A recent analysis by the US-based Tufts Center for the Study of Drug Development, quantifying the financial value of DCTs, provides an opportunity to open up the discussion. The Tufts report found evidence of substantial value in DCT strategies, as measured by changes in expected net present value (eNPV).

The Tufts study looked at three measurable factors with a known impact on the financial value of drug development: clinical-phase cycle times; screen failure rates; and the number of substantial protocol amendments. All of these KPIs improved in the DCT setting. In Phase II, for example, substantial protocol amendments fell from an average 3.3 (non-DCT) to 2.4, screen-failure rates from 31.5% to 24.1%, and Phase duration from 30 to 27 months.

In both Phase II and Phase III, the Tufts analysis calculated that, on this parameter, the increase in sponsor eNPV from DCTs in Phase II was $8.8m per investigational drug. That amounted to base-case RoI of x 4.62. On the same parameter, base-case eNPV inn Phase III rose by $41.2m to deliver RoI of x 13.2.

The Impact Of Time On Cost

Not all of these components had equivalent value in relation to costs, though. In some instances (e.g. Phase II protocol amendments and screen failures), investment in DCT methodologies did end up diluting RoI for those particular elements. Nonetheless, points out Harpreet Gill, vice president, decentralized clinical trials at ICON, factors such as protocol amendments, “aren’t necessarily baked into the initial trial budget and the impact is difficult to predict at the outset”.

However, reductions of 27% in substantial protocol amendments at Phase II, and of 6% at Phase III, are “going to affect the long-term lifecycle of the overall drug-development programme”, Gill comments. “Logically, that will improve the return on your investment and reduce the overall cost of drug development.”

As the Tufts study underlined, duration is a key driver of cost inflation in clinical trials. This can be mitigated in DCTs through faster patient recruitment and site start-up, that are typically inflationary components.

Decentralization increases the speed of patient recruitment and reduces costs through digital and community outreach campaigns. This increased direct to patient outreach will often decrease the number of sites needed to recruit the same number of patients and associated site initiation costs including, Institutional Review Board (IRB) approval.

Driving Value With Patient Diversity and Retention

DCTs also deliver economic value by addressing patient diversity and retention.

Direct and broader digital patient recruitment also expands the diversity of patients with access to trials, an area that is seeing increased interest from regulators. As Gill points out, regulatory bodies such as the US Food and Drug Administration have been vocal about the importance of diversity in clinical trials. Here, ICON has seen some “quite phenomenal” outcomes, such as 17% diversity in a heart-failure study, higher than would be expected from this type of study. Typically, a clinical trial will involve a very specific patient cohort, then regulators may ask for additional studies to provide evidence from different study populations. Covering a broader patient base from the outset should help reduce this demand and associated costs from follow-up studies.

Once patients are recruited, there is the further challenge of patient retention and compliance: 85% of clinical trials fail to retain enough patients and the average dropout rate is 30%. Here, the decentralized model increases patient centricity and optionality, by offering services such as home health. This reduces the burden on patients and increases retention and compliance. Moving the trial increasingly onto the patient’s own turf, lowers the barrier to participation and brings benefits in terms of patient diversity, protocol compliance, engagement and patient retention with patients no longer having the burden of travel to the study site. According to a Baird report on DCTs, with remote visits, 38% fewer patients discontinue early and patient completion rates improve to 89% versus 60% in traditional trials.

One other key challenge and cost driver is delays due to data quality. DCTs alleviate this risk by driving better compliance generating data directly from source leading to higher-quality more reliable data. The Baird analysts found a 33% reduction in data variability for decentralized clinical versus traditional studies.

As Gill explains, DCTs enable the sponsor to be more agile with the collection of data directly from patients in real time. They can take early action to avoid protocol deviations or patient non-compliance, while delivering “cleaner” outcomes and outputs over the longer term.

Where The Value Sits

In making the economic case for DCTs, ICON draws on experience from more than 60 decentralized or hybrid studies conducted over the last few years, as well as over 400 in-home service projects. These have yielded “very clear proof points” of where DCT methodologies generate value, Gill says.

For example, providing focused support to patients throughout the trial, and within the patient’s own ecosystem, whether through home-health visits or concierge services, “really does improve patient retention, reduce drop-out rates and keep the patient engaged in the study”, Gill notes. In economic terms, this may be less about baseline costs *per se* than how costs shift with the transition to a decentralized model.

For example, the initial impact and investment of setting up home-health or digital health technology may be inflationary. On the other hand, and depending on the needs of the study, there may be compensatory deflationary elements that balance the investment out, such as fewer sites, reduced on-site monitoring, reduced fees for IRB reviews.

Concierge services may be seen as an additional cost to the sponsor upfront however, steering the patient through every step of the clinical-trial journey will ultimately bring real benefits to the study. These services can include everything from timely provision of sensors & wearables, ensuring patients can set up and log on to the technology, training older patients to manage the technology, helping a patient prepare for a pending telehealth visit, to providing ongoing technical support where necessary.

All of this helps to avoid protocol deviations and keep patients’ interest levels up – both key components of value in clinical trials. “Every time you recruit a patient, there is cost involved,” Gill points out. “If your patients don’t drop out and are compliant, that’s also going to have an overall effect on the economic outcome and value of the study.”

85%
of clinical trials fail to retain enough patients and the average dropout rate is
30%

Driving Metrics That Reflect Economic Value

These are the kinds of metrics ICON is now focusing on, and will continue to measure and quantify throughout its studies, to drive home the message that DCTs really can elevate the bottom line. That means first sitting down with clients, right at the start of the study, taking them through the DCT model, and showing where costs are likely to arise and/or shift.

“Most of the studies are going to be hybrid, so there will be some movement,” Gill elaborates. “From there on, though, we want to concentrate very much on the metrics: things like compliance with eCOAs (electronic clinical outcome assessments), recruitment rates, speed of recruitment, patient retention. We can look at all those factors during the study as leading indicators to see how DCT methods influence the study’s economic value.”

For the moment, publications such as the Tufts study are helping to put these issues into perspective for clients who may wonder where and when the economic benefits from DCTs are really going to emerge. “Some clients have never worked on a heavily decentralized study, and they view these as a risk,” Gill acknowledges. “Industry research really does help us to have these discussions and develop the narrative around increased value.”

Pfizer Leads An Unusual Year For The Scrip 100

Pfizer catapulted back into the lead in the pharmaceutical rankings on the strength of COVID-19 revenues while BioNTech and Moderna both made the list for the first time.

BY **JESSICA MERRILL,** SENIOR EDITOR, US

It was an unusual year for the Scrip 100 rankings as revenues from the sale of vaccines and treatments for COVID-19 skewed the leaderboard in ways that could not have been anticipated before the virus emerged in 2020 and sparked a global health crisis.

Pfizer Inc. reclaimed the number one spot in the drug company rankings based on 2021 pharmaceutical revenues, while two young biotechs – BioNTech SE and Moderna, Inc. – debuted in the rankings for the first time, with BioNTech breaking into the top 20 at number 15 and Moderna breaking in at number 21.

Demand for COVID-19 vaccines in 2021 and a global mass vaccination campaign resulted in two new brands – Pfizer/BioNTech's Comirnaty and Moderna's Spikevax – that are larger by revenue than most pharmaceutical companies included in the Scrip 100. Industry's response to COVID-19, which also resulted in monoclonal antibody drugs and antivirals, contributed to higher revenue growth for the Scrip 100 companies overall.

Pharmaceutical revenues for the 100 companies in the Scrip 100 combined grew 20.5% in 2021 to reach $1.1tn.

While the successful commercialization of vaccines against COVID-19 were a boost, particularly for Pfizer, BioNTech and Moderna, maintaining those positions long term will be challenging as the COVID-19 market transitions to a commercial one driven by regular boosters and demand for vaccines tapers off.

Pfizer and BioNTech are partnered on the commercialization of Comirnaty, which generated $39.9bn in 2021, while Moderna is commercializing Spikevax, which generated $17.7bn. Both products contributed to another year of strong financials for their developers in 2022, though Pfizer, in particular, is poised for an unprecedented year driven by sales of Comirnaty as well as the antiviral Paxlovid (nirmatrelvir/ritonavir), which was authorized in late 2021 and Pfizer owns sole rights to.

Smaller, Then Bigger

For Pfizer, returning to the top of the Scrip 100 was unexpected, coming after a multi-year strategic initiative to scale back the size and scope of the company. That effort involved narrowing the focus of the diversified big pharma primarily to innovative pharmaceuticals, culminating with the spin-out of Pfizer's Upjohn established products business in 2020 into a new company.

Now, on the strength of Comirnaty, Pfizer catapulted back up to the number one spot – and by a staggering margin.

Upjohn was merged with Mylan to form Viatris Inc., which ranked number 20 in the Scrip 100 rankings. Viatris is now in the midst of its own reshaping that will change the size and focus of the company as it looks to exit biosimilars and certain other businesses like women's health so that it can invest more into innovative pharmaceuticals in areas like ophthalmology and dermatology.

As a result of the Upjohn spin-out and that out of consumer health care as well, Pfizer became a substantially smaller company by revenue, and last year Pfizer relinquished the number one spot it had long held in the Scrip 100 rankings, dropping to number seven.

Now, on the strength of Comirnaty, Pfizer catapulted back up to the number one spot – and by a staggering margin. The company's 2021 pharmaceutical revenues of $79.56bn were more than $20bn above those of Pfizer's next big pharma peer – AbbVie Inc. – and more than $10bn higher than Pfizer's prior peak revenue of $67.81bn in 2010, the year after Pfizer merged with Wyeth and while it still retained patent protection for Lipitor.

BioNTech and Moderna – the mRNA developers behind the two vaccines – were also financially rewarded for their pandemic response.

Both companies joined the Scrip 100 in unprecedented positions for young biotechs having never previously generated revenue from the sale of commercial drugs. BioNTech made a debut at number 15 and Moderna at number 21, with those newcomers, along with the Chinese drug maker Sinovac Biotech Ltd. and Viatris, displacing Teva Pharmaceutical Industries Ltd., Biogen, Inc. and Astellas Pharma, Inc. in the top 20.

Regeneron Among Other Big Movers

Regeneron Pharmaceuticals, Inc.'s growth in the Scrip 100 was also notable, with the biotech jumping 10 spots in the rankings to number 22, driven in part by COVID-19. The company's 2021 pharmaceutical revenues increased 89% to $16.07bn, driven by solid growth of core brands Eylea (aflibercept) and Dupixent (dupilumab) and turbo-charged by the addition of monoclonal antibody treatments for COVID-19, which added $5.83bn to the topline. Regeneron ranked number 32 in the Scrip 100 in 2020.

Eli Lilly and Company also benefited from the sale of COVID-19 antibody therapeutics in 2021, and rose in the Scrip 100 rankings to number 12 in 2021, from number 14 the year before. The company's 2021 revenue grew 15% to $28.32bn, but excluding the antibodies for COVID-19, revenue grew 10%.

Changes at the top of the leader board, including Pfizer's return to the top spot and strong growth by AbbVie in the number two position and Johnson & Johnson in third resulted in Novartis AG and Roche Holding AG slipping in the rankings. Novartis topped the leader board in 2020 but fell to the number four spot in 2021, while Roche dropped from number three to number five.

While Novartis and Roche both experienced pharmaceutical revenue growth in 2021, that growth was outpaced by that of AbbVie, which grew 22.7% in 2021, and J&J's pharmaceutical business, which grew 14.3%. Both of the US companies have been on solid financial footing, but are approaching more challenging periods heading into 2023, when they are both poised to lose their top-selling drugs to biosimilar competition.

AbbVie's Humira (adalimumab) is set to face biosimilar competition beginning in January 2023, positioning the company directly into a strong headwind, given that Humira accounted for 37% of AbbVie's 2021 revenues. J&J's Stelara (ustekinumab) is also the company's top-seller, and the loss of exclusivity in the second half of 2023 will also be hard for the company to navigate, though to a lesser extent.

J&J is less reliant on any single drug; Stelara made up 17% of J&J's 2021 pharmaceutical revenues. The company has vowed to investors that the pharma business will grow through 2025 despite the loss of Stelara and has set a goal to reach $60bn in pharmaceutical sales by then.

The diversified health care company is also in the midst of a big transition, with the goal of becoming a leaner pharmaceutical and medical device-focused organization. The company is targeting a spinout of its consumer health care organization next year into a new company called Kenvue.

Scrip 100 Ranking	Company	Country	Pharma Sales ($m)
1	Pfizer	United States	79,557
2	AbbVie	United States	56,197
3	Johnson & Johnson	United States	52,080
4	Novartis	Switzerland	51,626
5	Roche	Switzerland	49,276
6	Bristol Myers Squibb	United States	46,385
7	Merck & Co	United States	42,754
8	Sanofi	France	39,379
9	AstraZeneca	United Kingdom	37,417
10	GlaxoSmithKline	United Kingdom	33,714
11	Takeda	Japan	32,514
12	Eli Lilly	United States	28,318
13	Gilead Sciences	United States	27,305
14	Amgen	United States	25,979
15	BioNTech SE	Germany	22,446
16	Novo Nordisk	Denmark	22,393
17	Bayer	Germany	21,703
18	Sinovac Biotech Ltd.	China	19,375
19	Boehringer Ingelheim	Germany	18,090
20	Viatris	United States	17,886
21	Moderna, Inc.	United States	17,675
22	Regeneron Pharmaceuticals	United States	16,072
23	Teva	Israel	15,878
24	Baxter International	United States	12,784
25	Astellas	Japan	11,383
26	Biogen	United States	10,982
27	CSL	Australia	9,980
28	Otsuka Pharmaceutical	Japan	8,905
29	Fresenius SE & Co. KGaA	Germany	8,508
30	Bausch Health	Canada	8,434
31	Merck KGaA	Germany	8,385
32	Vertex Pharmaceuticals	United States	7,574
33	Eisai	Japan	6,889
34	UCB	Belgium	6,471
35	Servier	France	5,589
36	Sun Pharmaceutical	India	5,199
37	Grifols, S.A.	Spain	4,720
38	Abbott Laboratories	United States	4,718
39	Sumitomo Dainippon Pharma	Japan	4,700
40	Shanghai Fosun Pharmaceutical Group	China	4,461
41	Daiichi Sankyo	Japan	4,456
42	Sino Biopharmaceutical	Hong Kong	4,165
43	Jiangsu Hengrui Medicine Co. Ltd.	China	4,016
44	Shanghai Pharmaceutical Group Co., Ltd.	China	3,891
45	STADA	Germany	3,844
46	Asahi Kasei Pharma	Japan	3,789
47	Mitsubishi Tanabe Pharma	Japan	3,516
48	Alexion Pharmaceuticals[1]	United States	3,337
49	CSPC Pharmaceutical Group Ltd.	Hong Kong	3,250
50	Horizon Therapeutics plc	Ireland	3,226
51	Kyowa Hakko Kirin	Japan	3,209
52	Aurobindo	India	3,173
53	Ipsen	France	3,126
54	Jazz Pharmaceuticals	Ireland	3,079
55	Endo International	Ireland	2,993
56	Cipla	India	2,939
57	Chiesi	Italy	2,862
58	Sichuan Kelun Pharmaceutical	China	2,679
59	Lundbeck	Denmark	2,592
60	Dr Reddy's	India	2,567
61	Ferring Pharmaceuticals	Switzerland	2,557
62	Shionogi	Japan	2,510
63	Joincare Pharmaceutical Group Industry Co., Ltd.	China	2,466
64	Shandong Buchang Pharmaceuticals Co., Ltd.	China	2,444
65	Incyte	United States	2,322
66	Santen	Japan	2,274
67	Ono	Japan	2,241
68	Mallinckrodt	Ireland	2,209
69	Lupin	India	2,191
70	Amneal Pharmaceuticals	United States	2,094
71	Zydus Lifesciences (earlier Cadila Healthcare)	India	2,043
72	Harbin Pharmaceutical Group Co., Ltd.	China	1,985
73	CSL Vifor	Switzerland	1,919
74	Livzon Pharmaceutical Group	China	1,870
75	Hikma Pharmaceuticals	United Kingdom	1,856
76	KRKA	Slovenia	1,852
77	BioMarin Pharmaceutical	United States	1,846
78	Recordati	Italy	1,812
79	Swedish Orphan Biovitrum AB	Sweden	1,810
80	Sawai	Japan	1,766
81	Gruenenthal	Germany	1,735
82	Meiji Holdings	Japan	1,712
83	United Therapeutics	United States	1,686
84	Teijin Pharma	Japan	1,672
85	Celltrion	South Korea	1,671
86	Gedeon Richter	Hungary	1,667
87	Glenmark Pharmaceuticals	India	1,665
88	Nichi-Iko	Japan	1,631
89	Leo Pharma	Denmark	1,584
90	Seattle Genetics Inc. (Seagen)	United States	1,574
91	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	China	1,569
92	Jiangsu Hansoh Pharmaceutical	China	1,540
93	Yuhan Corp	South Korea	1,475
94	Exelixis	United States	1,435
95	Zhejiang Medicine Co., Ltd.	China	1,415
96	CR Double-Crane Pharmaceuticals Co., Ltd	China	1,413
97	Towa	Japan	1,411
98	Samsung BioLogics	South Korea	1,371
99	Genmab A/S	Denmark	1,349
100	GC Pharma	South Korea	1,344

1 Alexion was acquired by AstraZeneca in July 2021; figure is for H1 2021 only.

The Scrip 100 ranking is based on Citeline's analysis of fiscal year 2021 prescription pharmaceutical sales data for the top 100 biopharmaceutical companies. For more information contact: Eleanor.Malone@informa.com.

Outlook 2023

The Scrip 100 universe gathers 2021 financial performance data and compares the activities of the top biopharma businesses, ranked by pharmaceutical sales.

WHO GETS IN?

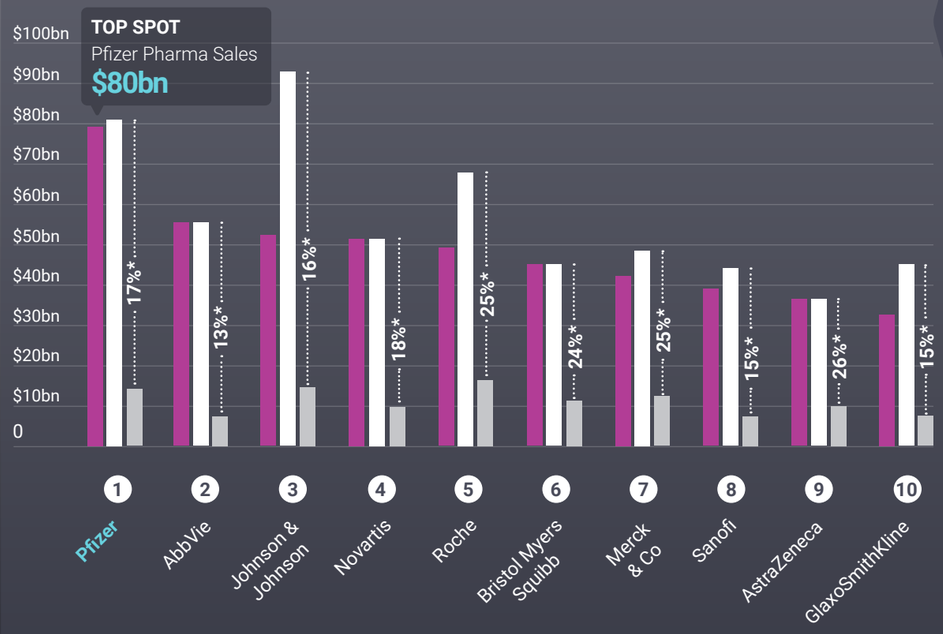
Top 100 companies based on pharmaceutical sales only for fiscal year 2021

Combined Pharma Sales

Number of people employed by Top 20

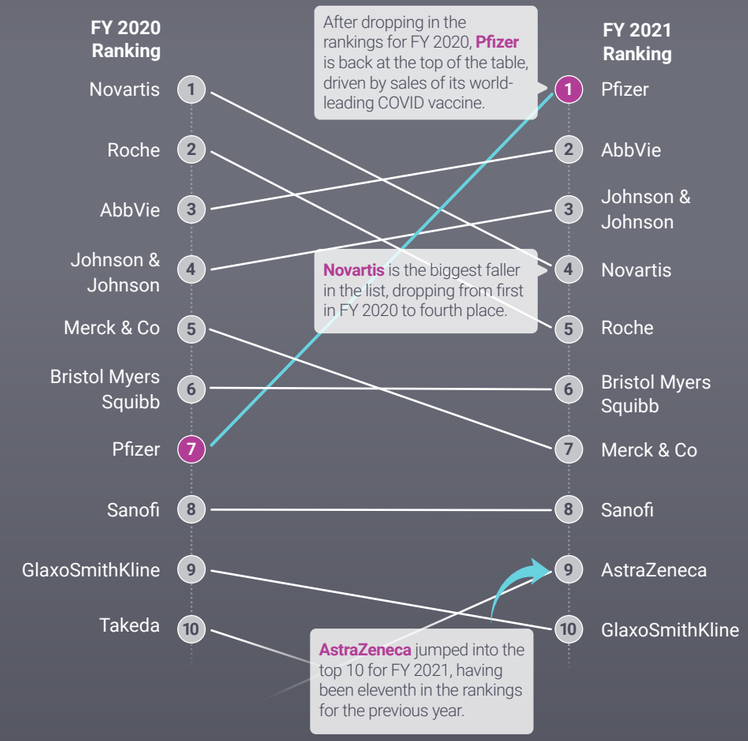
1.8 million

A Closer Look At The Top 10

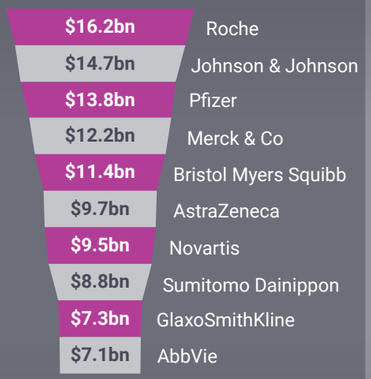


Who's Up Vs. Who's Down

For the first time in recent years, the top 10 list in the Scrip 100 has seen a dramatic shuffle.

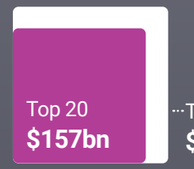


R&D Highest Spenders



Having increased its R&D spend in FY 2021, **Roche** remains top of the table for another year.

R&D spend*

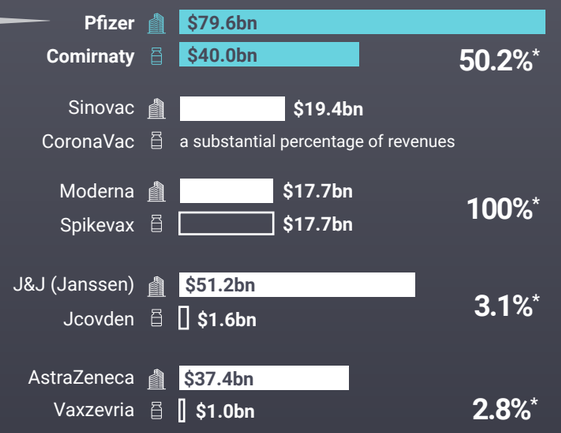


*Some companies do not report R&D expenditure; R&D spend not limited to Pharma only in all cases

COVID-19 Influence: 2021 Sales

Companies with marketed COVID-19 vaccines rose in the latest Scrip 100 ranking, as products were bought by governments and health care systems worldwide to tackle the coronavirus pandemic. The best selling product is **Pfizer** and **BioNTech's** mRNA based vaccine, **Comirnaty**.

Company Vaccine



Moderna catapulted into the Scrip 100 ranking this year, landing just outside of the top 20 list at number 21 by FY 2021 pharma sales. Its only marketed product is an mRNA based COVID-19 vaccine; **Spikevax** is approved in more than 70 countries.

* % of pharma sales

Comirnaty sales figure represents sales booked by Pfizer. Sinovac does not break down individual product sales but the vast majority of its 2021 sales were for CoronaVac. Before COVID-19, its 2019 sales were $246m.

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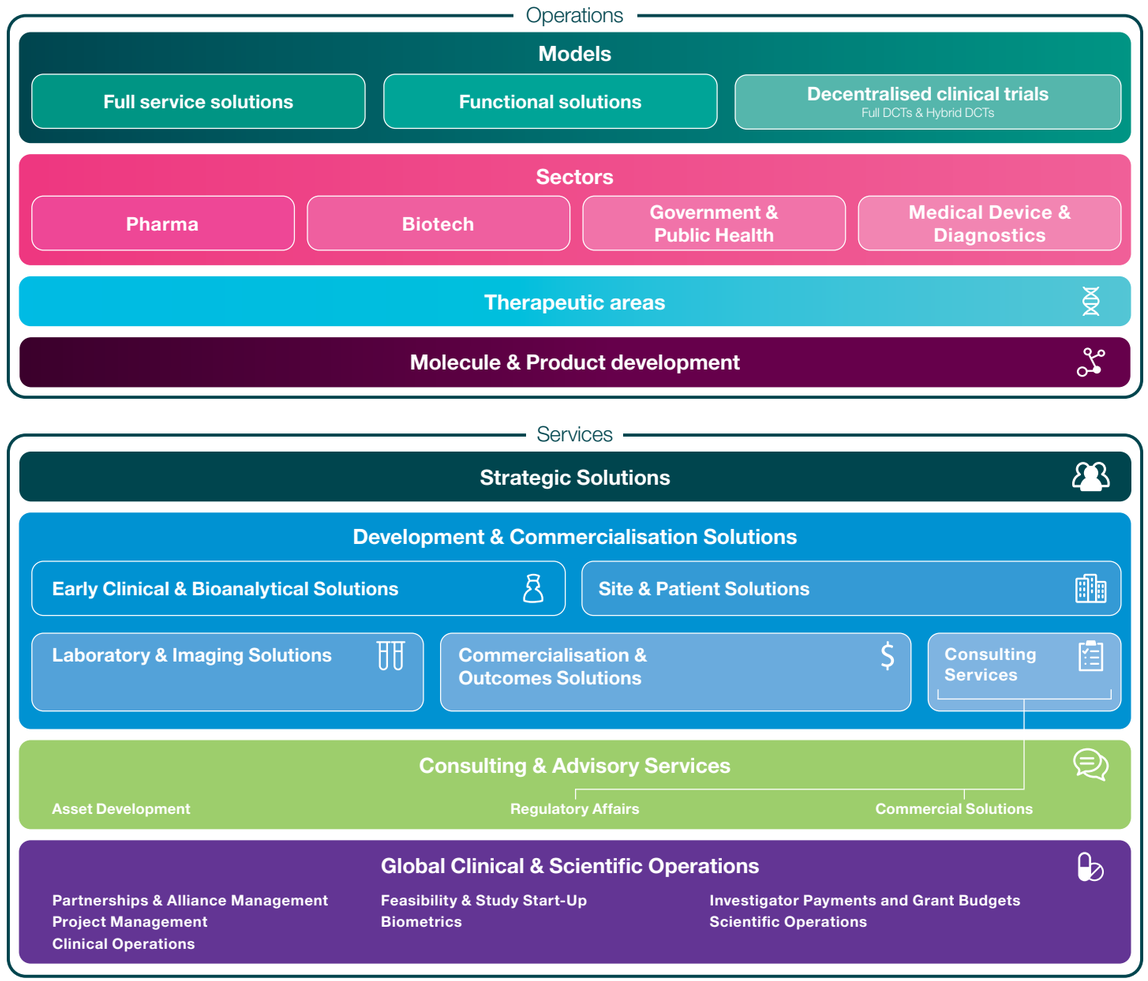
ICON offers the most comprehensive suite of integrated clinical development services in the industry. We've designed fully customisable solutions to help our customers achieve their goals across a seamless delivery model spanning their product's entire lifecycle.



ICON has established relationships with a majority of the world's top pharmaceutical and biotech companies, offering:

Scale: With an expansive portfolio of integrated clinical, commercialisation and consulting services, global presence, depth in therapeutic expertise, and data-driven healthcare technology, we deliver globally scaled expertise & solutions for all customers and patients. ICON is:

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- Global number 2 in full service Ph 2/3 clinical research
- Global number 2 in Early Phase clinical research
- Global number 3 in Late Phase & RWE
- Global number 4 in Central & Speciality Laboratory Services

Focus: With no ownership from a parent organisation with different business lines or models, and no distractions from 'near adjacencies', we are completely committed to achieving clients' clinical development programs. Our 40,500+ employees have a singular focus on successful clinical research and commercialisation, leveraging transformational technology and innovation to execute clinical trials from Phase 1 to post-approval studies with the highest quality, expertise and speed.

Speed to market: Our extensive services portfolio, digital and data technology capabilities, and enhanced access to more diverse patient populations, have been combined with flexible delivery approaches and partnership models – all with the aim of reducing development time and costs.

Flexible partnership models: We have partnerships with a majority of the world's top biopharma and biotech companies worldwide. We are the global leader in Functional Service Provision and a top global provider of full service clinical research. Regardless of the size of your organisation or your project, we work your way.

Delivering integrated decentralised clinical trials: Clinical research should engage with patients wherever they are. ICON's customised, integrated decentralised clinical trial solutions can help you achieve better outcomes, while maximising recruitment and retention of diverse patient populations.

ICON has all the service components to deliver decentralised clinical trials and the experience and expertise to provide integrated, customised solutions.

Access to patients: Patients are at the heart of everything we do at ICON. We provide the most comprehensive and connected patient journeys across the largest and most diverse patient populations. Our site networks, patient recruitment expertise, and in-home services unlock access to millions of patients. ICON streamlines the clinical trial process, accelerating study-startup, and ensuring patient recruitment and retention meet or exceed targets.

ICON offers customers enhanced access to a larger global pool of more diverse patients through its global site network (Accellacare), specialised oncology network (Oncacare), a paediatric site network, in-home services and a network of six Phase I clinical research units across the United States and Europe.

Quality: The quality of our work is vital to our mission of bringing better medications to patients around the world. We are committed to maintaining, supporting, checking and improving our quality systems to exceed the quality standards demanded by our clients, patients and regulatory authorities. ICON's Quality Management System (QMS) comprises our mechanisms for ensuring that all our services are performed to the highest ethical standards, conform to all relevant regulatory requirements and satisfies contractual obligations.

Emerging therapies: ICON offers deep experience in the unique challenges of developing emerging treatments such as Immuno-oncology and other cell and gene therapies, with several approved treatments already on the market.

With headquarters in Dublin, Ireland, ICON employed approximately 41,150 employees in 113 locations in 53 countries as at September 30, 2022.

ICONplc.com

Big Three Lead From The Front With Medtech Back On Solid Growth Footing

Most Of The Medtech Top 10 Got Back To Winning Ways On Revenues With Some Unexpected Exceptions

Abbott Laboratories and Johnson & Johnson joined Medtronic in putting a clear distance between themselves and other global medtechs in the Top 10 by revenues for 2021. Post-COVID-19 procedure growth, and, for Abbott, a strong rebound in non-COVID diagnostic demand, were key drivers.

BY **ASHLEY YEO,** EXECUTIVE EDITOR, EUROPE

Abbott Laboratories joined Medtronic in recording more than $30bn in revenues in 2021, the first year that the medical devices and diagnostic industries have had two companies exceeding this threshold.

In the next year or two, Johnson & Johnson might also join the club if it consolidates progress made in putting on almost 18% more revenues in 2021 to reach $27.1bn. The company's medtech segment continued to grow during 2022, albeit at a slower pace, with $20.7bn revenues booked at the nine-month stage.

J&J will be able to add annualized revenues of $1bn from circulatory support company Abiomed, Inc. if its $16.6bn M&A offer made on 1 November completes as planned within Q1 2023.

The post-COVID recovery in procedure volumes was the main reason for the New Brunswick, NJ company's rebound in 2021, after an extremely COVID-19-impaired 2020. Noteworthy was that J&J's 2021 revenues were over $1bn (4.2%) higher than those in pre-COVID 2019.

All J&J franchises grew in 2021, from spine & sports (+7%) to interventional solutions (+30%). The disposal of Advanced Sterilization Products and other transactions led to a net negative M&A impact on revenues of 0.6%.

Medtronic Still No. 1 In 2021

The medical device industry's average growth of mid-to high-single digits growth was the result at the world's largest company, Medtronic plc, whose revenues expanded by 5.2% in 2021 on the back of the post-COVID recovery in procedure volumes.

Pandemic-related supply chain disruption dampened progress, particularly in the company's fourth fiscal quarter (January to April 2022). The timing of its fiscal year also meant that the COVID-19 lockdown in China in late March 2022 was reflected in the company's latest annual figures.

Of Medtronic's four business segments, only diabetes care (at $2.3bn, the smallest) saw lower revenues (down by 3%), while cardiovascular, medical-surgical and neuroscience all expanded roughly equally, at or around the company's average growth.

As part of a portfolio value creation drive, CEO Geoff Martha announced in October 2022 the separation within 12-18 months of the company's patient monitoring and respiratory interventions businesses, which are currently operating units within medical-surgical.

These businesses contributed combined revenues of $2.2bn to Medtronic's total $31.7bn revenues in fiscal 2022. The businesses are not expected to be separated before the April 2023 fiscal year end.

The industry felt the negative impacts of staff shortages, COVID-19 on procedure volumes, and supply chain issues.

In common with the industry generally, Medtronic felt the negative impacts of health care system staff shortages and COVID-19 holding back procedure volumes, in addition to supply issues. Adding to supply chain pressures for some medtechs was the Russia-Ukraine conflict that started on 24 February. In Medtronic's case, however, the two countries represented less than 1% of the company's consolidated revenues.

Indeed, those Top 100 companies whose accounts closed after the calendar year end were having to factor into their latest P&L business risks that emerged in 2022, including price inflation, rising interest rates and fluctuations in currency exchange rates.

Many were also impacted by China's, national and provincial tender pricing for certain products, which became a growing concern for global companies accessing the world's second-largest devices market.

Abbott Displaces J&J

The 33% rise in Abbott Laboratories' revenues in 2021 placed it above J&J in our annual ranking. Its medical devices segment sales increased by 19% in 2021, and it saw double-digit growth across all divisions, led by structural heart, electrophysiology and diabetes care. The FreeStyle Libre continuous glucose monitoring system brought in sales of $3.7bn (+37%) in 2021.

In the second half of the year, with the spread of the Delta and Omicron COVID-19 variants and demand for rapid COVID-19 tests rising again, Abbott's diagnostics business experienced significant growth. The division's revenues expanded by 43% in the whole of 2021.

Higher demand for its routine lab diagnostic tests was partially offset by lower demand for COVID lab-based tests in the company's molecular diagnostics business.

In the first nine months of 2022, Abbott's diagnostics business expanded by a further 19%, while medical devices was up by 3%, delivering combined revenues of $24.2bn for the period.

Numbers Four To 10

In any other year, Roche Holding AG's diagnostics division would have topped the growth table of the mega-medtechs, given its 29% rise in Swiss franc revenues, to CHF17.8bn in 2021. Most of this growth came from COVID-related products (totalling CHF4.7bn), but routine testing also rebounded across the company.

That performance helped the Swiss company to rise four places and above Philips Healthcare in our dollar-ranked Top 100 table for 2021. Philips was a $20bn company in 2020, but the usually steadily-growing company had a "challenging year" in the words of outgoing CEO Frans van Houten.

The company was not spared supply chain disruptions in the second half of 2021, but the Dutch company also had to initiate a voluntary field action to remediate component quality issues for certain Philips Respironics products.

This action eclipsed much of Philips' positive news from R&D programs, partnerships and M&A. Its 2021 connected care revenues dropped by 23%, compared with a powerfully COVID-enhanced performance in 2020. The company's diagnosis and treatment businesses was up by 8% in 2021, and personal health performed well.

Despite a comprehensively applied renew-and-replace action, in late summer 2022, with 2021 Euro-rated revenues having dipped by 1% to €17.2bn, Philips Healthcare designated its connected care division chief Roy Jakobs as its new CEO.

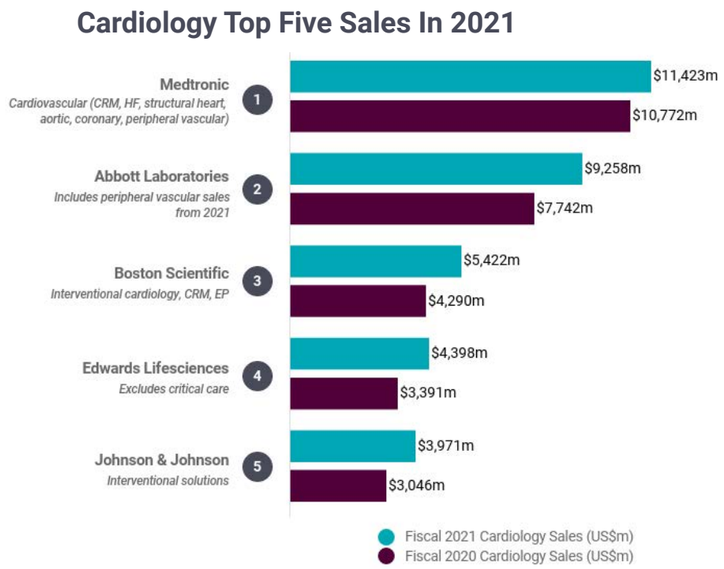
ResMed, Inc. on the other hand saw gains, with increased demand for its sleep and respiratory care devices helping it put on almost 12% more revenues in 2021-22, consolidating its position just outside the global medtech top 30.

CEO Mick Farrell lamented that supply chain disruptions did not allow the company to fully exploit the opportunity

TOP 10 MEDTECH COMPANIES BY SALES

Medtronic	1	$31,686
Abbott Laboratories	2	$30,011
Johnson & Johnson	3	$27,060
Siemens Healthineers	4	$25,692
Roche Diagnostics	5	$19,433
Philips HealthCare	6	$19,351
Becton Dickinson	7	$18,870
GE HealthCare	8	$17,725
Stryker	9	$17,108
Cardinal Health	10	$15,887

All sales in $M.



Source: Company Annual Reports

before it, predicting that the impacts would last into ResMed's 2022-23 fiscal year.

In March 2021, GE Healthcare sold its BioPharma division (drug discovery, biopharmaceutical production and cellular and gene therapy technologies), which had been an $830m business in 2020. The imaging company's health care systems revenues (up 5% to $15.7bn in 2021), and those of pharma diagnostics (up 13% to $2bn), made up for some of shortfall. GE HealthCare will be spun off into a separate and independent company on 3 January 2023, the company announced in early December.

In 2020, GE's revenues were $3.5bn more than Stryker Corporation's, but in 2021, the gap slimmed markedly after the Kalamazoo, Michigan company's revenues jumped by 19% on the back of a 6% positive M&A effect and a 13% boost from increased unit volumes.

Stryker's 2021 Med-Surg/neurotechnology revenues were up 14%, while its orthopedics and spine revenues increased 26%. The two business segments have been newly established to "align with Stryker's internal reporting structure."

The medical segment of Cardinal Health, Inc. saw growth in its at-home solutions, but that did not prevent an $800m decrease in its 2021-22 revenues. As was the case for GE HealthCare, this followed a major divestment: Cordis to Hellman & Friedman for $923m. Also included in the transaction was extravascular closure devices business Access Closure.

Fellow global top ten companies Becton, Dickinson and Company and Siemens Healthineers AG both have September year-ends, as does Hologic, Inc., whose revenues in 2020-21 jumped 54% to $4.97bn, including product sales of $4.2bn. Revenues were affected by lower sales of COVID-19 assays and supply chain challenges related to semiconductor chips in its breast health. (A full breakdown of the company's 2021-22 annual sales was not available by our publishing date, for which reason our tables reflect the company's 2020-21 revenues.)

Siemens Healthineers reported a nominal-basis revenues rise of 21%, to €21.7bn, in 2021-22. This is equivalent to $25.7bn using the MT 100 year-end 2021 currency exchange rates (although it is worth noting that the euro and dollar were more or less at parity when the Erlangen, Germany company closed out its latest fiscal year). On a comparable basis, the company's revenues climbed 6% versus 2020-21.

A full year of Varian's radiotherapy revenues, €3.1bn, was included in Siemens Healthineers' 2021-22 figures. The acquisition was completed in April 2021. Healthineers CEO Bernd Montag gave guidance on 9 November that revenues, net of COVID antigen test sales, would rise by 6%-8% in 2022-23. Flat growth is forecast once those tests' sales are included in the company's figures.

BD (Becton Dickinson) the very next day (10 November) reported base business revenues for 2021-22 of $18.4bn, netting out $511m of COVID diagnostic revenues. The previous year included $1.96bn of COVID diagnostic revenues. Total revenues for the latest year were $18.9bn, down 1% from a restated comparable figure for 2020-21 of $19.1bn (historical diabetes care revenues were classified as discontinued operations after the 1 April 2022 completion of the Embecta spin-off).

Just outside the leading 10, Boston Scientific Corporation once again topped $10bn revenues, the 11th company to exceed the threshold in 2021, with reported revenues up by $1.9bn at $11.9bn. Boston has traditionally been among the most active medtech M&A players. The company completed four acquisitions and one divestiture in 2021. It maintained that rhythm into 2022, bringing in electrophysiology addition Baylis Medical Co. in February for a provisional $1.75bn.

More Top 20 Performers

Danaher Corp.'s diagnostics revenues increased by 33% in 2021, driven by molecular diagnostic tests for COVID and improvements in testing volumes for non-COVID product lines as the public resumed visits to health care providers. Core clinical lab sales increased, and the company saw strong demand for chemistry and immunoassay product lines, and blood gas consumables and immunoassay products.

Fujifilm Corp. entered the top 20, ranked 17th, and also became the biggest Japanese medtech in the global market in 2021-22, after a 37% rise in revenues.

Erstwhile leading Japanese company Olympus Corporation kept its top 20 status with a 15% sales uplift. The company has implemented a strategy to focus purely on medical activities in its 2018-23 five-year plan. The company set up a corporate VC fund, Olympus Innovation Ventures, to build relationships with early-stage companies in endoscopy and minimally invasive surgery.

Spinning In Vogue

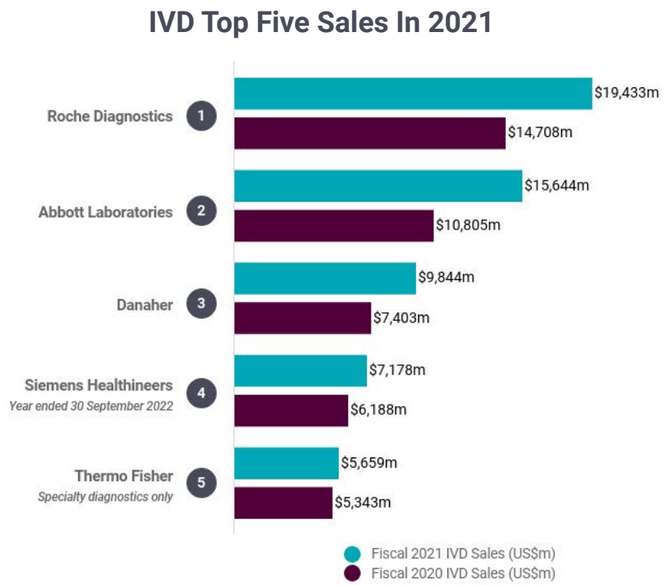
Strong early demand for respirators and rising elective procedure volumes in the first six months of 2021 buoyed 3M's medical solutions sales. Its oral care revenues were driven by higher year-on-year dental procedures.

It also joined the trend towards spin-offs. In mid-2022, 3M announced it would create a standalone, diversified health care technology company focused on wound care, oral care, healthcare IT and biopharma filtration. The spin-off is expected to be completed by year-end 2023. 3M is also active in separation and purification, food safety and health information systems.

A spin-off was completed at Zimmer Biomet Holdings, Inc. Spine and dental activities were formed into a new public company, ZimVie, as announced in February 2021.

Zimmer Biomet's annual revenues grew by 12% in 2021, driven by positive volume trends and a lighter impact from COVID on its elective surgical procedures. In its fourth quarter of 2020, it acquired sternal closure company A&E Medical and arthroscopy company Relign, thereby expanding in the craniomaxillofacial and thoracic (CMFT) and sports medicine markets.

But it failed to match its 2019 revenues, given the persisting deferrals of elective surgical procedures in 2021 – notably at the beginning of the year, before COVID vaccines were widely available – and during the Delta and Omicron variant surges.



Source: Company Annual Reports

Eyecatchers Among The Top 30

Baxter International Inc.'s $10.5bn (net of debt) acquisition of HillRom, which completed in mid-December 2021, added $212m to its full-year 2021 revenues. Baxter's renal care sales increased by 4%, fueled by global patient growth in peritoneal dialysis, partly offset by lower in-center hemodialysis sales. Overall medtech sales at the Deerfield, Illinois company were up by 9% in 2021.

Level-pegging companies in 2020, Intuitive Surgical, Inc. and Edwards Lifesciences Corp. both comfortably exceeded $5bn in revenues in 2021, and both overtook Smith & Nephew plc in the process. The UK-headquartered orthopedics and wound care company cited supply chain headwinds and volume-based procurement implementation for hip and knee implants in China among the issues affecting its business in 2021. S&N acquired Integrated Diagnostics, Inc.'s extremity orthopedics business in January 2021.

Intuitive added a half a billion extra sales in 2021. The company reported that as of 31 December 2021, with an installed base of 6,730 da Vinci surgical systems, it carried out 28% more procedures in 2021. The Ion endoluminal minimally invasive biopsy system had been placed at 129 sites by the end of 2021.

Despite pandemic-related challenges, Edwards increased its 2021 net sales by $846m, driven by its TAVR products. US TAVR procedures grew in the first half of 2021 as a result of declining COVID-19 hospitalizations and higher vaccination rates. The firm reported that procedure volumes were negatively impacted in the second half due to the impact of the Delta and Omicron variants on hospital resources.

Alcon Inc. added $1bn revenues to its surgical franchise in 2021 with net sales of implantables, consumables and equipment, and other surgical products reaching $1.5bn, $2.4bn and $800m, respectively.

Top 50 player PerkinElmer, Inc. recorded diagnostics revenues for fiscal 2021 of $2.9bn (including $0.96bn of service revenues), an increase of 42%. Acquisitions contributed $96m while increased demand for COVID-19 product offerings boosted its immunodiagnostics revenues by $749m.

The Challenge Of China

The Chinese government has given a lot of support to home-grown medtech companies in the expectation that they will go on to challenge for higher shares in the global market.

It has also introduced measures to strengthen Chinese companies' positions in the domestic market (such as continuing with certificate-of-origin needs for overseas companies, implementing ultra-low-priced tenders for stents and orthopedic joints and pursuing volume/state-based procurement).

For future Medtech Top 100 rankings, this implies that more Chinese companies (listed

on a stock exchange and traded publicly) will feature more prominently in the listings in the next decade.

Shenzhen-listed Mindray Medical International Ltd., which became a public company once again in 2018, is the largest of the local players. In 2021, it made dollar-ranked sales of over $3.9bn, its local currency sales increasing by 20% to CNY25.3bn (including: imaging CNY5.43bn; IVDs CNY8.45bn; patient monitoring and life support CNY11.15bn).

United Imaging is sure to feature soon after its mid-2022 initial public offering (IPO), creating another medtech capitalized at over CNY100bn.

Four companies have had a constant presence in the lower half of the annual listing (Shinva, Jiangsu Yuyue Medical Equipment & Supply Co Ltd, MicroPort, and Lepu Medical Technology (Beijing) Co., Ltd.). A new entry in 2020 was SonoScape, but it slipped out of the 2021 ranking. Beijing Wandong Medical Technology Co. is also just outside the Top 100, with sales of $179m in 2021.

Into The Medtech History Books

Some of these, and other fast-rising medtechs, are likely to fill voids left by high-level M&A, which in 2021 again resulted in the disappearance of established names. UK company Smiths Medical was one, its COVID-interrupted acquisition by ICU Medical, Inc. finally being completed in January 2022.

For ICU, the acquisition adds syringe and ambulatory infusion devices, vascular access, and vital care products.

IVDs player Luminex Corporation was acquired by DiaSorin SpA/Diagonal for $1.7bn in July 2021. Luminex's board estimated in an SEC filing that proforma sales would have reached $484m for full-year 2021.

QuidelOrtho Corporation and Ortho Clinical Diagnostics Inc. combined their diagnostics portfolios to form QuidelOrtho, a company with 2021 pro-forma revenues of $3.5bn (including OCD's transfusion medicine) and 6,000 employees. OCD went public in January 2021, raising $1.3bn in an IPO.

In July 2022, brain disorder and neural pathways screening and diagnosis company Natus Medical Incorporated was acquired by the MED Platform II fund of the ArchiMed health care industries investment firm. The firm says it will intensify Natus' R&D and pursue complementary bolt-ons.

Elsewhere, a portfolio change saw LivaNova PLC complete the disposal of its heart valve business to Gyrus Capital in June 2021.

OraSure Technologies, Inc. decided to use the tail-end of the COVID pandemic as an opportunity to evaluate how it can transform into a higher growth and more innovative organization.

Medtech 100 Ranking 2021 (2020)	Company	Fiscal 2020 Sales ($m)	Fiscal 2021 Sales ($m)	2021 Notes	Industry Activity
1 (1)	Medtronic	30,117	31,686	Year ended 29 April 2022	Cardiovascular, medical surgery, neuroscience, diabetes
2 (3)	Abbott Laboratories	22,592	30,011		IVDs, rhythm management, EP, HF, cardiovascular, diabetes
3 (2)	Johnson & Johnson	22,959	27,060		EP, neurovascular, orthopedics, surgery, vision
4 (5)	Siemens Healthineers	20,556	25,692	Year ended 30 September 2022	Imaging, IVDs, radiotherapy, advanced therapies
5 (9)	Roche Diagnostics	14,708	19,433		IVDs, tissue diagnostics, POC, patient self-testing, next-gen sequencing, lab automation, IT, decision support
6 (4)	Philips Healthcare	21,869	19,351	Excludes IP & licensing income	Diagnosis & treatment, connected care, personal care
7 (6)	Becton Dickinson	20,248	18,870	Year ended 30 September 2022	Medication delivery, syringes, needles, infusion therapy, delivery systems, IVDs, surgery, critical care, urology, peripheral intervention
8 (7)	GE HealthCare	18,009	17,725	Healthcare systems & pharma diagnostics	Imaging, ultrasound, acute care systems, contrast and molecular imaging agents
9 (10)	Stryker	14,351	17,108		Orthopedics, medsurg, neurotech, spine
10 (8)	Cardinal Health	16,687	15,887	Medical sales; year ended 30 June 2022	Sharps, incontinence, nutritional delivery, wound care, fluid suction, urology, OR supplies, electrode products
11 (11)	Boston Scientific	9,913	11,888		Endoscopy, urology, CRM, EP, neuromod, cardio & peripheral vascular
12 (14)	Danaher	7,403	9,844		IVDs/lab diagnostics, critical care, molecular & analytical pathology
13 (12)	B Braun	8,482	9,300		Infusion, nutrition and pain therapy, infusion pumps & systems, surgical, suture materials, hip and knee implants, dialysis equipment, ostomy, disinfection, wound care
14 (13)	Baxter International	8,120	8,860	Excludes pharma, biopharma services, clinical nutrition	Dialysis, IV solutions, infusion systems, parenteral nutrition therapies; inhaled anesthetics; generic injectables; surgical hemostat and sealant products; smart bed systems; patient monitoring and diagnostic technologies; respiratory health devices
15 (15)	3M	7,150	8,090	Excludes food safety & purification sciences	Skin & wound care, infection prevention, dentistry, reimbursement software
16 (16)	Zimmer Biomet	7,025	7,836		Orthopedic recon, sports medicine, biologics, extremities & trauma products; spine, craniomaxillofacial and thoracic; dental implants
17 (21)	Fujifilm	5,322	7,306	Healthcare; year ended 31 March 2022	X-ray, ultrasound, cell culture media, pharma, life sciences
18 (18)	Olympus	5,863	6,717	Year ended 31 March 2022	Endoscopy & therapeutic solutions
19 (19)	Terumo	5,754	6,402	Year ended 31 March 2022	Interventional systems, neurovascular, cardiovascular, hospital systems, infusion pumps
20 (17)	Grifols	6,100	5,837		Blood plasma-based products, devices, clinical lab reagents
21 (24)	Intuitive Surgical	4,358	5,710	Includes service income	Robotic-assisted surgery products
22 (20)	Thermo Fisher	5,343	5,659	Specialty diagnostics	IVDs, reagents, culture media, instruments
23 (23)	Edwards Lifesciences	4,386	5,233		TAVR, TMTT, structural heart, critical care
24 (22)	Smith & Nephew	4,560	5,212		Advanced wound management, sports medicine, ENT, orthopedics
25 (31)	Hologic	3,227	4,967	Year ended 25 September 2021 (excludes service income)	IVDs, breast, gyne, skeletal health, products for women
26 (28)	Alcon Laboratories	3,710	4,703	Surgical sales only	Ophthalmic surgery
27 (25)	Fresenius Medical Care	4,277	4,429	Healthcare products (excludes services)	Dialysis, disposable renal products
28 (26)	Canon Medical Systems	4,087	4,378		CT, MR, X-ray, ultrasound, healthcare informatics, ophthalmic equipment
29 (29)	Dentsply Sirona	3,342	4,251		Dental equipment & consumables
30 (39)	Align Technology	2,472	3,953		Dental scanners, alignment technology

MEDTECH 100

Medtech 100 Ranking 2021 (2020)	Company	Fiscal 2020 Sales ($m)	Fiscal 2021 Sales ($m)	2021 Notes	Industry Activity
31 (-)	Mindray	3,047	3,922	Listed In Shenzhen in October 2018	Imaging, IVDs, critical care & patient monitoring
32 (27)	Zoll Medical	3,823	3,790	AK healthcare division (health and critical care)	Pharma & diagnostic reagents, artificial kidneys, therapeutic apheresis, virus removal filters, AEDs, wearable defibrillators
33 (32)	ResMed	3,197	3,578	Year ended 30 June 2022	Respiratory & sleep products, software as a service
34 (35)	Sysmex	2,859	3,315	Year ended 31 March 2022	Hematology, urinalysis, immunochemistry, reagents, robotics
35 (34)	bioMérieux	2,954	3,299	Excludes industrial and other	IVDs
36 (30)	Getinge Group	3,250	3,154	Acute therapies, life sciences, surgical workflows	Acute care, disinfection products
37 (33)	Shimadzu	2,957	3,139	Year ended 31 March 2022	X-ray, fluorescence imaging
38 (36)	Coloplast	2,841	3,090	Year ended 30 September 2021	Ostomy, urology, continence, wound care
39 (38)	Teleflex Medical	2,537	2,810		Vascular access, anesthesia, urology, respiratory products, OEM activity
40 (40)	HU Group (Miraca)	2,090	2,487	Year ended 31 March 2022	IVDs (SRL, Fujirebio, Nihon Stery companies)
41 (41)	Dexcom	1,927	2,449		Diabetic care continuous glucose monitoring
42 (37)	Dräger	2,630	2,442		Critical & neonatal care, anesthesia, monitoring
43 (44)	Qiagen	1,870	2,252		IVD kits & instruments, bioinformatics
44 (50)	Straumann	1,521	2,212		Dental implants, scanners, orthodontics
45 (42)	ConvaTec	1,894	2,038		Wound, continence & critical care, ostomy, infusion products
46 (-)	PerkinElmer	1,784	1,971	Excludes service revenues; year ended 2 January 2022	Diagnostic tools for reproductive health & applied genomics
47 (49)	Carl Zeiss Meditec	1,525	1,948	Year ended 30 September 2021	Ophthalmic technologies
48 (47)	Bausch Health	1,566	1,903	Devices only	Intraocular lenses, ophthalmic surgical equipment, aesthetics devices
49 (43)	Nihon Kohden	1,872	1,869	Year ended 31 March 2022	EEG, ECG, AEDs, pacemakers, monitors
50 (52)	Exact Sciences	1,491	1,767		Cancer screening, IVDs
51 (45)	Quidel	1,662	1,699	Renamed QuidelOrtho in May 2022 on acquiring Ortho Clinical Diagnostics	Rapid diagnostic testing solutions
52 (51)	Elekta	1,500	1,696	Year ended 30 April 2022	Radiotherapy, surgery, brachytherapy
53 (53)	Teijin	1,394	1,673	Human chemistry division (includes pharma); year ended 31 March 2022	Othopedics, home healthcare, pharma
54 (55)	Integra LifeSciences	1,372	1,542		Neurosurgery, instruments, tissue technologies
55 (57)	Bio-Rad Labs	1,305	1,516	Clinical diagnostics only	IVDs
56 (56)	Shinva Medical Instrument	1,326	1,472		Sterilization equipment
57 (67)	DiaSorin	1,007	1,464		IVDs, instruments
58 (61)	Colfax (DJO Global)	1,121	1,426	Renamed Enovis in 2022	Orthopedics
59 (-)	Ortho Clinical Diagnostics	1,154	1,350	IPO completed January 2021; year ended 2 January 2022	IVDs (clinical lab)
60 (58)	ICU Medical	1,271	1,316		Infusion therapies and systems, critical care
61 (60)	Masimo	1,144	1,239	Year ended 1 January 2022	Pulse oximetry, monitoring
62 (65)	Cochlear	1,032	1,233	Year ended 30 June 2022	Hearing implants, acoustics
63 (48)	Omron	1,154	1,212	Year ended 31 March 2022 (2021 US$ figure restated)	Blood pressure monitors & thermometers
64 (54)	Fukuda Denshi	1,376	1,204	Year ended 31 March 2022	Diagnostic & monitoring equipment, pacemakers, ventilators
65 (64)	Integer	1,038	1,183	Excludes non-medical sales	Cardio, vascular, CRM, neuromod, surgical, orthopedics
66 (59)	Smiths Medical	1,178	1,167	Year ended 31 July 2021; sale to ICU Medical closed 6 January 2022	Infusion systems, vascular access, critical care
67 (63)	NuVasive	1,051	1,139	Hardware, surgical support	Spinal solutions
68 (69)	Merit Medical Systems	964	1,075		Cardiology, radiology, oncology, critical care, endoscopy devices
69 (68)	Jiangsu Yuyue Medical Equipment	975	1,070		Respiratory, cardiovascular & endocrine system devices
70 (70)	LivaNova	934	1,035		Cardiovascular, neuromod
71 (74)	Abiomed	848	1,032	Year ended 31 March 2022	Circulatory support, oxygenation
72 (72)	CONMED	862	1,011		Minimally invasive general and orthopedic surgery
73 (66)	Konica Minolta	1,023	1,002	Healthcare, includes pharma services; year ended 31 March 2022	Digital radiography, precision medicine
74 (71)	Haemonetics	870	993	Year ended 2 April 2022	Blood & plasma collection, surgical suite, hospital transfusion services
75 (77)	Globus Medical	789	958		Orthopedics, robotics
76 (82)	LePu Medical Technology	493	957		Lab consumables, cardiovascular, hemodialysis, surgical, IVDs, orthopedics
77 (73)	Invacare	851	872		Non-acute DME (respiratory, wheelchairs)
78 (75)	Guerbet	814	866		Contrast media
79 (76)	AGFA Healthcare	805	808		Radiology & healthcare IT
80 (78)	MicroPort Scientific	649	779		Cardiovascular, CRM, heart valves, orthopedics, neurovascular

Medtech 100 Ranking 2021 (2020)	Company	Fiscal 2020 Sales ($m)	Fiscal 2021 Sales ($m)	2021 Notes	Industry Activity
81 (79)	Cooper Companies	588	771	Year ended 31 October 2021	CooperSurgical: fertility, diagnostics & contraception
82 (90)	Myriad Genetics	280	667	Year ended 31 December 2021 (exceptional six-month year in 2020)	Molecular diagnostic testing
83 (80)	Varex Imaging	585	644	Medical only; year ended 1 October 2021	X-ray imaging
84 (81)	Hamamatsu Photonics	499	602	Year ended 30 September 2021	Electron tubes
85 (83)	Ypsomed	461	508	Year ended 31 March 2021	Delivery systems & diabetes care
86 (86)	Natus Medical	416	473	Acquired by ArchiMed July 2022	Neuro, newborn, hearing
87 (87)	Orthofix Medical	407	465		Biologics, spine & extremities
88 (88)	Accuray	396	430	Includes service revenues; year ended 30 June 2022	Radiotherapy solutions
89 (-)	NeoGenomics	382	404	Acquired Inivata (liquid biopsy) in June 2021	Cancer-focused testing labs, molecular diagnostics, liquid biospy
90 (-)	Steris	n/a	361	Year ended 31 March 2021 (dental only – Cantel Medical acquired in June 2021)	Dental
91 (92)	Stratec Group	286	340		IVDs, life sciences
92 (89)	Hogy Medical	342	335	Year ended 31 March 2022	Surgical kits, intruments, sterilization
93 (93)	iRhythm Technologies	265	332		Ambulatory ECG monitoring
94 (95)	Meridian Bioscience	254	318	Year ended 30 September 2021	IVDs
95 (91)	AngioDynamics	291	316	Year ended 31 May 2022	Vascular access, minimally invasive devices
96 (97)	Guardant Health	236	304	Excludes development service revenues	Precision oncology testing
97 (96)	CryoLife	253	299	Rebranded under new name Artivion in January 2022	Aortic disease tissues, devices
98 (98)	AtriCure	207	274		Cardiac arrhythmia management
99 (105)	ATEC Spine/Alphatec Holdings	145	243		Spine, spine surgery
100= (94)	Cardiovascular Systems	259	236	Year ended 30 June 2022	PAD/CAD devices
100= (99)	Horiba	197	236	Year ended 31 December 2021	IVDs, hematology analyzers for POC testing

The Medtech 100 ranking is based on Citeline's analysis of fiscal year 2021 revenues data (unless noted) for the top 100 publicly-owned medtech companies. Average annual US dollar exchange rates for calendar year 2021 are used for all entries for comparative purposes. For more information contact: Ashley.Yeo@informa.com.

The European Pharmaceutical Strategy: What's In A Name?

EVELINE VAN KEYMEULEN, PARTNER AT LATHAM & WATKINS

SINI ESKOLA, DIRECTOR REGULATORY STRATEGY AT EFPIA

The European Commission published the EU Pharmaceutical Strategy in 2020, aiming to improve access to medicines and enhance innovation and affordability in the region. The publication comes at a time when the EU, owing to regulatory complexities (among other reasons), lags behind in incentivizing innovation. What proposals does the strategy introduce? How can the proposals put Europe at the forefront of medical innovation? And what should pharmaceutical companies be aware of with regard to these proposals?

Eveline Van Keymeulen, a partner in Latham's Healthcare & Life Sciences practice, spoke with Sini Eskola, director of regulatory strategy at the European Federation of Pharmaceutical Industries and Associations (EFPIA), about these and other related topics in this interview.

Eveline: The European Commission's Pharmaceutical Strategy includes a revision of a two-decade-old EU pharmaceutical legislation. Can you explain the origin and objectives of the proposals and tell us, in your view, why the strategy is so important for pharma companies worldwide?

Sini: More than five years ago, the Commission brought together Member States into an expert group called STAMP, for Safe and Timely Access to Medicines for Patients. It was not clear whether that group was preparing legislative revision, but in 2020, with the new Commission, the EU Pharmaceutical Strategy was published. Its key objectives are access, availability, affordability, and innovation, which are the elements the Commission will now prioritize when proposing legislative change.

We have never had a strategy for pharmaceuticals in the EU and it is therefore good to see health prioritized in European decision-making. The COVID-19 pandemic underlined the need for a better EU-wide strategy on how we manage access, availability, and affordability for European citizens. Without pharmaceutical innovation, the pandemic and the impact to the citizens would have been much worse. The strategy shows the direction in which the region wants to travel, with legislation (Medicinal Products Directive 2001/83 and Regulation 726/2004) as the cornerstone.

Unfortunately, Europe sits behind the US as the world's leading driver of medical innovation. What are the reasons for this dwindling competitiveness of Europe, and how can the pharmaceutical strategy incentivize innovation in the region?

The way medical research and innovation is leaving Europe is a serious concern. Europe was in a leading position and now, in many different ways, is lagging behind — whether in the number of investments made or in the pace of regulatory approval processes.

From a regulatory perspective, it is the complexity of the decision-making that makes that process quite slow, partly explained by the fact that of course Europe is not one country. We would like to see processes more streamlined and duplication reduced to the minimum. Innovation drives access, so we have to support innovation to get more products to market faster and make them more broadly available to European patients.

A big positive of the strategy is its clear recognition of the need to support small and medium-sized enterprises and make that environment more viable. We need more cross-fertilization of expertise between academia and business, which is an area where the US takes a win.

The Commission has already given us some insights into the legislative proposals it is considering with respect to medicines in general and medicines for rare diseases and children. Could you briefly summarize what pharmaceutical companies should have on their radar, even if most of these proposals — in their final form — are not likely to materialize for a number of years?

For pharmaceutical companies, the key cornerstone for innovation has been incentives and IP, but we see a clear push for reduction of that, which is worrisome. The Commission has been smart because the number of years for which you can get incentives and data protection is largely untouched, but they come with more conditionality. For instance, you need to clearly demonstrate that a new product addresses an unmet medical need (UMN), though the criteria for that are unclear for the moment. EFPIA believes the criteria that the Commission suggested for UMN is unrealistically strict, because it would directly negatively impact the eligibility to expedited regulatory pathways (e.g., priority regulatory review, or PRIME, and accelerated assessment) and securing regulatory data protection (RDP), which covers a third of approved products as their last data protection. Would Europe be ready to send such signals to global investors and pharmaceutical companies, not to mention patients?

There are big pushes to also address sustainability through this legislation, which is important given the changes proposed to the environmental risk assessment of medicines and EFPIA has long been advocating for a lifecycle approach to it.

And maybe the third thing to highlight is the way access to market is being completely rethought. This is also considered in conjunction with conditional RDP. We have seen the Commission would favor the option in which a market launch needs to take place within two years of marketing authorization application to receive RDP. This is in contrast to the industry's proactive initiative put in place in spring 2022 to require all EFPIA companies to file for pricing and reimbursement within two years from an approval, and demanding the reasons behind any delays are transparently reported afterwards, to determine whether they are market specific or caused by issues relating to national legislation or the marketing authorization holder.

What is your general view on the current proposals? Do you think they will incentivize innovation in Europe?

We are pleased that some of our regulatory priorities have been covered in the initial draft impact assessment, such as support to the enhanced expertise-driven decision-making. The Commission is also proposing to introduce PRIME as a key accelerated pathway in the legislation, which is good news, and move towards electronic product information, which is great for patients. Today, 25% of the pipeline consists of drug-device combination products, and there is a clear willingness to try to address that group of products more effectively to have an integrated pathway, which is also a positive.

We would say these proposals clearly move the needle and put Europe at the forefront of innovation, but they currently do not go far enough based on the documents we have seen from the Commission. So there is a risk of missing an opportunity to make Europe first in the world to attract and support medical innovation.

The Regulatory Scrutiny Board first rejected the Commission's impact assessment on the potential changes to the pharmaceutical legislation. What do you think will be the impact of this red light?

We were originally expecting the Commission's proposal for the revised legislation by December this year but in September the Regulatory Scrutiny Board rejected the Commission's original impact assessment which caused some delay. As the Regulatory Scrutiny Board questioned the balance between innovation and affordability and access, there have been high-level political discussions to solve the way forward. As a lot of work has gone into this strategy and impact assessment of proposed policy changes by the Commission and others, we are however unlikely to see dramatic changes, especially with respect to the more regulatory-focused topics. The latest intelligence suggests that the Regulatory Scrutiny Board has now given its green light to the revised impact assessment and the Commission's work is currently being finalized. The Commission's proposal is now expected in the first quarter of 2023.

Alongside these proposals, the EU Health Technology Assessment (HTA) Regulation was adopted earlier this year, creating a legislative framework to enable collaboration between Member States on health technology assessments. What opportunities and challenges does the life sciences industry face there?

The EU HTA Regulation was a disappointment and did not go as far as we would have liked. The commitment between Member States to share assessments and thereby help to speed access was not fully realized so it did not achieve its objectives, which is a pity. In many ways it is the product of the legislative process, involving different institutions and different Member States, so it is a compromise.

That said, there are quite some good things in that regulation that will enable more scientific collaboration between regulators and HTA bodies at an earlier stage. That collaboration has been supported by the innovative industry and will drive better evidence generation earlier in product development to achieve speedier assessment and access, so we need to work with industry and stakeholders to make sure it is a success.

Do you have any final views you would like to share with us?

I think one positive outcome of the COVID-19 pandemic was that it helped many citizens and patients to understand more about the regulatory and decision-making processes behind pharmaceuticals and vaccines. That creates an opportunity to engage with different stakeholders for a dialogue on patient needs and key areas for improvement. I look forward to having that dialogue in the coming years to really hear stakeholders' views.

RNA Medicines: Advancements Leading To Investments

Improvements in generating, purifying and delivering RNA material, as well as addressing challenges with degradation by enzymes, have made the RNA class more attractive to drug developers.

BY **AMANDA MICKLUS,**
PRINCIPAL ANALYST,
DATAMONITOR HEALTHCARE

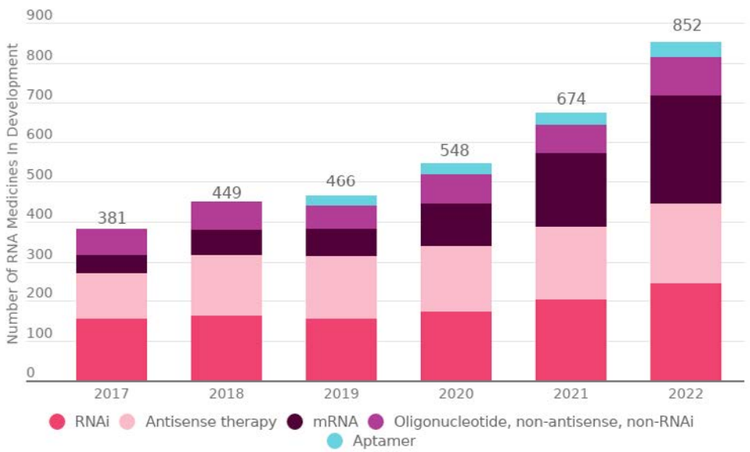
The concept of RNA as a medicine is not new. The act of using ribonucleic acid molecules to treat or prevent diseases by affecting biological pathways has been pursued for almost 50 years. Antisense oligonucleotides were first synthesized in the 1970s, aptamers first described in the 1990s, the first use of exogenous mRNA to induce the expression of a protein *in vivo* occurred in the 1990s, and microRNA was discovered in 1993.

These efforts and proofs of concept have been translated into actual commercial products. Since 2004, 18 RNA therapeutics or vaccines have been launched, mainly antisense and RNAi therapies. The latest approval, in September 2022, saw the EMA authorize Alnylam Pharmaceuticals Inc.'s RNAi product Amvuttra (vutrisiran) for adult patients with stage 1 or 2 polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis. FDA approval came a few months before, in June 2022.

Approved RNA medicines have been around for almost 20 years. But what has changed more recently are improvements in generating RNA material, as well as purifying and delivering it, and addressing challenges with degradation by enzymes. All together, these improvements have made the RNA class more attractive to drug developers. Their relatively simpler manufacturing leading to lower cost of goods, and ability to reach drug targets not previously accessed by small molecules make RNA especially attractive. According to a 2022 survey by consulting firm CRB Horizons, industry respondents say they are either planning or have already made significant investment in the short term in new RNA manufacturing capacity, and intend to dedicate a substantial proportion of investment toward large-scale production of RNA products.

Moreover, within the last two years, the investment in RNA has accelerated thanks to the rapid development and success of preventative mRNA vaccines for the COVID-19 pandemic. Effectiveness of the COVID-19 vaccines has paved the way for companies to step up resources not only toward development of mRNA, but for RNA medicines as a whole.

Exhibit 1: Growth In RNA Pipeline Has Doubled Since 2017



Notes: Chart includes candidates in development from preclinical through pre-registration. Annual snapshots taken in May.

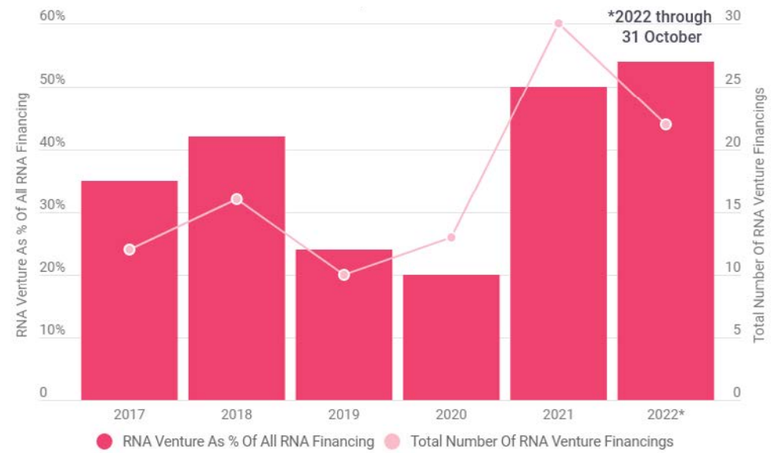
Source: Pharmaprojects

RNA Pipeline Is Growing

The number of RNA medicines in the pipeline across all modalities – RNAi, antisense therapies, mRNA vaccines and therapeutics, oligonucleotides (non-antisense and non-RNAi) and aptamers – has more than doubled since 2017, growing from 381 to 852 therapies in preclinical testing through pre-registration as of May 2022. RNA clinical trial starts have also been trending upward, including a nearly doubling of actual trial starts from 104 in 2020 to 197 trials in 2021, and 2022 seeing a healthy number of 136 trial starts as of 31 October. Companies leading the charge and most active in the pipeline include Moderna, Inc., Ionis Pharmaceuticals, Inc. and BioNTech SE.

Biopharma companies and venture capitalists have taken notice and increased investments in the RNA field through financing and dealmaking. This increased attention is expected to continue over the upcoming years, with potentials for breakthroughs emerging in the process.

Exhibit 2: RNA Technologies: Source Of Increasing Venture Capital Investment



Source: Biomedtracker

Venture Investment In RNA Has Increased In Recent Years

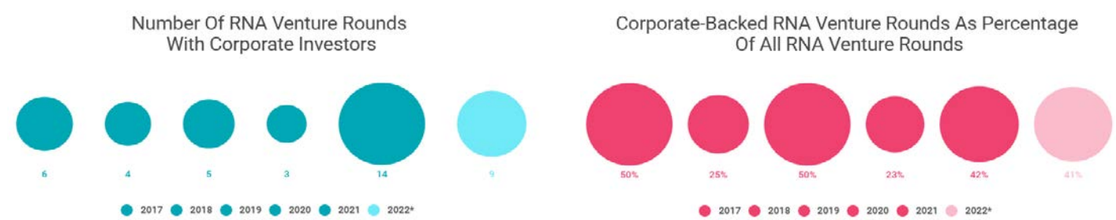
RNA technologies have been a big driver of venture capital investment over the past five years, as VC firms look to get involved earlier in companies' lifecycles and hope for bigger returns as these companies exit. The number of RNA company venture rounds nearly tripled in 2021 compared with the levels in previous years, reaching a total of 33 financings. And 2022 is on its way to another strong year for RNA venture financing with 22 completed through the end of October, and only needing another 11 to match 2021's full-year total. Further, venture financing as a proportion of total RNA fundraising (including all financing types) is rising, accounting for more than half (54%) of the funding in 2022 so far, a slight increase over the 50% proportion seen in 2021.

In the last few years, some of the biggest venture rounds have gone to mRNA vaccines developers. These players were drawing attention well before the COVID-19 pandemic, a strong indication of the promise of this technology. Notably, Moderna brought in $560m in its Series G round in 2017, while BioNTech raised a combined $595m in Series A and B financings during 2018–19. That excitement has continued through the pandemic era: In 2021, Chinese mRNA vaccine start-up Suzhou Abogen Biosciences closed over $700m in its Series C financing led by Temasek Holdings and GL Ventures.

Corporate Investors Are Taking Note Of RNA

An important metric in venture financing is participation from corporate venture arms, or direct investments by pharma or biotech companies themselves, as this is another way to take a pulse of the investment interest by key industry players. RNA venture activity including corporate or biopharma investors had not fluctuated much since 2017; in fact, it was trending slightly downward through 2020. But in 2021, the number of corporate-backed RNA venture financing increased

Exhibit 3: Corporate-Backed RNA Financing On The Rise



*2022 through 31 October

Source: Biomedtracker

BUSINESS

substantially with 14 rounds announced, and accounting for almost half (42%) of the venture rounds done that year. 2022 also looks to be on its way to a strong year in which nine RNA financings through October have included corporate backers. At 41%, this volume has nearly already reached full-year 2021's proportion of RNA corporate venture rounds as a percent of all RNA venture financings.

Lilly and Company has been the most active corporate/biopharma company investor over the past five years, participating in six RNA venture rounds. Alongside its corporate venture arm Lilly Asia Ventures, the combined entity has been involved in a total of 10 financings. Eli Lilly is no stranger to RNA, having signed five partnerships each worth at least $1bn since 2017. Its partners have included CureVac NV, Evox Therapeutics Limited, MiNA Therapeutics, ProQR Therapeutics N.V., and Dicerna Pharmaceuticals, Inc. (now owned by Novo Nordisk A/S), whose 2018 RNAi agreement in the areas of cardio-metabolic and neurodegenerative diseases could be worth almost $4bn if all milestones are met.

To date, Lilly has joined in with investors to back three $100m-plus venture rounds. In 2019, the big pharma put in $15m toward Avidity Biosciences, Inc.'s $100m series C financing to support the start-up's work on antibody-oligonucleotide conjugates for myotonic dystrophy type I. Avidity went on to IPO a year later. In 2021, Lilly was part of the investor syndicate for DTx Pharma's $100m series B round, helping to advance the biotech's work around the FALCON (Fatty Acid Ligand Conjugated OligoNucleotide) platform. And

Looking ahead to the rest of 2022 and beyond, some of the biggest investments may go into novel RNA technologies if the latest partnerships are any indication.

the big pharma joined many other corporate investors to back Capstan Therapeutics Inc.'s $102m series A financing in 2022. Capstan is looking to address multiple therapy areas, including oncology, inflammation, fibrosis, and blood diseases, with mRNA-encoded CARs and gene editing.

Partnering RNA Assets Gaining Steam

Licensing and collaborations to enable progression in RNA development is another form of investment that industry players have leveraged. RNA partnerships have steadily gained traction, reaching a high of 60 deals in 2020 after steadily increasing in volume since 2017. Annually, average deal values for most years has fallen in the $600–800m range, but in 2018 the average ballooned to over $1bn thanks to the aforementioned Lilly/Dicerna deal, as well as a potential $4bn agreement between Janssen Pharmaceuticals Inc. and Arrowhead Pharmaceuticals, Inc. around ARO-HBV, an RNAi therapy (now called JNJ-3989) for HBV.

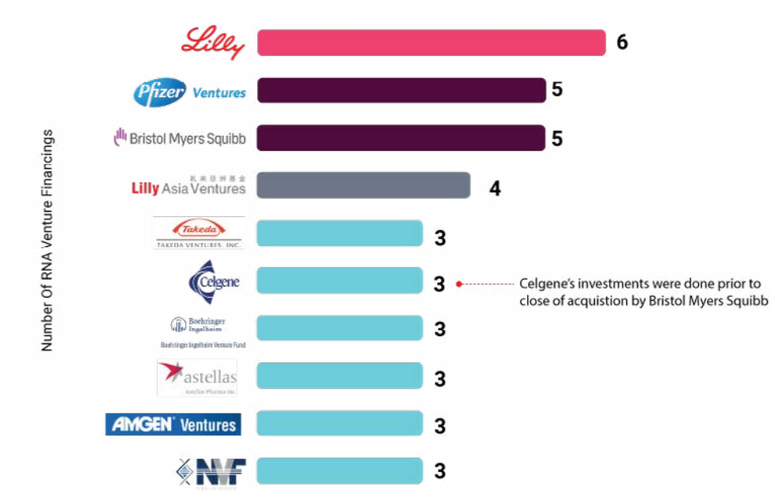
Notably in 2022 so far, the average partnership value is trending on the higher side, at $857m. Looking ahead to the rest of 2022 and beyond, some of the biggest investments may go into novel RNA technologies if the latest partnerships are any indication. The most expensive deal of 2022 to date focuses on circular RNA (circRNA). Merck & Co., Inc. may pay Orna Therapeutics, Inc. up to $3.65bn in up-front and milestone fees for development of circRNA-based vaccines and therapeutics in infectious disease and oncology. Orna has been well funded by venture investors as well, raising over $300m from its Series A and B rounds. CircRNA may have many advantages over linear RNA, including resistance to exconuclease degradation and better stability. Even so, circRNA is very much a nascent field, with only eight therapies in the pipeline. All of the drug candidates are currently in preclinical studies, with CirCode being the most active at four therapies in development.

In another big money deal in 2022, Beam Therapeutics Inc. will use its mRNA and lipid nanoparticle technologies to deliver *in vivo* based editors to treat rare liver, muscular, and genetic diseases. That agreement resulted in partner Pfizer Inc. paying $300m up front and potentially another $1bn in milestones.

An additional area of excitement in the RNA field are self-amplifying mRNAs, which have the potential for reduced dosing and longer protein expression. In early November 2022 (just past *in vivo*'s data cut off), Arcturus Therapeutics Ltd signed a deal worth up to $4.5bn granting CSL Seqirus rights to use its self-amplifying mRNA technology for development of COVID-19, influenza, and respiratory infectious disease vaccines.

Volume is generally low in RNA-focused acquisitions – only a total of 21 have been done since 2017, making it difficult to understand trends over time even with the small numbers, it is worth noting a shift: A greater number of companies in the mRNA space – including mRNA vaccines and therapeutics, and mRNA cell-based therapy – have been targeted for acquisitions, while fewer companies involved in RNAi have been bought recently. This increased concentration on mRNA acquisitions is yet another result of the success that the industry has seen with mRNA vaccine development, which has trickled into investment in mRNA therapies.

Exhibit 4: Most Active Corporate/Pharma Investors In RNA Venture Rounds Since 2017



Data through 31 October 2022

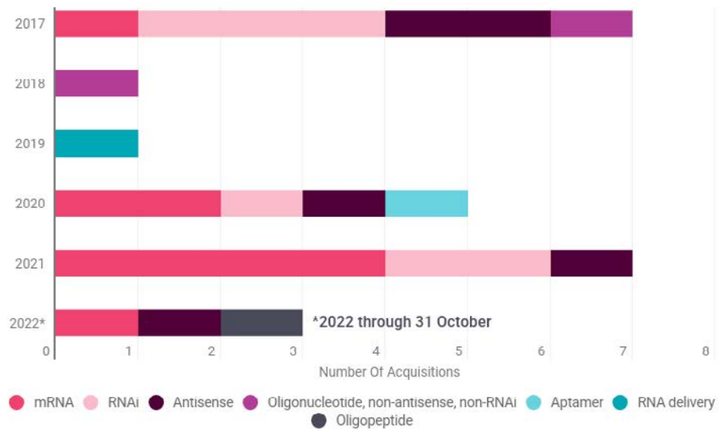
Source: Biomedtracker

Exhibit 5: RNA Partnerships Are Growing With Average Values >$500M

Note: Size of bubble represents average deal value for that year
* 2022 through 31 October

Source: Biomedtracker

Exhibit 6: Shift From RNAi To mRNA: RNA Acquisitions By Modality



Notes: mRNA category includes vaccines, therapeutics, or cell therapies.
Deals that include >1 RNA modality were counted more than once

Source: Biomedtracker

Looking Ahead In RNA Investment

There is strong reason to believe that the momentum gained in recent years with investment in RNA medicines will continue for the foreseeable future, as advances are made drawing increased venture funding. Peer-to-peer dealmaking between smaller biotechs in RNA has been the norm, but many multinational players have already signed deals, and the expectation is for the trend to increase. The current environment is encouraging, but similar to other advanced therapies like cell and gene therapies, the question still remains how commercially viable the RNA market will be, considering the investment in research, development, and manufacturing while ensuring that patients eventually have access to these life-saving medications.

The Busiest Dealmakers Of 2022

2022 Deal-Making Led By Sanofi, J&J And Roche

BY **JOSEPH HAAS,** SENIOR WRITER, US

With weeks to go in 2022, the three major pharmas each had inked between 16 and 20 deals. Meanwhile, Pfizer has been less busy with 12 deals, but those include M&A totaling $18.2bn.

As 2022 draws to a close, an unusually low number of marquee deals have been made in the biopharma sector. But it has been a hectic year nonetheless, with a high volume of deal-making and the lower valuations reflecting broader economic factors and continuing trends seen in recent years toward smaller, easier-to-manage deals.

Macroeconomic concerns stemming from inflation and rising interest rates, supply-chain uncertainty earlier in the year and the continuing war in Ukraine have imposed a dampening effect on the biopharma sector, creating a tailwind in the financing environment as well as the business development arena. But while this has weighed especially hard on biotechs, big pharmas continue to face the perennial pressure of filling the R&D pipeline, underscored by a looming patent cliff for several players.

That has helped to maintain a high volume of deal-making in the sector, although the biopharma industry continued a trend toward bolt-on acquisitions and away from major M&A deals this year, similar to the deal activity seen in 2021. As of mid-November, Biomedtracker recorded 16 biopharma M&A deals valued at $1bn or greater, with the Pfizer Inc./Biohaven Pharmaceutical Holding Company Ltd. $11.6bn takeout the largest of 2022. That mirrors 2021, with 16 M&A deals of $1bn or greater through mid-November, with the largest being Merck & Co., Inc.'s acquisition of Acceleron Pharma, Inc. for slightly more than $11bn. But analysts had been hoping 2022 would mark the return of mega-mergers.

Biopharma M&A was very constrained through the first three quarters of 2022 compared to the previous year. M&A transaction volume only declined slightly – from 116 deals in the first three quarters of 2021 compared to 104 deals during the same period in 2022 – but total M&A deal value in 2021 stood at $118.1bn through the first three quarters. In 2022, total M&A deal value was $50.7bn at the end of the third quarter.

Big pharma did its part, with seven companies making 10 or more M&A or alliance deals during this year. Twenty companies have made at least five deals, and that group includes some less familiar names, like NexImmune, Inc. and Twist Bioscience Corporation.

But large pharma is leading the charge, with Pfizer – although only sixth in deal volume – coming in second by total deal value, accounting for nearly 40% of reported M&A value in the biopharma sector so far this year as it emphasizes external R&D.

On the other side of the M&A picture, four of the seven busiest deal-makers – Eli Lilly and Company, Roche Holding AG/Genentech, Inc. , Johnson & Johnson, and Sanofi – combined for less than $1bn in M&A activity through 15 November. Sanofi reported no M&A spend for the year; J&J subsidiary Janssen Pharmaceuticals Inc. purchased Anakuria Therapeutics, Inc in February but no financial terms were disclosed.

Meanwhile, J&J initiated the biggest health sciences M&A deal of the year, agreeing to buy heart, lung and kidney implantable device maker Abiomed, Inc. for $16.6bn on 1 November. That not-yet-closed deal, along with the Pfizer/Biohaven takeout, are the only $10bn-plus M&A transactions of 2022 to date.

Company	Number Of Deals[1]	Total Deal Value[2]	M&A Deal Value[3]
Sanofi	20	$21.3bn	$0
Johnson & Johnson	16	$2.3bn	$0
Roche/Genentech	16	$13.4bn	$250m
Eli Lilly	13	$5.6bn	$720m
Bristol Myers Squibb	13	$14.2bn	$4.1bn
Pfizer	12	$20.6bn	$18.2bn
Merck & Co.	11	$10.1bn	$1.4bn

Source: Biomedtracker, Scrip

1 - Includes M&A, R&D and commercial partnerships, and licensing agreements. Does not include clinical trial collaborations, financings or manufacturing and supply agreements.

2 - Total deal value includes contingent future payments, such as milestones and royalties, which may not be realized.

3 - Report figures - not all M&A transactions have publicly disclosed valuations.

Here are snapshots of the five busiest deal-makers of 2022 so far:

Sanofi

Through mid-November, Sanofi is the sector's busiest deal-maker by both volume and total value. Not typically a stranger to M&A activity – having made six acquisitions in 2021 with a total reported value of nearly $6.8bn – the French pharma has focused on partnerships in 2022, including seven with a reported total potential value of more than $1bn a piece. The company appears to be more focused on earlier-stage R&D collaborations at present, in areas such as artificial intelligence-driven drug discovery, monospecific/bispecific antibody R&D, RNA-based medicine and gene editing.

Sanofi inked AI technology platform alliances with Exscientia Ltd. in January, Atomwise, Inc. in August and Insilico Medicine on 8 November, with each deal valued at more than $1bn including potential milestones and royalties. Those follow an equity investment and collaboration Sanofi made with French AI specialist Owkin in November 2021; the biotech then poached Sanofi's global head of partnering Alban de La Sablière to serve as its initial chief business officer in October.

Sanofi has remained an industry leader in harnessing AI to aid with discovery. In the tie-up with Oxford, UK-based Exscientia, Sanofi got potential license rights to small molecule candidates for oncology and immunology targets derived from patient samples. The pharma paid $20m to San Francisco-based Atomwise for computational drug discovery and development against five targets, and made a $21.5m upfront payment to Hong Kong-based Insilico to advance candidates against up to six targets.

Sanofi also signed several potential billion-dollar partnerships with antibody-focused biotechs during 2022, looking both east and west for innovative partners. In January, it teamed with China's Adagene Inc. on masked monoclonal and bispecific antibodies for precision cancer therapy in a deal valued at $2.52bn and in March inked a potential $1.06bn partnership with ABL Bio Corp. to co-develop the South Korean firm's preclinical bispecific antibody targeting alpha-synuclein and IGF1R for Parkinson's disease.

Cancer was the focus of most of the French pharma's business development activity. In March, Sanofi unveiled a potential $6.17bn collaboration with California's IGM Biosciences, Inc. on antibody agonists against three targets in cancer and three more in immunology/inflammation indications. The pharma also paired up in March with antibody-drug conjugate specialist Seagen Inc. at undisclosed terms to design, develop and commercialize up to three ADCs for cancer.

SANOFI/EXSCIENTIA PARTNERSHIP

- Collaboration and license agreement to develop up to 15 novel small molecule candidates across oncology and immunology, leveraging Exscientia's AI-driven platform utilizing actual patient samples.
- Exscientia gets $100m up front.
- Each program could yield research, clinical development, regulatory and commercial earnout of up to approximately $343m, including up to $193 in the aggregate for R&D and regulatory milestones, and up to $150m in commercial milestones. Aggregate milestones could top $5bn.

In September, Sanofi paid $25m up front to Scribe Therapeutics, Inc. in a deal worth up to $1.02bn to use CRISPR gene-editing technology in an effort to develop natural killer (NK) cell therapies for cancer.

The Paris-headquartered pharma also made four divestment transactions this year, with financial terms revealed for only one – it got $3m from Rallybio Corp. for rights to KY1066/RLYB331, a matriptase-2 antibody thought to offer potential therapeutic benefit in forms of anemia. Sanofi also offloaded late-stage central nervous system candidates to Terran Biosciences, Inc.; a 17-product portfolio of CNS, pain and vascular products to Neuraxpharm Arzneimittel GmbH; and a small interfering RNA (siRNA) therapeutics portfolio to Rona Therapeutics.

The Cambridge, MA-based firm can realize more than $1bn in earnouts under the agreement, bringing the aggregate potential value to about $1.07bn.

Johnson & Johnson

Johnson & Johnson and its Janssen subsidiaries have been busy deal-makers this year with 16 biopharma transactions in total, but only one M&A deal, for which no financial terms have been disclosed – the acquisition of Navitor Pharmaceuticals, Inc. subsidiary Anakuria on 2 February. The deal brings J&J a portfolio of selective rapamycin analog mTORC1 inhibitors, including Phase I AT-20494, a first-in-class opportunity in autosomal dominant polycystic kidney disease.

Otherwise, J&J's business development activity this year – amounting so far to $2.3bn in announced valuation – reflects its broad range of therapeutic focus and modalities.

EVOTEC'S BUSY PARTNERING YEAR

In addition to its R&D alliance with J&J, Evotec also:

- Signed partnerships with Lilly in metabolic disease; with Boehringer Ingelheim GmbH in stem-cell research for ophthalmology; with Sernova Corp in diabetes; and with Almirall SA in dermatology.
- Acquired Italy's RigeneranD Srl to expand its cell therapy production and capabilities and launched antimicrobial resistance-focused Aurobac Therapeutics SAS in a joint venture with BI and bioMerieux Inc.

On 3 February, it paid Mersana Therapeutics, Inc. $40m up front under a collaboration to develop cancer antibody drug conjugates against three specific targets. The Cambridge, MA-based firm can realize more than $1bn in earnouts under the agreement, bringing the aggregate potential value to about $1.07bn.

Two weeks later, the pharma committed $45m in upfront cash to another Cambridge biotech, Remix Therapeutics, to team up on discovery and development of small molecule therapeutics that modulate RNA processing using the latter's REMaster drug discovery platform.

J&J gets rights to oncology and immunology candidates under the agreement, which could yield more than $1bn in total for Remix.

On 14 June, J&J announced a collaboration with Germany's Evotec SE – itself one of 2022's busiest deal-makers, with seven transactions to date – using the latter's Target AlloMod platform technology to screen specified targets and then partner on hit identification and lead optimization of promising candidates. Therapeutic focus areas were not disclosed and financial details were vague, with Evotec getting research funding and potential research and commercial milestones of up to $220m per program.

Roche/Genentech

The Swiss conglomerate comprising Roche, Genentech and Chugai Pharmaceutical Co., Ltd. also made 16 deals to date in 2022, including the acquisition on 7 September of privately held Good Therapeutics, Inc. for $250m at closing with potential for development, regulatory and commercial milestone payments to the Seattle biotech's shareholders. Despite a relatively low M&A total, Roche has made upfront and downstream commitments of more than $13bn this year.

Roche's focus in buying Good is on a conditionally active PD-1-regulated interleukin-2 receptor agonist candidate for immuno-oncology, but the smaller firm's overall focus is on regulated, context-dependent molecules that combine an antibody sensor directed against a specific marker and a therapeutic component active only when the sensor has bound its target. Under the sale agreement, which closed on 30 September, Good's personnel and non-IL-2 programs will spin out into new company Bonum Therapeutics.

Much of Roche's deal-making this year has centered on cancer, with an emphasis on immuno-oncology and cell therapy. The pharma's potentially biggest deal of the year came on 3 August when it paid Poseida Therapeutics, Inc. $110m up front with another $110m in near-term milestones to partner on allogeneic CAR-T cell therapies for hematologic cancers. All told, the San Diego biotech could realize more than $6bn under the deal, which gives Roche global licensing rights to the Phase I P-BCMA-ALLO1 for multiple myeloma, and three preclinical CAR-T candidates, including P-CD19CD20-ALLO1, an allogeneic dual CAR-T for the treatment of B-cell malignancies.

ROCHE/GOOD BUYOUT AT A GLANCE

- Acquisition closed on 30 September for $250m in cash plus potential milestones to Good shareholders tied to predetermined regulatory, development and commercial achievements.
- Founded in 2016, Good Therapeutics focuses on generation of a new class of drugs that offer potent activity only where needed.
- After closing, Good management spun out Bonum Therapeutics to focus on design of conditionally active therapeutics in immuno-oncology, autoimmune diseases, metabolic disease and pain management.

In other cancer-related deals with high earnout potential, Roche obtained license rights to HOOKIPA Pharma Inc.'s HB-700 for KRAS-mutated cancers and an option for a second undisclosed novel arenaviral immunotherapy. The 20 October agreement brought the Austrian firm $25m up front, a $15m option-exercise fee for the second candidate and total potential value of $958m.

Meanwhile, Roche subsidiary Chugai inked a licensing agreement on 22 August for rights to fellow Japanese firm Noile-Immune Biotech, Inc.'s PRIME (Proliferation-Inducing and Migration-Enhancing) CAR-T technology, intended to enhance immune cell function through the expression of the cytokine IL-7 and the chemokine CCL19 from CAR-T cells. Although the financial terms weren't disclosed in detail, Noile-Immune can realize more than $146m under the agreement including upfront cash and earnouts.

Across all of its life sciences interests, the Roche conglomerate has made more than 20 deals this year, including four diagnostics tie-ups by its subsidiary Foundation Medicine, Inc.

Eli Lilly

Eli Lilly's 13 deals so far in 2022, with a total reported potential value of $5.6bn, are highlighted by its most recent transaction, the $610m takeout of the genetic medicine firm Akouos. Lilly has agreed to pay $12 per share for the Boston biotech, estimated at $487m, with another $123m in contingent value payments possible for Akouos, Inc. shareholders. Founded in 2016, Akouos is developing a portfolio of first-in-class adeno-associated viral gene therapies for the treatment of inner ear conditions, including sensorineural hearing loss.

The Indianapolis pharma's deal-making to date also includes seven alliances with potential value of greater than $200m apiece. It began the year in January with a pair of partnerships – teaming with Canada's Entos Pharmaceuticals, Inc. on its nucleic acid delivery technology to develop products targeting the central and peripheral nervous system, and with China's Abbisko Therapeutics Co., Ltd. to develop novel molecules addressing an undisclosed target for cardiometabolic diseases of unmet medical need. Lilly ended the month with a third collaboration, with Evotec in a deal centered on diabetes and kidney disease that could yield the German firm more than $1bn.

As the year went on, Lilly began signing alliances with US biotechs, including two Boston-area firms. In February, it paid $13m up front to ImmunoGen, Inc. for rights to cancer antibody-drug conjugate therapies by applying the biotech's camptothecin technology to targets selected by Lilly.

In October, Lilly signed on with Nimbus Therapeutics, Inc. to deploy that company's computational drug discovery platform for novel targeted metabolic disease therapies that target an isoform of AMPK. Nimbus can earn up to $496m under the pact.

The pharma also partnered in May with San Francisco's Genesis Therapeutics in an AI-driven discovery and development pact for up to five targets across a range of therapeutic areas. Genesis got $20m up front tied to the first three Lilly-selected targets and could realize up to $670m in earnouts under the agreement.

LILLY'S TIE-UP WITH NIMBUS

- Focused on activating isoforms of 5' adenosine monophosphate-activated protein kinase (AMPK) for metabolic disease.
- Nimbus to conduct initial research; Lilly will assume development and commercialization responsibilities.
- Nimbus can earn up to $496m in upfront cash and milestone payments plus tiered, double-digit sales royalties.

Bristol Myers Squibb

With a financial commitment of more than $14bn (including potential downstream payments), BMS is big pharma's third-largest spender so far in 2022, trailing Sanofi and Pfizer. It inked one of the year's largest M&A transactions, paying $4.1bn in June to acquire Turning Point Therapeutics Inc., while also negotiating five collaborations with total valuations of $1bn or greater.

The Turning Point deal closed in August, bringing BMS a pipeline of cancer medicines intended to target the most common mutations associated with oncogenesis. Lead asset repotrectinib is a next-generation, potential best-in-class tyrosine kinase inhibitor targeting the ROS1 and NTRK oncogenic drivers of non-small cell lung cancer (NSCLC) and

other advanced solid tumors. Repotrectinib has been granted three breakthrough therapy designations from the US Food and Drug Administration.

BMS's total of 13 deals through 15 November also incorporates a licensing agreement signed in May with China's LaNova Medicines to pick up rights to LM-302, a novel ADC targeting Claudin18.2.

To date, BMS has signed four cancer-focused alliances that each could top the billion-dollar mark. In January, the pharma paid $100m up front and made a $50m equity investment in Century Therapeutics, Inc. to license rights to up to four induced pluripotent stem cell (iPSC)-derived, engineered natural killer cell and or T-cell programs for hematologic malignancies and solid tumors.

In March, BMS placed a wager on synthetic lethality, paying $30m up front in a potential $1.13bn tie-up with Volastra Therapeutics, Inc. to combine its oncology expertise with the latter's understanding of chromosomal instability.

During Q2, BMS aligned with Scotland's Amphista Therapeutics to discover, develop and license small molecule protein degraders derived from the biotech's Eclipsys platform and with Immatics N.V. to develop autologous T-cell receptor (TCR) therapeutics. Amphista got $30m up front in a deal that could total $1.25bn, while Immatics got $60m up front with potential for up to $700m per program in its alliance with BMS, for a total potential value of $4.26bn. That deal built upon an existing relationship between Immatics and Celgene Corporation, which was furthered by a license agreement between BMS and the German biotech in December, which brought Immatics $150m up front.

BMS/CENTURY PARTNERSHIP

- Research and licensing collaboration centered on up to four induced pluripotent stem cell-derived, engineered natural killer cell (NK) and or T-cell programs.
- Focused on both hematologic cancer and solid tumors, with initial programs in acute myeloid leukemia and multiple myeloma.
- Century has a co-promotion option under the agreement and also received a $50m equity investment from BMS under the deal, priced at 57% premium.

Pfizer, Merck Busy As Well

Beyond the five busiest biopharmas in deal-making this year, Pfizer and Merck both have hit the double-digit mark for deals already. Although our analysis does not include clinical trial collaborations without licensing or financial commitments as deals, if it did, the continued hectic pace of collaborations to test novel cancer drugs with Merck's anti-PD-1 stalwart Keytruda (pembrolizumab) would make the New Jersey pharma the busiest deal-maker of all.

Pfizer's 12 deals this year have been among the most impactful in the biopharma space given that the New York-based firm has spent more than $18.2bn on M&A due to its Biohaven and Global Blood Therapeutics, Inc. acquisitions in May and August, respectively. Pfizer's business development activity this year also includes a potential $1.65bn *in vivo* base-editing tie-up focused on rare diseases with Beam Therapeutics Inc. and a cancer-focused antibody discovery and development partnership valued at $1.02bn with Dren Bio, Inc.

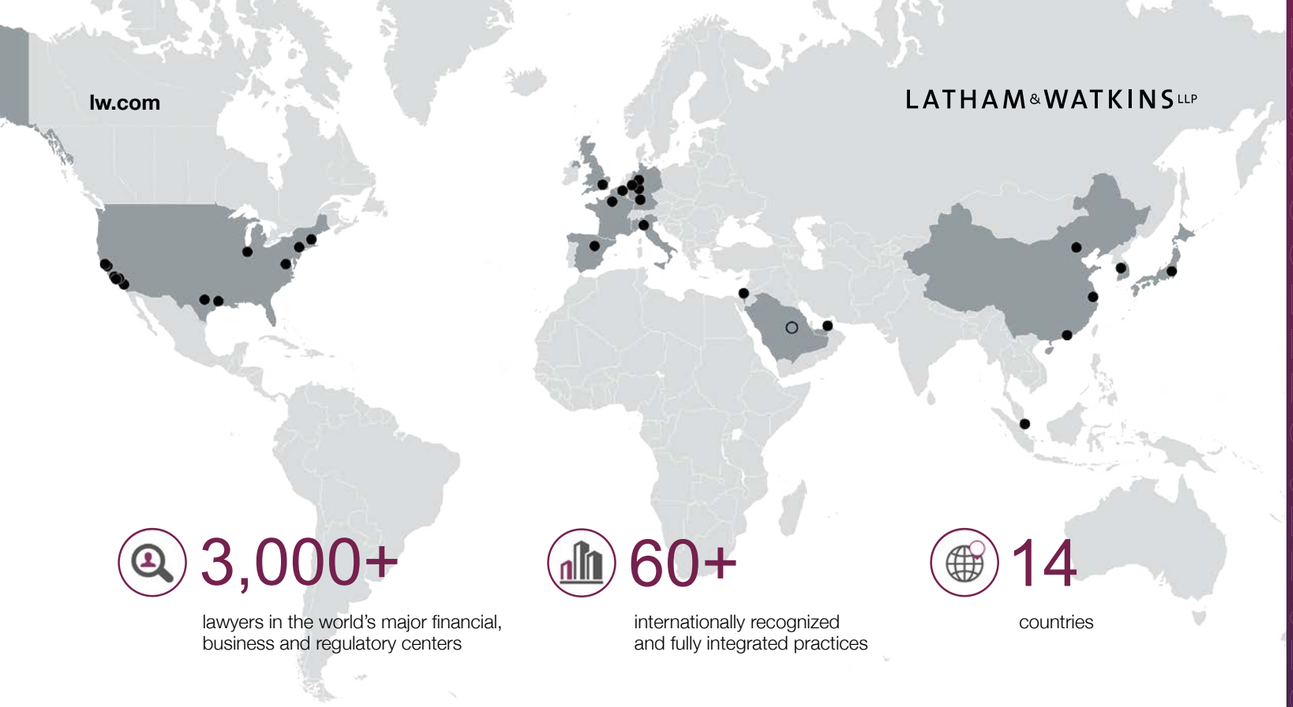
Merck's deal-making to date is highlighted by the potential $1.41bn it has agreed to pay China's Sichuan Kelun Pharmaceutical Co Ltd. for rights to an undisclosed macromolecule cancer project. The two firms inked a second licensing pact – giving Merck rights to an ADC candidate for solid tumors – in July.

The most notable action by Merck in 2022 might be the failure to complete a hotly rumored acquisition of Seagen. Already partnered with the ADC specialist on ladiratuzumab vedotin, in September 2020 Merck acquired $1bn worth of Seagen shares. The combination of Merck's need to reboot ahead of the Keytruda loss of exclusivity and the tumultuous exit of Seagen founder and CEO Clay Siegall raised expectations of a pending announcement.

A Merck-Seagen merger would have been valued at upwards of $30bn and become the clear bright spot in a rather drab year of deal-making.

However, Seagen's hiring of a high-profile CEO – David Epstein, most recently a partner at the venture capital firm Flagship Pioneering and previously president of Novartis AG's Pharmaceuticals division – seems to be a signal the company is intent on determining its own strategic path rather than a merger.

A Merck-Seagen merger would have been valued at upwards of $30bn and become the clear bright spot in a rather drab year of deal-making. But even in a year without flashy mega-mergers, the business end of business development continues – this year's crop of the busiest players shows the type of transactions that keep the biopharma engines running.



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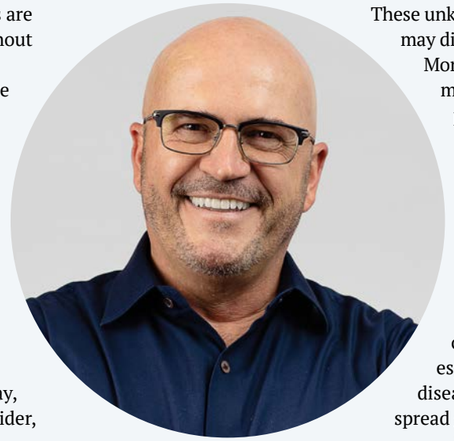
Amplifying The Patient Voice To Build More Inclusive Clinical Trials

In the clinical trial ecosystem, patients are imperative to successful research. Without enrollment, engagement, buy-in, participation, and retention, studies are simply unviable. After many years of investment of both time and finances into R&D activities, being unable to complete this stage of the process is disheartening to all stakeholders involved. Studies have shown only about 30% of clinical trials will meet enrollment goals and timelines.

The impact of this failure in the process on trial sponsors cannot be underestimated, according to Scott Gray, CEO of patient concierge services provider, Clincierge. Gray states, "The biggest consequence is the trial could fail. If it cannot be conducted, all of the R&D money spent leading up to the point of being able to do human trial testing is lost." Even if trials ultimately succeed, the costs of delays are significant, even ruinous, for some companies. Gray shares loss estimates of between $600,000 to $8m for every day a study is prolonged.

These risks can be mitigated by taking a patient-centric approach to clinical trials. However, existing barriers to participation must first be overcome.



SCOTT GRAY, CEO, CLINCIERGE

Navigating Financial, Travel, And Support Challenges

Identifying a patient for a clinical study is only the beginning of ensuring their ability to participate in and ultimately complete the trial. Firstly, there are various financial implications to consider. Patients may need to take time away from work to visit clinical sites and receive treatment in a study, and the cost of travel in itself can be significant, depending on the trial location. Even if these expenses are reimbursed, patients may not be in a position to make the initial payments necessary to participate.

There are also logistical barriers when traveling to sites, and Gray notes patients have a number of questions when considering their participation. "They ask: 'Is there a site that is near, or do I have to drive across town, the state, or even to another state? What is the duration of the visit and follow-ups?'" These unknowns require advance planning, which may dissuade patients from participating.

Moreover, some disease states may impact mobility or cognition, compromising a patient's ability to travel.

In a study conducted by Clincierge, 62% of patients and 59% of caregivers stated that travel-related challenges, and their subsequent financial implications, prevented them from taking part in a trial. Unfortunately, it is not feasible to ensure all patients within a study can avoid long journeys to participate, especially in indications such as rare diseases where populations may be spread globally.

It is, therefore, critical to support patients by arranging their travel and removing the immediate financial burdens of participation. "We have designed Clincierge's services to solve this challenge, making purchases on behalf of the patients and coordinating the logistics so they can get to the site easily," says Gray.

The Impact Of COVID-19

Study operations were significantly impacted by the COVID pandemic, with new, decentralized trial models implemented to continue research when travel was restricted, and clinical sites were closed. The success of decentralized clinical trials (DCTs) has been met with excitement from the industry, as they can significantly reduce the travel burden on patients. In some instances, site visits can be replaced with in-home visits from health care workers, while mobile technologies can be utilized for remote patient monitoring.

While DCTs undoubtedly offer benefits for patients in certain circumstances, Gray stresses they are not a one-size-fits-all solution and must be structured with the patient experience at the top of mind. "Interestingly, we have discovered there are patients who do not want site staff visiting them at home. For example, we saw in many instances with Alzheimer's patients, their only social experience out of the home was when they went to the trial site and interacted with the team," he notes. Moreover, there are many rare diseases where specific tests such as MRIs are needed and cannot be conducted in the home.

Innovative thinking was needed during the pandemic for studies where decentralized models were not applicable to ensure patients could remain enrolled in trials. There are several examples Clincierge experienced which stand out to Gray. "In one instance, the Spanish rail and bus system was shut down. We hired a private car to pick up the patient and drive them across the country and arranged overnight hotel accommodations for both the patient and the driver. In a separate instance, there was an immunocompromised patient who had their final site visit, and we sought authorization for private air travel to transport them. It was extremely important to the patient that after many months of participation, their data could be included and make a difference in the trial."

The Human Approach To Patient Support

These examples show the benefits of a patient-centric approach to clinical trials. Such solutions are only achievable by offering individualized services considering each participant's circumstances. This human touch is at the heart of Clincierge's ethos. "Our coordinators work one-on-one, person-to-person, through all of the logistical and financial obstacles which could prevent the patient from participating or cause them to drop out if these burdens were directly put on them," says Gray.

This concierge level of service is of paramount importance, especially given the stresses already upon patients suffering from a disease warranting clinical intervention. Clinical trial participation comes with a whole host of considerations outside a patient's day-to-day life; managing these logistics without support would be untenable. Gray continues, "Everyone needs a place to call for help. Let's say they are trying to use a system to request transportation to the site. Think of their emotional state at the time. They are struggling with a disease, and now there's a device or software that is frustrating them. A phone call is favored so they can talk to someone."

> **"If you are able to get your outcomes data on time, you can submit for approval sooner and go to market to begin recovering huge R&D investment."**
>
> Scott Gray, Clincierge

The data speaks for itself when comparing trials offering one-on-one patient support services to those that do not. Retention rates for studies supported by Clincierge are well over 90%, where the average rate is usually less than 70%.

The Importance Of Inclusivity

The benefits of trial accessibility on patient experience are obvious and are all part of a bigger picture for the success of treatments. Enabling more patients to participate in research, regardless of socio-economic background or demographic group, ensures treatment efficacy and safety across different genetic makeups.

Regulators such as the US Food and Drug Administration (FDA) have identified trial diversity as a critical area for improvement, as study populations notoriously lack appropriate representation from different socio-economic groups. Gray notes that traditionally, 60%-70% of study participants in the United States have been white males, primarily because they can afford travel costs and time away from work. The African American, Hispanic, and Asian American communities account for 13.4%, 18.1%, and 6% of the US population, respectively, yet they account for only 5%, 1%, and 1% of trial participants. "It is a huge challenge, and lots of work needs to be done to level the playing field, so we get better outcomes data across the spectrum of genetic makeup," he states.

By taking a human-centric approach to supporting patients, opportunities to participate in clinical trials are made as inclusive as possible. This move towards inclusion will be imperative as diversity requirements in drug development become more stringent. However, these guidelines will also ensure the patients' experiences are positive and they stay engaged in the trial throughout. Increasing retention rates is the key to expediting drug development and achieving a return on investment from the many years of R&D prior to the beginning of the clinical trial phases. Gray concludes, "If you are able to get your outcomes data on time, you can submit for approval sooner and go to market to begin recovering huge R&D investment and provide treatment for other patients. That is the biggest factor of why we feel this human-to-human connection is essential."

Clinical Trials: Have We Finally Reached The New Normal?

BY **HEIDI CHEN,**
ASSOCIATE
DIRECTOR, CITELINE

Pent-up trial demand during 2020 plus trial modernization strategies yield bumper performance in 2021 as research priorities revert to pre-pandemic trends.

The COVID-19 pandemic brought acute disruption to the clinical trials landscape in 2020. While there was an explosion of trials initiated in infectious disease, clinical trials in other therapeutic areas endured setbacks in enrollment and progression. With the uptake of vaccinations from late 2020 through 2021, and the rollercoasters of variants that dashed hopes of returns to normalcy, the entire health care industry is learning to coexist with COVID-19. Clinical research, however, has adapted more quickly and early signals of recovery have translated into an impressive full-year performance in 2021. Exploring the trends within clinical trials that initiated during 2021, contrasting against pre- and peri-pandemic themes, reveals whether a post-pandemic, new normal has now been established.

New Clinical Trial Starts Surpass 10k Mark

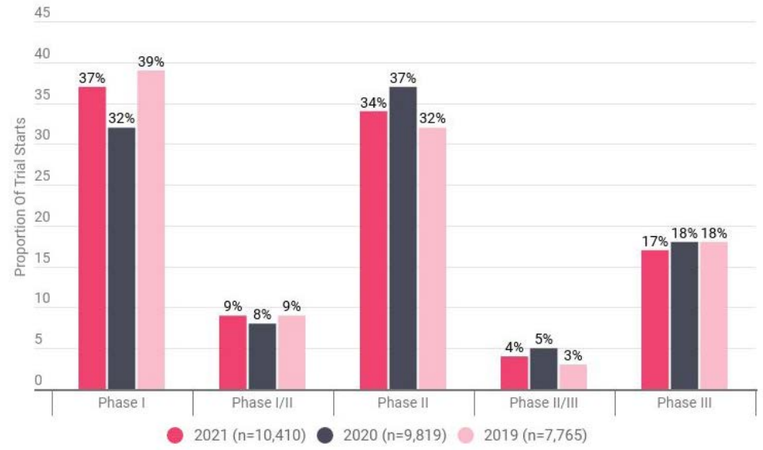
According to the industry-leading clinical trial database Trialtrove, 2021 saw more than 10,000 Phase I–III clinical trials initiated for the first time in a calendar year. This figure is 6% higher than 2020, which itself saw a surge in new clinical trial initiations, despite the pandemic disruption. However, within the 26% rise witnessed during 2020 was a 4% decline in traditional research priorities, hidden among the influx of almost 2,500 COVID-19 clinical trials, as shown in Exhibit 1. By contrast, 2021's top-line growth of 6% includes an incredible 22% resurgence of non-COVID-19 studies, as a new normal baseline of activity was established. By way of comparison, 2019 saw just 2% growth in the final pre-pandemic year, although this was unusually low compared to 12% in each of the two years prior.

Exhibit 1: Phase I–III Clinical Trial Activity By Volume And Growth

Year Of Trial Initiation	2019	2020	2021
Trial count	7,765	9,819	10,410
Year-on-year growth (%)	2%	26%	6%
Trial count (excluding COVID-19 trials)	7,765	7,424	9,077
Year-on-year growth (excluding COVID-19 trials, %)	2%	-4%	22%

Source: Trialtrove, June 2022

Exhibit 2: Distribution Of Phase I–III Clinical Trials By Phase



Source: Trialtrove, June 2022

Trial initiations in 2021 largely comprised Phase I (37%) and Phase II (34%) research (*see Exhibit 2*). The exact balance between these earlier stages of clinical development has varied in the last three years, as 2020 saw an increase in mid-stage trials, presumably driven by repurposing efforts against COVID-19. The normal sequence was restored in 2021 with increases in Phase I and I/II activity. This recovery reflects projects and new research activities that resumed after being held back in 2020. By contrast, Phase III has held steady over the last three years, with such larger and more expensive studies being less affected by short-term pandemic effects.

Oncology Reasserts Its Dominant Position

Oncology has consistently been the most active therapeutic area based on trial initiations over the last decade, although its lead in 2020 was threatened by activities from COVID-19 trials. Normal service was resumed in 2021, as oncology trials bounced back with 20% growth. With a combined 3,784 trials, oncology accounted for 36% of all clinical trials initiated in 2021.

Many of the other major therapy areas followed a similar trajectory, with 2020 showing either flat or slightly retreating trial counts, before growing strongly in 2021. Cardiovascular was one exception, with new trials growing relatively consistently despite the wider disruption in 2020. As expected, infectious diseases was a major outlier. With the addition of almost 2,500 clinical trials in a disease that only entered human circulation in late 2019, the wider infectious disease group saw over 300% growth in 2020. Trial counts only retreated a modest 9% in 2021, as the pandemic leaves a longer-lasting legacy for anti-infective research. It is highly likely that infectious diseases will be the second-ranked therapy area for a considerable period, as drug developers seek to improve upon current COVID-19 therapies, bolster pandemic preparedness efforts, and evaluate new technologies such as mRNA and viral vector vaccines against different pathogens.

AstraZeneca Defends #1 Position, Jiangsu Hengrui Ascends

The top 10 list of leading trial sponsors in 2021 is largely consistent with that in 2020, with some minor shuffles in rankings and a modest increase of trial counts per company. AstraZeneca kept its crown as the most active sponsor, while GlaxoSmithKline Pharmaceuticals Ltd. replaced Sanofi in the number 10 position. After claiming the top spot in 2019, Bristol Myers Squibb Company continues to fall through the ranks, which was a likely scenario after the consolidation of its portfolio with that of Celgene Corporation. As a result, BMS is now in eighth position and has the fewest new Phase III trials of its peers, counterbalanced by a bias towards early-stage research, which is also an indicator of its strong oncology focus.

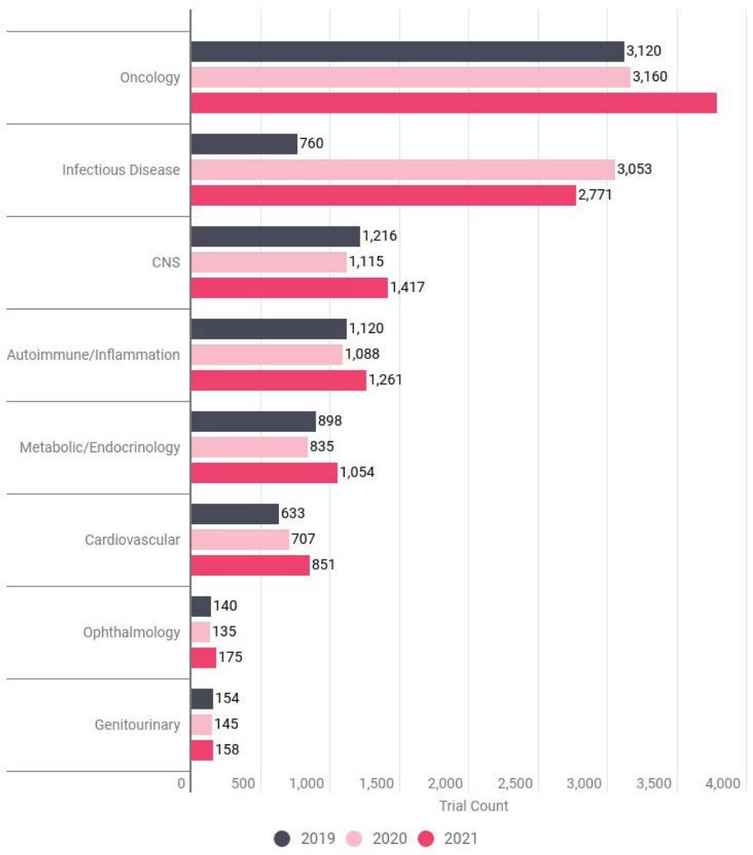
Pfizer Inc. and Jiangsu Hengrui Pharmaceuticals are also heavy on early-phase trials, with over half of their 2021 trials being Phase I or I/II. Pfizer has consistently placed in the top five, although Jiangsu Hengrui has extended its remarkable rise from 69 trials in 2019 to 130 trials in 2021, overtaking Pfizer into fourth place. Such a rise reflects the growing influence of Chinese biopharmaceutical companies on the global stage, and it would not be a surprise if Jiangsu Hengrui – or one of its peers – were to claim the top spot in future editions of this analysis.

Of all the companies in the 2021 top 10, Novartis AG has the largest share (and absolute number) of trials at Phase III. Like its peers, Novartis places a strong emphasis within oncology, although its late-stage clinical activity is diversified across a range of therapy areas, also including immunology, cardiovascular, metabolic/endocrinology, CNS and ophthalmology. Such an investment is difficult to maintain in the long-term: 2020's Phase III leader Roche has pivoted strongly towards earlier-stage clinical trials with its 2021 portfolio.

China Overtakes US As A Trial Location For The First Time

In prior years, the US and China have contended for the top two spots in terms of most new studies. For 2021, China finally reigned as the number one destination for trials, with 3,795 new clinical trials initiated in the year, compared to 3,310 in

Exhibit 3: Phase I–III Clinical Trial Initiations By Therapeutic Area



Source: Trialtrove, June 2022

the US. 6% annual growth in new clinical trials in the US was greatly overshadowed by a remarkable 37% increase in Chinese trials, with this considerable momentum expected to create a growing gap in future years.

The major European countries of France, Germany, Italy, Spain, and the UK, alongside Canada, Japan, and Australia, constitute the rest of the top 10 locations for clinical trials initiated in 2021. This top 10 is highly consistent, with the same countries appearing in the 2019 and 2020 lists (except for a pandemic-boosted Iran replacing Italy in 2020).

Exhibit 5 additionally compares the top 10 countries by therapeutic area from 2019–2021, and shows that most of the top countries are largely consistent with prior years, with steady year-on-year growth. There is a clear and definite trend of decreased trial volumes in 2020 across most therapeutic areas, the major exception being Infectious Disease. Trial volumes in 2021 exhibited resilient recovery, many exceeding pre-pandemic levels in countries that suffered significant setbacks with trial enrollment and delays.

Notable datapoints include 80% and 79% year-on-year increases in the numbers of CNS trials in China and the UK, respectively. The number of oncology trials in China also jumped sharply, rising 46%. Coincidentally, 46% is also the total share of all clinical trial activity for oncology in China. The top 10 locations for infectious disease trials sees the greatest deviation from the overall top 10 rankings, with India, Iran, Brazil, and Russia all featuring. Clinical trial infrastructure established in these countries during the pandemic may have a legacy to provide the foundations for these regions to become more internationally competitive across other therapeutic areas in the future.

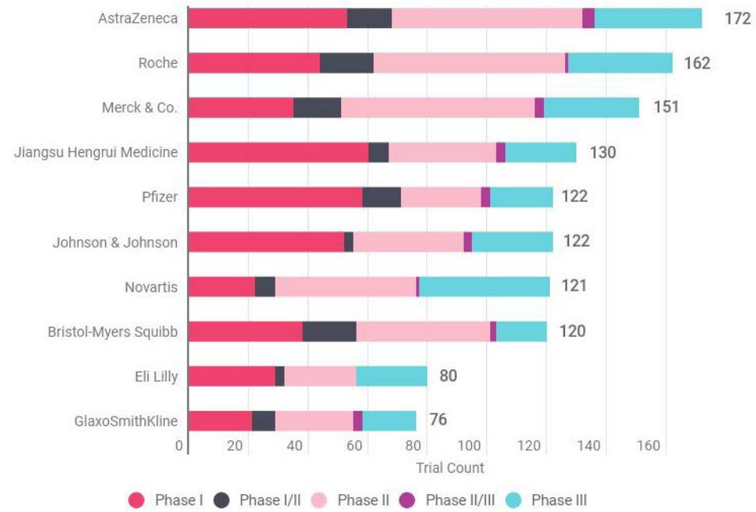
Are We Back To The New Normal?

Any disruption observed to the clinical trial landscape in 2020 proved to be short-lived, as 2021 saw a resilient recovery of clinical trial activity across all therapeutic areas. Not only did 2021 trials show a strong return, but we witnessed all-time high trial volumes. This is partly due to the influx of COVID-19-related clinical research, but also aided by the broader resumption of normal R&D priorities, in particular for the major oncology indications, other high-burden chronic and rare diseases, and encouragingly, new Phase I programs.

Although the main sponsors, disease priorities, and locations for trials in 2021 are generally similar to the pre-pandemic observations, there is a broader shift in progress. Namely, China is becoming a dominant force in the clinical trial landscape. More studies were initiated in China than any other country in 2021, and the leading domestic sponsor, Jiangsu Hengrui, is beginning to challenge the largest multinational pharmaceutical companies for R&D activity. Meanwhile, the established companies are continuing to coalesce around similar research priorities, with intense clinical activity in solid tumor indications.

Underpinning all of these trends is the strength of the clinical trial ecosystem. Technological advances in digital health, clinical trial decentralization, improved patient engagement, and an emphasis on diversity have allowed the industry to successfully navigate through the challenges of the pandemic and enter 2022 with considerable momentum. We can confidently conclude that – in the world of clinical trials, at least – we have reached a new normal and the lingering effects of the pandemic are behind us. The future appears brighter than ever.

Exhibit 4: Top 10 Industry Sponsors/Collaborators By Number Of Phase I–III Trials



Source: Trialtrove, June 2022

This article has been adapted from a white paper, 2021 Clinical Trials Round-Up, using Citeline's gold-standard clinical trials intelligence solution Trialtrove. To read the white paper in full, please visit https://pharmaintelligence.informa.com/resources/product-content/2022/10/06/13/24/the-clinical-trials-landscape.

CLINICAL TRIALS

Racial And Ethnic Diversity In Clinical Trials: A Social And Scientific Imperative

From new FDA guidance and community engagement efforts to the challenges of precision medicine and decentralization, *In Vivo* spoke with industry experts about racial and ethnic diversity in the context of clinical trials.

BY **AYISHA SHARMA**, REPORTER, SCRIP, EUROPE

On average, 20% of drugs approved each year have different response rates depending on a patient's race or ethnicity. Enrolling a diverse patient population in clinical trials allows industry to identify differences in efficacy and safety across different sub-populations which in turn facilitates the delivery of effective drugs for all, Pfizer Inc.'s head of clinical trial experience Judy Sewards told *In Vivo*.

A spokesperson from Bristol Myers Squibb Company concurred and told *In Vivo* that "diversity in clinical trials is both a social and scientific imperative." However, while almost 40% of Americans belong to a racial or ethnic minority group, Caucasian participants account for around 80% of those recruited into US clinical trials.

"Unfortunately, for a lot of people, underrepresentation of some groups wasn't brought up much prior to the pandemic even though race has been an issue from almost the onset of clinical research," LaShell Robinson, Takeda Pharmaceutical Co. Ltd.'s head of diversity and inclusion in clinical trials, told *In Vivo*.

She highlighted the case of the Tuskegee Experiment, which spanned decades and was conducted by US public health authorities on 400 African-American men with syphilis. The men were left untreated even though their disease was entirely treatable by the end of the study, resulting in more than 100 deaths.

Ethical atrocities of this sort have engendered mistrust in some communities of color that echo through to this day and while such events have diminished with time, unconscious bias can still prove a barrier to diverse enrolment. Other roadblocks for participants include the inaccessibility of trials and language barriers.

Furthermore, sponsors can also face challenges on their end when attempting to enhance diversity in clinical trials, including the perception that doing so will result in a loss of speed and a lack of investigators and other staff from a minority background at some trial sites, Sewards explained.

Regulators Join Industry Efforts

However, the tide is starting to turn. In April, the US Food and Drug Administration released draft guidance for industry aimed at improving the enrolment of underrepresented racial and ethnic populations in clinical trials. The FDA recommended that firms submit a 'Race and Ethnicity Diversity Plan' for medical products at the investigational new drug or investigational device exemption application stage.

Sponsors are advised to use the plan to "define enrolment goals for underrepresented racial and ethnic participants" and start the document with "an assessment of any data that may indicate the potential for a medical product to have differential safety or effectiveness associated with race or ethnicity."

Some firms are already ahead of the curve. "We've been proactively developing and submitting equity action plans for all planned clinical trials since 2021," Amgen, Inc.'s head of representation in clinical research Jude Ngang told *In Vivo*, adding it was "refreshing" to see a regulatory agency push industry on this front. The major's internal Representation in Clinical Research program is dedicated to enhancing equitable access to clinical trials.

Robinson agreed the plans were a step in the right direction but cautioned "nothing's going to be perfect right out of the gate." She nonetheless praised the inclusion of a trial metric recommendation in the FDA's guidance. "It's important to aim towards a specific goal rather than arbitrarily saying 'we want more diversity'," she explained.

The BMS spokesperson confirmed the company had incorporated the plans into its R&D process, adding they could help stakeholders get better understanding of drug safety and efficacy across the whole population. However, it is unclear how far regulators will go to enforce their guidance.

In October, the FDA faced criticism for failing to penalize a sponsor for missing diversity targets in an oncology clinical trial, prompting industry players to call for more information about potential negative consequences. The regulator responded by highlighting it could be appropriate to conduct post-approval studies if diversity targets are not met.

Furthermore, not all experts were impressed by the FDA's guidance. In July, FDA commissioner Robert Califf said the push to increase clinical diversity could serve as a "distracting manoeuvre from the underlying issue of lack of equity in our health care system." While Robinson and Sewards said they would not characterize the efforts as a distraction, they both agreed with Califf's underlying sentiment that latent disparities across health care more broadly must be addressed.

Takeda's head of equity and patient affairs Charlotte Owens told *In Vivo*, "There are inequities in the health care system all along the way, which make it harder for some to even receive appropriate medical attention and diagnosis let alone treatment and care and it's important to understand that addressing clinical trial diversity is just one part of this."

She added industry must be mindful not to lose sight of the social determinants of health underlying broader inequities when discussing clinical trial diversity. The determinants include a range of economic and social conditions that can affect access to health care including where people are born, live, study and work.

Community Engagement And Education Indispensable

One major issue that firms will have to grapple with in the future is maintaining diversity in trials as precision medicine gains traction. Precision medicine is an emerging approach across health care that factors in individual variability in genes, environment and lifestyle for each patient to optimize outcomes. In the context of drug development, this can mean designing drug candidates for niche subpopulations of a disease with specific genetic mutations.

Once again, historical events have engendered distrust of pharmacogenomics in some groups of colour, as illustrated by the case of Henrietta Lacks, an African-American woman whose cervical cancer cells formed the source of the 'immortal' human cell line known as HeLa. Lacks' cells were shared among researchers without her consent and her genome was even published online after her death without her family's consent.

The concerns people may have about how their genomic information could be used is exacerbated in the context of today's digital age, Robinson highlighted. "The education piece becomes very important, which includes informing people what their information will be used for, how it's going to advance medicine and how it will contribute to their family and community," she added.

Education requires community-level outreach, one of the tasks Owens is responsible for in heading up Takeda's equity and patient affairs division. "We will engage communities through patient advocacy groups while some patients will directly engage with trusted partners and organizations," Owens explained.

Ngang highlighted that Amgen holds community advisory boards with representatives from underrepresented groups to share their guidance and lived realities. Meanwhile, Pfizer last year pledged a three-year $10m grant to Columbia University to help establish and expand a joint clinical trials diversity initative. The BMS spokesperson highlighted that as of July 2022, 56% of the firm's clinical trial sites were located in highly diverse areas of the US, surpassing its initial goal to achieve 25% by this year.

"Another headwind for the development of precision medicine is the historical lack of diverse representation in genomic research even though we are a couple of decades away from completion of the human genome project," Ngang said, adding that appropriate participation and representation in biobanks and genomic research would be necessary to ensure the gap does not widen further as next-generation therapies are developed.

Decentralization A Doubled Edged Sword

Elsewhere, industry will have to adapt to the increasing decentralization of clinical trials, an approach that has gained traction since the onset of the COVID-19 lockdowns. Robinson said she thought decentralized and hybrid trials were here to stay but added companies needed to consider how to apply these approaches equitably.

In some ways, decentralization has helped improve trial diversity by enabling enrolment of people beyond those who happen to live near the major hospitals or academic centres which serve as trial sites, thereby unlocking unexplored demographics. However, they simultaneously raise challenges for diverse enrolment including heavy reliance on electronic tools.

Technology can create opportunities and expand access but only for people who had access to begin with," Owens highlighted. A recent report from the Brookings Institute showed 15%-24% of Americans lacked some sort of broadband connection to the internet which makes it very challenging to use mobile health technology, she added.

Furthermore, when engaging with patients virtually, trial site staff lose some aspects of contact that enable improved assessment of patients such as observing nonverbal clues that could relay important information about their condition, Owens said. Robinson admitted Takeda had struggled with "throwing too much technology at trial sites" in the past.

For example, she explained how a past trial had required participants to use an iPhone but the demographics of iPhone users skew towards a white male population. Rather than just thinking about the digital elements, it is important to utilize mobile health sites, home nursing services and even local pharmacies to bring the trial site closer to patients, Robinson concluded.

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- Rail Travel
- Hotel Accommodations
- Travel for Site Staff
- IP/Specimen/Sample Shipment
- Caregiver Support

PATIENT PAYMENTS
- Stipend Payments
- Meal Reimbursements
- Meal Per Diem
- Wage Reimbursement
- Travel Reimbursement (mileage, tolls, parking)
- Childcare Reimbursement
- Laboratory Payments
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DIGITAL

How Digitalization Can Transform Patient Safety Outcomes

During the COVID-19 pandemic, patient monitoring became heavily digitalized due to travel and social distancing restrictions. Technology – such as wearables and other devices – is an increasing part of disease management and offers a much more convenient approach to previously laborious health care processes, along with enhanced insights for pharma sponsors.

Moving forward, one of the key opportunities for expansion of digitalization is to handle patient safety proactively, in real time. *In Vivo* spoke with IQVIA's Updesh Dosanjh, practice leader in safety AI, about his hopes for the future to improve patient outcomes.

UPDESH DOSANJH, PRACTICE LEADER IN SAFETY AI, IQVIA TECHNOLOGIES

In Vivo: With regards to data arising from adverse events (AEs), what problems can arise in the traditional reporting process?

Dosanjh: Traditionally, if a patient experiences an AE, they go to the doctor, they report it, and that event is analyzed to determine the existence of a problem. There are a lot of gaps within that process. Firstly, you expect the patient to recognize they've had an AE related to that drug, then that they will report it to their doctor. Realistically, patients may not know they've had an AE, and if they do, they may not understand that it is related to their treatment. There may also be barriers preventing them going to the doctor and reporting it.

Even once the AE has been reported, there is a very clunky process with many different people involved before the information makes it to the safety team who are qualified to make an assessment. This causes notable delays, but also distortion in the circumstances of the AE, which could result in the wrong judgement from safety personnel.

Devices can help because they are monitoring constantly, so there is more data for pharma companies to review and react to after an AE is communicated. But again, if we consider that less than 10% of patients who experience these events actually report it, that still leaves 90% of patients untouched. What I think this technology has the opportunity to do is move us from being reactive to proactive.

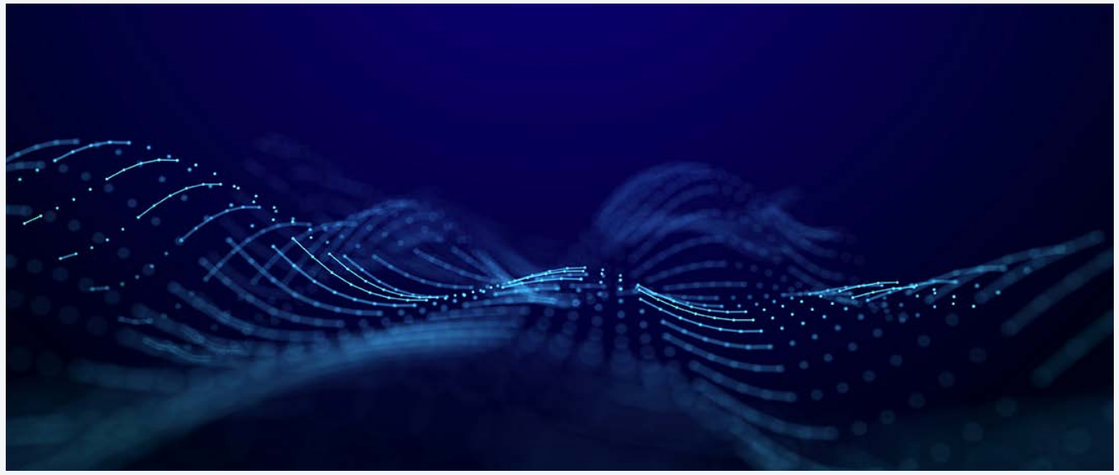
While we can never eliminate AEs, with the right platforms in place these can be detected as they're happening, and information communicated to the safety team right away, who can give patients and their physicians the correct advice. Within the ecosystem of wearables now, we can see what happens physiologically each time they take their treatment. If that changes from the baseline, a set of questions can pop up on their phone, asking if they have done any abnormal activity. We can move into the world of continuous safety monitoring, enabling us to proactively manage patient health care.

How can pharma companies directly benefit from mitigating these communication bottlenecks in AE reporting?

The real benefit to you as a company is that you can start using the data. For example, you can drive understanding of additional patients who you can access by getting a much more targeted understanding of where the risk-benefit for patient groups is. There could be a whole group to expand into that they are currently not targeting but now can because they know more information about them. Additionally, we can get extremely close to real-time analysis, which enables companies to carry out safety interventions much closer to the event. This will enable companies to make it much safer for patients to interact with their therapies.

How does *IQVIA Vigilance Platform* utilize data from wearables to improve safety operations?

As we discussed, there needs to be new infrastructure that can utilize the data. IQVIA Vigilance Platform (IVP) has the ability to handle massive data fast, an open architecture that allows simple integration of data sources, and a design that allows rapid, near real-time, analysis. IVP has the ability to receive data from any source, so you remove all the traditional barriers that exist today.



What other technologies are creating efficiencies and improving safety in pharma?

With all this data coming in, you can't then drop it into a traditional manual process and expect to keep up. This is where a platform designed for speed and automation helps. IVP has multiple capabilities that enable you to keep up with the flow of data:

- **Fast SaaS platform designed for billions of transactions**: without this, you can't receive or process data automatically;
- **Automated data trawling**: the system has to be able to analyze data without humans having to constantly specify parameters and run queries; for example the IVP Signal Module runs all the time, looking for signals;
- **Raw data analysis**: traditional systems need all of the data to be coded, then reports run, then human review. In IVP, Natural Language Processing lets you review data in its 'as-is' state and identify relationships between products, events and relevant temporal relationships in real time from the raw data. You don't need coded data to identify risks;
- **Fast and comprehensive data visualization tools**: if you need to export data to another system to view and manipulate it, you are going to be spending time cleaning up data, organizing it, etc. IVP's built-in visualization tools provide enterprise, big data-handling capabilities so you are reviewing data in near real-time;
- **Flexible platform**: it's critical to have a platform that allows simple data access for clients to allow feeding into other systems

What is your advice for anybody starting their digitalization journey, and how can IQVIA support this?

The two most important things are to choose the right partners, ones with industry experience and a shared vision, and to have a realistic assessment of your organization. IQVIA's Safety Automation Maturity Matrix (SAMM) enables companies to assess their current state, build a plan and associated business case, with step-by-step guides to take them from a manual organization to a digital organization. However you approach this, having a comprehensive approach is key to success. We are all familiar with the many failed projects in the industry and the reasons for failure today are the same as they have always been, so this is where SAAM helps organizations to avoid repeating the mistakes of the past through the digitalization journey.

What does the future hold for digitalization in safety?

Digitalization is coming, that isn't up for discussion. The only debate is whether you will be a company who waits, possibly to have newcomers bypass you and leave you looking in from the outside, or one who takes the right steps to move forward now with the right partners and embraces the changes to help you have better, safer products in more markets, more quickly.

> **"We can get extremely close to real-time analysis, which enables companies to carry out safety interventions much closer to the event."**
>
> Updesh Dosanjh, IQVIA Technologies

Solving The Data Problem For AI In Drug Discovery

While artificial intelligence has proven its value in drug discovery, for most companies, the power of their AI systems is only as strong as the data those systems are trained on. However, stakeholders – from individual companies to consortiums and service vendors – are finding creative approaches to overcome the so-called data problem and strengthen their AI models.

BY **DAVID WILD,** REPORTER, CANADA

AI-driven drug discovery platforms have been yielding impressive results. The first completely AI-driven drug is now in clinical trials and AI systems are being used to optimize the safety and efficacy of existing molecules. However, the performance of AI models remains limited by the amount of data they take in – the so-called data problem. Moreover, as AI models become more complex, their hunger for data becomes increasingly insatiable.

The problem may not last for long, however, as industry is finding ways to increase the amount of data available to individual AI platforms.

To be sure, AI has found its place in the drug discovery process and investment in AI is only increasing. According to the Boston Consulting Group, third-party investment in AI-enabled drug discovery companies – not including the amount put forth by pharma for in-house AI capabilities, or investments by Big Tech – more than doubled between 2020 and 2021, from $2.4bn to $5.2bn. In the biologics sphere, biotech companies using an AI-driven biologics drug discovery approach have seen their pipeline grow at an annual rate of 40% between 2010 and 2022.

Recent developments in AI-driven molecule-generation have been exciting, with Insilico Medicine advancing the first AI-developed drug into clinical trials, employing AI from target identification to molecule creation.

However, as the number of possible organic molecules is a staggering 1060 and as existing deep learning models are becoming exceedingly complex and powerful, the amount of data required to train these deep learning systems and improve their accuracy and efficacy increases.

The Sweet Sounds Of The MELLODDY Project: A Federated Data Approach For The Common Good

Pharma companies are recognizing that overcoming the data problem collaboratively can benefit all parties involved. One recent collective approach was the MELLODDY Project, coordinated by Owkin, a French-American AI biotech. The three-year project, which wrapped up in July 2022, included some of the world's largest pharma companies, such as Amgen, Inc., Astellas Pharma, Inc., AstraZeneca, Bayer AG, Boehringer Ingelheim GmbH, GlaxoSmithKline plc, Janssen Pharmaceutica NV, Merck KGaA and Novartis AG, as well as a number of tech and academic partners. The project was funded by Innovative Health Initiative (IHI), a collaboration between the European Union and partners in the European Federation of Pharmaceutical Industries and Associations (EFPIA). It involved over 100 experts in computational chemistry, data science, algorithmics, software engineering and deployment, IT operations and security, and project management.

Participants worked with each other to develop a stronger AI drug discovery platform than any one of them could have built strictly using their own internal data. The collective dataset included billions of experimental data points documenting the behavior of more than 20 million chemical small molecules taken from over 40,000 biological assays. Data consisted of descriptors of the small molecules and assay results for a range of parameters, from solubility and toxicity to binding affinity with specific therapeutic targets of interest.

The AI learning model uses a federated approach facilitated by Owkin. That means the AI is trained with inputs from multiple sources but proprietary data are kept on contributors' servers. Only algorithms and predictive models travel between servers and pharmas are thus able to preserve privacy.

"The goal of the approach is for each participant to benefit from a larger pool of data than their own, resulting in increased machine learning performance, while respecting data ownership and privacy," Mathieu Galtier, chief data officer at Owkin, told *In Vivo*.

The results of the initiative indeed demonstrated the value of enlarging a data training set for a given AI model: after federated learning, the AI model was 4% better at categorizing molecules as either pharmacologically or toxicologically active or inactive, 2% better on average at estimating values of toxicological and pharmacological activities and 10% more accurate in yielding confident predictions for new types of molecules. Some pharmas saw double-digit improvements in the performance of their assays under the federated model, compared to their individual models, while others saw less of an improvement.

Galtier said convening the 10 pharma companies was challenging because of the need to strike a balance between privacy and the promise of a better-performing AI model. The federated learning approach was well-suited to achieve those goals, he said.

"It allowed us to find the sweet spot where all the participants could communicate and collaborate with each other while maintaining very clear boundaries," Galtier said. "Because we all knew what the boundaries were, the pharmas were able to exchange information within these boundaries with a very strong sense of trust in each other."

With the project now complete, participants have presumably been applying the model to their operations. However, any benefits of the model will remain confidential and, "to some extent, I'll never know if it brought them money or will save lives, which is frustrating," said Galtier.

Owkin will be offering a commercial version of its federated learning platform to other pharma companies in 2023, but, "it won't be a free-for-all and open to everyone."

"The concern for a given pharma company is that they don't want to be contributing disproportionately while a competitor provides only a few data points and benefits from a model that improves their performance," Galtier said. To address that concern, Owkin will be building multiple consortiums and participants will be able to vet each other, ensuring they are comfortable with their partners' data contributions.

"Because we all knew what the boundaries were, the pharmas were able to exchange information within these boundaries with a very strong sense of trust in each other."

Mathieu Galtier, Owkin

Complementing AI With Molecular Modeling

Other companies are taking their own approaches to expanding their AI datasets and overcoming the limitations imposed by the data problem.

For example, Verseon Corporation has developed a platform that combines computational molecular modeling with AI. Its discovery process begins with its AI machine learning model establishing a possible testing roadmap by analyzing Verseon's in-house protein database and its systems biology and gene networks. Because AI's capacities for drug design are limited by the breadth of its learning datasets and the availability of experimental binding data, the next steps of the drug discovery process are taken over by a proprietary physics-based molecular modeling system, which identifies, models and predicts the interactions of novel drug-like molecules. Compound synthesis, biochemical testing and structural optimization are also performed using this combination of molecular modeling and AI and the resulting information is fed back into the AI system to enlarge the training dataset and improve the performance of the platform.

"AI is terrible at extrapolating and making leaps, so most drugs coming out of AI-based discovery are for the most part

tweaks of existing molecules," noted Adityo Prakash, CEO of Verseon, in an interview with *In Vivo*. "AI can be used profitably in concert with methods like molecular modeling to make drug discovery more efficient, but where you don't have existing training databases for AI to learn from, you have to do *de novo* design using computational chemistry and molecular physics."

Prakash asserts that molecular modeling not only allows his company to generate and feed important training data into its AI system, but it can also identify synthetically-feasible, drug-like small molecules "within the uncharted regions of a vast chemical space currently inaccessible to most AI due to insufficient experimental data."

In another effort to overcome AI-based drug discovery's data problem, Verseon recently acquired Edammo, an AI company that has built a novel technology with a purportedly lower error rate than other machine learning models when using small datasets.

Since its founding in 2002, Verseon has explored over one billion novel molecular scaffolds and synthesized over 10,000 novel molecules, tested 16 drug candidates and currently has a varied range of eight clinical programs in place, testing treatments for multidrug-resistant cancer, oral prophylaxis for diabetic vision loss, and oral anticoagulants.

Large Language Models With Large Datasets

NVIDIA is helping individual companies harness the power of AI models trained with very large datasets, the size of which are out of reach for most organizations. NVIDIA recently announced the upcoming release of NVIDIA BioNeMo, its AI-powered drug discovery cloud service, which includes three large language models, one of which is MegaMolBART, a generative chemistry model that was pretrained with a dataset of 1.4 billion molecules included in the Zinc-15 database.

The tool can be used by developers at individual companies to then train their own AI models, along with their in-house data. Feeding the power of MegaMolBart into their own models can thus enhance the ability of those models to uncover patterns in their in-house biological datasets and to predict molecular reactions, generate molecules *de novo* as well as optimize existing lead molecules.

Kimberly Powell, vice president of healthcare at NVIDIA, told *In Vivo* that BioNeMo uses a natural language processing approach to understand the languages of chemistry and biology – in SMILE strings for chemistry and FASTA sequences for biology – in the same way it would make sense of English, for example. It thus can run unsupervised and decode labeled as well as unlabeled data.

Powell said it will take some time to evaluate the impact of the tool, "because we're still upstream of the actual drug development process."

"However, as drug discovery is a funnel, the more you can explore and the stronger your tools are, due in part to the data inputs, the higher the probability you'll have of finding a successful candidate," she said.

While efforts like these may still only skim the surface of possible chemicals and compounds, as advances in computing power and AI learning capacity continue, the data problem may not be around for long.

Digital Health And Pharma Still Defining Rules Of Engagement

Pharma is still searching for how to best bring digital therapeutics on board

BY **MARK RATNER,** CONTRIBUTING WRITER, IN VIVO

Despite all of the buzz around adoption of digital health tools and whopping VC investments in consumer-facing digital health firms, pharma has yet to articulate a business model for co-development or integration of behavior-modifying digital therapeutics into their portfolios.

Given the prevalence of behavioral health issues that often accompany chronic diseases, pairing a pharmacotherapy with a digital therapeutic aimed at driving behavioral change would at first blush seem a natural fit. For example, many psychiatric conditions including depression, anxiety and sleep disorders occur during or as a consequence of treatment of all sorts of diseases. In 2021, psychiatry-related prescription digital therapeutics accounted for 37% of digital therapeutics across all phases of development as well as the majority of digital care programs, according to data from IQVIA.

More generally, behavioral change, including treatment with conventional cognitive behavioral therapy (CBT), can improve outcomes in many major diseases and evidence exists that digitized CBT, delivered through an app, can improve outcomes. Plus, biopharma regularly uses randomized controlled trials to test the effects of a new drug candidate as an addition to a standard-of-care drug therapy. So why not use an equivalent clinical trial design for a digital therapeutic?

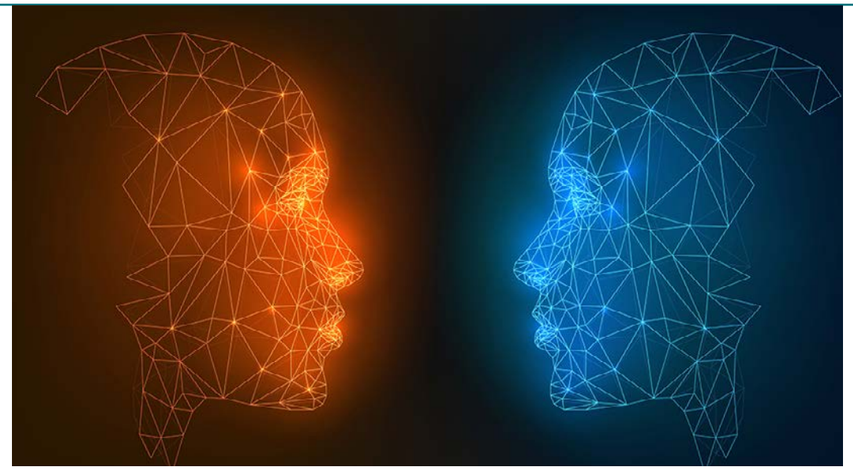
Yet pharma does not appear to be chomping at the bit to explore pairing behavioral-health focused digital therapeutics with its drugs to generate added revenues from the combination.

"We've been seeing the idea for a long time that if you have pills, why not bundle apps with them together and use them together," noted Omar Manejwala, CMO of DarioHealth Corp. "I think that is interesting but it is also the least interesting potential way digital therapeutics and pharma can partner. For a digital therapeutic to achieve the greatest impact, at scale, with the strongest evidence, across the ecosystem, it is going to take more than a piggy-back ride."

Attempted Partnerships

The graveyard is littered with the headstones of attempted partnerships between digital health and pharma, Manejwala said. "The primary reason for that, I think, is because pharma thought to treat digital therapeutics like a pill. That strategy failed at various stress points along the journey." The paradigm took too little advantage of what pharma can offer – data analytics, infrastructure, commercial capabilities, R&D capabilities, he said.

Notable recent partnership failures have highlighted the difficulties that digital therapeutics companies and pharma have had in establishing the right model for collaboration. In late 2019, Sanofi's incoming CEO Paul Hudson called his firm's participation in Onduo LLC, a 2016 joint venture in diabetes disease management with Alphabet Inc.'s research arm Verily Life Sciences, an over-investment, with Sanofi restructuring its role in the JV. Around the same time, Sandoz International GmbH ended its involvement with Pear Therapeutics Inc. around the latter's digital therapeutics to treat substance abuse disorders. In June 2020, Sandoz parent Novartis AG also



terminated its collaboration agreement with Pear due to schizophrenia and multiple sclerosis product candidate development programs.

Since then, commercial product-specific deals have largely been tightly tailored. For example, Biogen, Inc. teamed up with Twill (formerly Happify Health) in June 2022 to develop a health and wellness support tool to connect multiple sclerosis patients with MS and mental health providers and communities. Chiesi Farmaceutici S.p.A., which is heavily focused on respiratory diseases, especially asthma and COPD where behaviors such as physical activity and isolation play a large role in outcomes, is collaborating with Kaia Health GmbH to leverage its expertise and footprint in respiratory diseases to get their digital COPD intervention into the hands of patients in Europe.

"It's very easy as a pharma company to shoehorn these interventions, minimizing them by thinking 'it's just an app'," Ameya Phadke, patient non-pharmacological solutions leader for Chiesi USA, Inc., said. But there is a certain business opportunity associated with addressing a given behavioral need, and a digital therapeutic could be a way to tap into that separate value pool, he noted.

Sanofi Ventures remains a prominent investor in Click Therapeutics, Inc., having led a $17m round in 2018 and contributing to a $52m round in 2021. Otsuka Pharmaceutical Co. Ltd. has maintained its commitment to develop Click's app providing cognitive exercises for patients with major depressive disorder. Similarly, Boehringer Ingelheim GmbH is supporting Click's development of a prescription digital therapeutic for schizophrenia.

The corporate VC Leaps by Bayer recently invested in Woebot Health, whose apps deliver continuous mental health care remotely. It also has stakes in Huma, which is focusing on remote patient monitoring and digital biomarkers, and Ada Health, which has developed an AI-powered symptom tracker to identify and differentiate medical conditions and direct patients towards appropriate care. "We are trying to transform health with digital applications," said Jürgen Eckhardt, Leaps by Bayer's CEO. "One way is to change the treatment paradigm to be more efficient in triaging patients and getting them into the health care system." Its interest in digital health is not around a payer product or a companion app to a pharmaceutical product. "Companion apps around products is not our prime focus. It is about rethinking healthcare altogether," Eckhardt told *In Vivo*.

What's The Deliverable?

In diseases like depression, anxiety, bipolar or schizophrenia, data shows that if a digital tool is used along with pharmacotherapy, patients do better. "But we also know that the vast majority of these patients don't get good pharmacotherapy," noted Yuri Maricich, CMO of Pear Therapeutics. In some cases, a digital therapeutic may be used first line, he noted. In individuals with chronic insomnia, for example, clinical guidelines map out a hierarchy of "Step" therapy: first treating with digital CBT, then face-to-face CBT or digital CBT plus a medication.

"There hasn't been a solidification of the perspective of what the goal is," Maricich said. While pharma companies have hired more tech into drug development groups, they have different and very early exploratory goals. "The idea of using tech and selling tech in some way is very novel to many of these companies," he said. It may be to generate more real-world evidence, to bring in new products that independently are more revenue-generating, or help sell more drugs indirectly and thus be contributory to the revenue stream.

Pharma, medtech and other potential collaborators cite the need to make the patient journey or clinical workflow more seamless, Maricich pointed out. "That's where the partnership opportunity comes in," he said, both in terms of adding efficiencies and, as part of that, presumably improving engagement with the health care system, in contrast to as a stand-alone that will generate additional revenue for them. "It's very hard for a pharma to think of a different model or transition to a different business model," he told *In Vivo*. "Industry needs more use cases before many companies feel comfortable with co-developing a digital therapeutic alongside a drug in development."

While it may make sense from a compliance perspective that an app directed at influencing behavior helps a patient stick to a therapy, if it doesn't generate significant revenue and is mostly used to bring in real-world evidence the pharma can use for its own purposes, the opportunity may not be clear. More to the point, consumer-facing digital companies are very experienced in getting people engaged in what they do: getting that patient engagement builds a stronger connection. A consumer-facing digital health app can also potentially be a channel for introducing or expanding the patient services a pharma company wraps around its products.

Pharma has a limited capability to understand and influence behavior outside the formal treatment setting, Manejwala said. On the other hand, digital reaches that part – the opportunity to see and influence "life in-between" events – that pharma does not. "It makes sense that if you combine digital therapeutics approaches with pharma's core capabilities, you have a new ability to influence health in a way that doesn't exist separately," he said.

"When we look at the most common chronic diseases, you can attribute up to 80% of costs coming from those diseases to a handful of behavioral choices people make," added Alex Condoleon, Sanofi's VP and head of digital healthcare, US. These include lifestyle choices, what they eat, their level of physical activity, their mindfulness about whether they are hydrating, whether they smoke and whether in a timely fashion they are interfacing with the healthcare system and following health advice including the medications they are taking. "Those are the elements we are focused on trying to solve," he said. "The provider system, the therapeutics, play an important part, but this large dimension is driven by engagement."

Patients will likely only have interactions with the provider system a handful of times during the year, Condoleon pointed out, but they are living with a condition 24/7. "When we think about that whole person need, we do begin to think about their capacity to manage their health, drive their own change, stay motivated, identify when they are experiencing mental health challenges and the choices they can make in their day-to-day life to impact beneficially their health," he said. "All of that is possible when we think about digital's ability to scale supportive behavioral change measures and mental well-being measures. As a pharmaceutical company, that is a great complement to what we do."

> **"We need to educate our stakeholders about what this digital segment is and magnify the impact we have."**
> Alex Condoleon

In March 2022, Sanofi established a partnership with DarioHealth focused on engaging people with chronic diseases to try to help them with behavior change. The pairing of DarioHealth's platform, which supports behavioral health in chronic conditions including diabetes and hypertension to prevent cognitive dysfunction from occurring, with Sanofi's drugs is not top of mind. "We have quite purposefully taken it through the lens of people with chronic disease, not through the lens of people who are on our drugs," Condoleon noted. "When we take it through that lens, we begin a learning journey to understand what are their full, whole-health needs."

The collaboration spans at-scale product commercialization and product and data development and data sharing, with both parties sharing data off the platform and collaborating to determine what an evidence generation plan should look like. "We are learning what is possible with the data that comes off these patient engagement platforms when you synergize it with the capabilities that already sit within Sanofi," Condoleon said. That will mean bringing new insights into the scientific literature and doing it relatively quickly, to guide Sanofi as to further innovation in order to demonstrate to payer-customers that there is value to be unlocked and to meet the needs of medical professionals to see where the platform fits.

Thinking about trial design is different in the digital space for several reasons, Condoleon said: the live stream of data from people using the platform and the fact that it is possible to continuously innovate. "Digital health solutions are not static," he said, "The methodology we use in approaching these studies is different, with a more fast-paced evolution. Also, when looking at life in-between moments, we start to see lots of variables that come into the journey." As opposed to a formal randomized control study of a drug, where almost all variables can be standardized, the goal is to demonstrate that supportive apps have a meaningful impact on those variables not traditionally controlled for in terms of health outcomes or the cost of care. "There is a level of innovation in how we think about evidence generation," he said, in order to address the needs of stakeholders. "It is only going to help the collective effort of the total company [digital] transformation," he told *In Vivo*.

The predominant focus in Sanofi's collaboration with DarioHealth is on health plans and the intermediaries that support work in the employer space. "We are all learning what are the different go-to-market models that are attractive," Condoleon said. "We need to educate our stakeholders about what this digital segment is and magnify the impact we have."

Over time, Condoleon foresees a natural convergence where these advances in digital health converge with therapeutic interventions on the drug or device side. "The product will come but it's not the starting point of the overall experience," he said.

"I have seen the industry evolve," said Better Therapeutics, Inc.'s chief strategy and commercial officer Deepti Sodhi Jaggi, who previously had stints at Astellas Pharma, Inc., Johnson & Johnson, Genentech, Inc, and Oracle Corporation. "It has gone from digitally curious to digitally motivated, openly saying they are still trying to figure it out."

Better Therapeutics is one of several digital health start-ups developing digital CBT accessed remotely via an app. The platform is linked to lifestyle behaviors that are root causes of cardiometabolic diseases and addresses similar behaviors across those diseases, with some customization depending on the specific disease. In September 2022, the company filed for FDA approval of its lead product BT-001 in type 2 diabetes, used alongside a pharmacotherapy. "We can imagine our technology platform in combination with certain drugs in certain disease states," Jaggi said. In terms of partnering with pharma to do this, "we are open," she said. "Nothing is certain now."

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Generics And Biosimilars Industry Reshaped By Transformations

Annual Top 50 Sees Leading Firms Change Position And New Entrants Join

The latest *Generics Bulletin* Top 50 ranking of global generics and biosimilars companies sees a new name in the top five amid transformations for some of the leading off-patent players. Meanwhile, a number of mid-level firms shift position and newcomers climb into the bottom of the table.

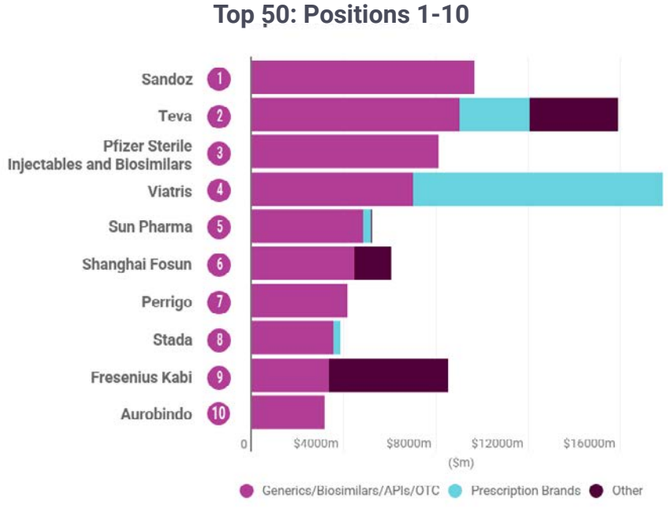
BY **DAVID WALLACE,**
EXECUTIVE EDITOR,
EUROPE

In the ever-evolving global generics and biosimilars industry, one constant that can be relied upon is change. Even as the upheaval of the COVID-19 pandemic recedes, fresh political and economic pressures are being felt by firms across the world, while specific local trends are also playing their part in the fortunes of regional players.

Alongside these external factors, active strategic decisions made by the world's off-patent industry leaders are also significantly reshaping the competitive landscape, transforming and reconfiguring some of the highest-profile companies in the sector to the extent that it does not look the same from one year to the next.

All of this is illustrated by the many changes seen in our latest annual *Generics Bulletin* Top 50, which ranks by turnover the top players in generics and biosimilars, according to our lead category of Generics/Biosimilars/APIs/OTC sales, with data based on publicly available reports and disclosures.

Even the initial top 10 companies – typically a fairly stable group – are not immune to dramatic changes, with a new entrant appearing in the top five this year and major changes in the pipeline for some of the others.



Sandoz Tops Table As Viatris Is Again Shut Out Of Top Three

As with last year's ranking, Sandoz has again topped the table this year, with 2021 sales that were more or less flat at $9.63bn.

While the firm has been candid about the challenges seen in the US market in particular, it has more recently taken a slightly more optimistic line, raising its guidance as it perceives the likely emergence of a bottom in the US generics sector.

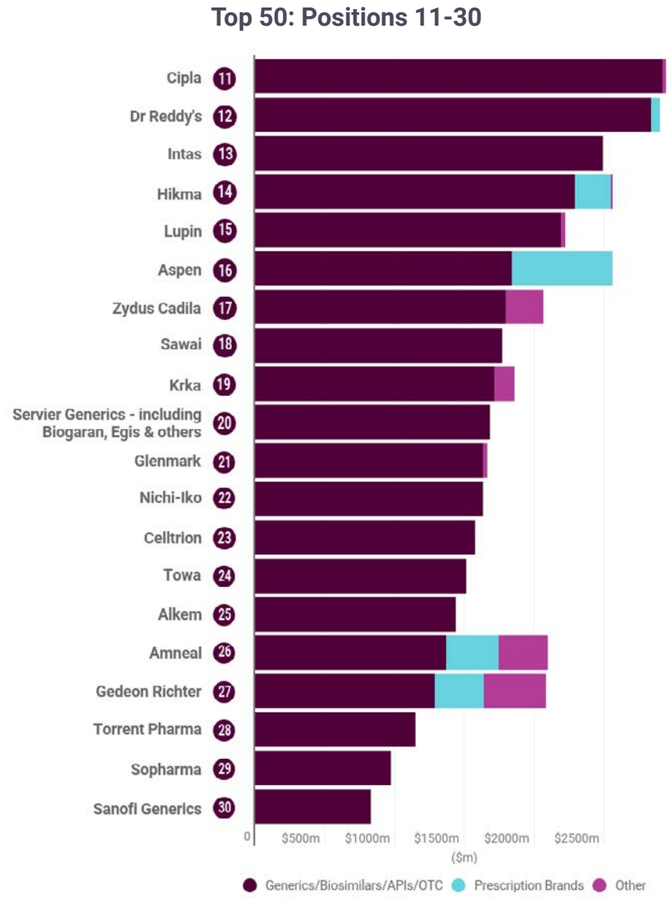
And major changes are on the horizon soon for Sandoz, with parent company Novartis AG having recently decided to spin the company off, following a strategic review of its ownership, with the process expected to be complete by the end of 2023.

Following on from Sandoz, Teva Pharmaceutical Industries Ltd. has retained its second place in the Top 50 ranking this year, with a Generics/Biosimilars/APIs/OTC total that was just shy of $9bn in 2021.

The firm recently set out ambitious plans for the next five years to return to revenue and earnings growth by targeting over 80% of off-patent opportunities. It has also celebrated removing a major legal overhang for the company in recent years by recently striking a US-wide settlement to resolve opioid-related claims against the company.

The Israeli firm's total sales – also including brand assets such as Copaxone (glatiramer acetate), Austedo (deutetrabenazine) and Ajovy (fremanezumab) and its Anda distribution business – came in at a hefty $15.9bn.

While Viatris Inc. may have been expected this year to regain the top-three status once held by its Mylan Pharmaceuticals Inc. division, the company reported 2021 generics sales of $5.63bn along with complex generics and biosimilars sales of $1.34bn that together fell short of the just over $8bn in sales achieved by Pfizer Inc.'s (part legacy-Hospira Ltd) biosimilars and sterile injectables business. This therefore once again pushed Viatris into fourth place.



Viatris is expected to once again appear in a very different form by the time next year's Top 50 rolls around, with the company having earlier this year committed to offload a large extent its biosimilars business to partner Biocon, Ltd., as just one part of a series of planned divestments.

Sun Rises To Displace Perrigo

As major firms like Sandoz, Teva and Viatris do not typically split out sales of OTC products separately from their prescription offerings, our ranking includes include OTC products alongside prescription generics and biosimilars.

This means that Perrigo Company PLC's extensive range of consumer health care products – many of which are approved through the generic abbreviated new drug application pathway in the US – make it eligible for inclusion in our comparison.

However, a major reshaping of Perrigo – that saw it divest its dedicated prescription pharma unit to Altaris in a $1.5bn deal – means that it has now fallen out of our top five and down to seventh place, replaced at position five by Indian giant Sun Pharmaceutical Industries Ltd., followed by Shanghai Fosun Pharmaceutical (Group) Co., Ltd.

At the bottom of the top ten table, three companies formed a close pack, with Stada Arzneimittel AG this year rising two places to leapfrog Fresenius Kabi AG, and with Kabi's intravenous drugs unit's turnover narrowly edging out Aurobindo Pharma Limited's total as the Fresenius company eyes growth opportunities with a recent deal to take control of mAbxience S.L.

The Stada data is based on a Generics/Biosimilars/OTC/APIs figure drawn from the German major's Generics and Consumer Healthcare segments, in addition to a further €365m sales figure provided by the firm for branded generics and biosimilars sales that are reported as part of the firm's Specialty unit total.

Mid-Table Movements See Firms Jostle For Position

With the significant movements seen among the 10 leading companies nevertheless leaving the ranking order of the handful of firms at the very top of that top-10 table undisturbed, a similar trend can be observed in the second part of our rundown, covering positions 11-30.

Compared to last year, the same five companies lead off this second table, in the same order – with Cipla Limited, Dr Reddy's and Intas Pharmaceuticals Ltd. representing an Indian trio at the top of the board, followed by Hikma Pharmaceuticals plc in 14th position and Lupin Limited following in 15th.

Following this initial grouping, however, a number of changes can be seen in our mid-table ranking. Aspen Global Inc. has leapt from 22nd to 16th place this year, overtaking the likes of Zydus Lifesciences Limited, Sawai and Nichi-Iko Pharmaceutical Co., Ltd.

Some of the major Japanese generics players have been disadvantaged by local disruption as well as the relative weakness of the country's yen in relation to the US dollar, the currency used by *Generics Bulletin* for comparison purposes.

Meanwhile, Nichi-Iko is an example of a firm that has also had specific problems of its own to deal with, leading the firm to drop from 18th to 22nd place this year. Conversely, Korean biosimilars specialist Celltrion, Inc. is continuing to rise among its peers, climbing two places from 25th to 23rd this year as it further secures its position in the industry.

And at the bottom of this second table, Endo has fallen out of the top 30, replaced by Bulgaria's Sopharma AD which has climbed from 31st position last year to 29th place this year.

Newcomers Climb Into Bottom Table

The third and final section of the ranking sees a handful of new entrants making their way into the bottom of the chart, while others exit altogether.

Leading off the third table, we see India's Biocon, Ltd. climbing from 35th to 31st position in our ranking, ahead of even greater growth for the company that is expected as a result of it recently agreeing to buy out partner Viatris' biosimilars business in a deal worth up to $3.3bn.

Endo, meanwhile, moves in the opposite direction, falling to 34th place from 30th last year amid sustained competitive pressures on products in its Generics segment, which shrank by 5% to $741m in 2021.

A little further down the ranking, we see Lannett slipping a place to 42nd position, another major industry player to be hit by intense pricing pressures over the past year.

On the other hand, Wockhardt Limited climbs four places this year to 43rd, largely on the strength of its vaccines business; while Amphastar Pharmaceuticals, Inc. also rises four places to 44th position following what the CEO described as a "turning point" for the company late last year.

Other noteworthy movements include Bangladesh's Beximco Pharmaceuticals Ltd. climbing the ladder from 50th to 47th on the back of plentiful product launches, international expansion and high-profile launches of COVID-19 treatments.

Among the new entrants into the Top 50 this year are Japan's Nippon Chemiphar Co., Ltd. at 49th position, as well as India's Natco Pharma Limited, which is back in the ranking at number 50 after just missing out last year.

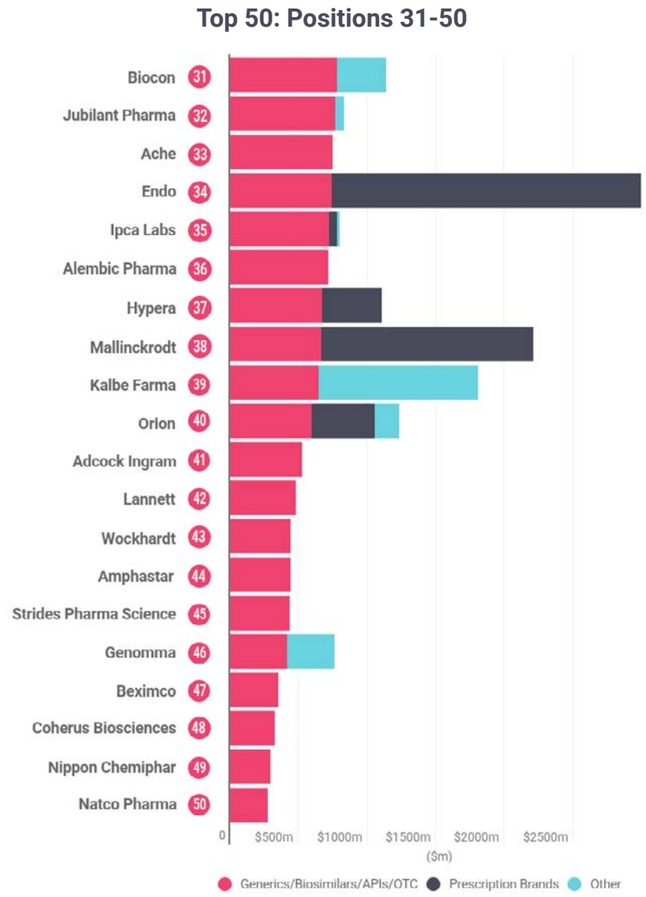
The two newcomers take up their positions after Bausch Health Generics dropped out of the rankings altogether this year, at the same time as Advanz Pharma Corp disappeared as a result of its newly private status following its takeover by private equity group Nordic Capital.

Meanwhile, Coherus BioSciences, Inc. – which had been a new entrant in our Top 50 ranking in 48th position two years ago, before rising to 43rd place last year – has fallen back down to 48th place after sales for its Udenyca pegfilgrastim biosimilar slid by almost a third to $327m in 2021.

However, Coherus has plans to secure future growth, including its recently-approved US interchangeable ranibizumab biosimilar and an on-body version of Udenyca.

With major global pressures, economic and otherwise, continuing to weigh on the off-patent industry, at the same time as a variety of strategic initiatives promises to reconfigure some of the leading off-patent players this year – and a major biosimilar opportunity looms on the horizon in the form of US competition to Humira (adalimumab) in 2023 – major change can be expected for the generics and biosimilars sector over the next 12 months.

We will see how the ranking has been affected when *Generics Bulletin* compiles its Top 50 again next year.



The Generics Bulletin Top 50 Data

The *Generics Bulletin* Top 50 ranking compiles sales data for 2021 – or the closest available reported year – across companies for which generics and/or biosimilars is a major part of their business. This excludes firms predominantly focused on active pharmaceutical ingredients, some of which report sales totals that would otherwise be sufficient to be featured in the list.

Also excluded are companies that do not split out generics, biosimilars, APIs and OTC sales from larger units housing mature, often off-patent brands. For this reason, Abbott and its Established Pharmaceuticals unit encompassing branded generics operations in emerging markets is not in the list.

Neither are firms with sizeable biosimilars interests such as Amgen, Inc. or Biogen, Inc., even though individual sales figures may be enough to otherwise put them in contention. Pfizer, on the other hand, treats its biosimilars and sterile injectables segments as distinct units, making them eligible for inclusion.

We also do not include companies that do not disclose detailed sales information, meaning that privately-held players – for example Apotex Inc. , Polpharma SA , Alvogen, Inc. or Zentiva Group a.s.– are absent from our rankings.

However, Servier's generics business is included in our ranking, in line with other major originators that operate generics, biosimilars, APIs and OTC businesses distinct from their branded interests – such as Novartis with its Sandoz unit. Similarly, Sanofi's generics business is still sizeable enough to make it into our Top 50 ranking.

GB 50 Rank	Company	Generics/ wBiosimilars / APIs/OTC ($m)	Prescription Brands ($m)	Other ($m)	Total turnover ($m)	Change %	Notes
1	Sandoz	9,631	n/a	n/a	9,631	0	Total includes $423m from sales of anti-infectives to third parties
2	Teva	8,987	3,042	3,849	15,878	-5	
3	Pfizer Sterile Injectables and Biosimilars	8,089	n/a	n/a	8,089	18	
4	Viatris	6,972	10,841	n/a	17,814	51	
5	Sun Pharma	4,838	315	35	5,188	16	Financial year ended 31 March 2022; Prescription brands is Ilumya sales; INR: 0.0135 dollars
6	Shanghai Fosun	4,460	n/a	1,586	6,046	29	Generics/Biosimilars/OTC/APIs figure is pharmaceutical manufacturing segment and includes Comirnaty COVID-19 vaccine; Chinese yuan: 0.155 dollars
7	Perrigo	4,139	n/a	n/a	4,139	1	Comprises $2,693m from Consumer Self-Care Americas and $1,446m from Consumer Self-Care International
8	Stada	3,521	323	n/a	3,844	8	Generics/Biosimilars/OTC/APIs figure is Generics and Consumer Healthcare total plus €365m branded generics and biosimilars from Specialty segment; Euro: 1.183 US dollars
9	Fresenius Kabi	3,331	n/a	5,178	8,509	3	Generics/Biosimilars/OTC/APIs figure is Intravenous Drugs unit; Euro: 1.183 US dollars
10	Aurobindo	3,166	n/a	n/a	3,166	-1	Financial year ended 31 March 2022; INR: 0.0135 dollars
11	Cipla	2,912	n/a	26	2,938	14	Financial year ended 31 March 2022; INR: 0.0135 dollars
12	Dr Reddy's	2,834	60	n/a	2,894	13	Financial year ended 31 March 2022; INR: 0.0135 dollars
13	Intas	2,486	n/a	n/a	2,486	11	Financial year ended 31 March 2022
14	Hikma	2,288	254	11	2,553	9	Figures based on estimated 90:10 split for generics and brands
15	Lupin	2,186	n/a	29	2,215	9	Financial year ended 31 March 2022; INR: 0.0135 dollars
16	Aspen	1,833	724	n/a	2,557	12	Generics/Biosimilars/OTC/APIs comprises $1163m from Regional Brands and $670m from APIs and FDFs; financial year ended 30 June 2021; South African rand: 0.0677 dollars
17	Zydus Cadila	1,794	n/a	267	2,061	6	Other = Consumer Wellness segment; Financial year ended 31 March 2022; INR: 0.0135 dollars
18	Sawai	1,764	n/a	n/a	1,764	4	Financial year ended 31 March 2022; Yen: 0.00910 dollars
19	Krka	1,713	n/a	139	1,852	2	Other' is Animal health products & Health resorts and tourist services; Euros: 1.183 US dollars
20	Servier Generics - including Biogaran, Egis & others	1,679	n/a	n/a	1,679	1	Financial year ended 30 September 2021; Euros: 1.183 US dollars

GB 50 Rank	Company	Generics/ wBiosimilars / APIs/OTC ($m)	Prescription Brands ($m)	Other ($m)	Total turnover ($m)	Change %	Notes
21	Glenmark	1,631	n/a	30	1,661	12	Financial year ended 31 March 2022; INR: 0.0135 dollars
22	Nichi-Iko	1,629	n/a	n/a	1,629	-5	Detailed breakdown of segments not available for this period; financial year ended 31 March 2022; Yen: 0.00910 dollars
23	Celltrion	1,575	n/a	n/a	1,575	11	KRW: 0.000873 dollars
24	Towa	1,507	n/a	n/a	1,507	7	Financial year ended 31 March 2022; Yen: 0.00910 dollars
25	Alkem	1,436	n/a	n/a	1,436	20	Financial year ended 31 March 2022; INR: 0.0135 dollars
26	Amneal	1,366	378	349	2,094	5	Other' is AvKare unit
27	Gedeon Richter	1,287	350	443	2,080	9	Prescription Brands is Vraylar/Reagila (cariprazine); Euros: 1.183 US dollars
28	Torrent Pharma	1,149	n/a	n/a	1,149	6	Financial year ended 31 March 2022; INR: 0.0135 dollars
29	Sopharma	969	n/a	n/a	969	11	Bulgarian lev: 0.6048 dollars
30	Sanofi Generics	827	n/a	n/a	827	-8	Euros: 1.183 US dollars
31	Biocon	776	n/a	358	1,134	14	Financial year ended 31 March 2022; INR: 0.0135 dollars
32	Jubilant Pharma	763	n/a	65	828	6	Generics/Biosimilars/APIs/OTC figure is Pharmaceuticals segment; Financial year ended 31 March 2022; INR: 0.0135 dollars
33	Ache	748	n/a	n/a	748	16	Brazilian real: 0.1855 dollars
34	Endo	741	2,252	n/a	2,993	3	
35	Ipca Labs	723	56	17	796	7	Financial year ended 31 March 2022; INR: 0.0135 dollars
36	Alembic Pharma	716	n/a	n/a	716	-2	Financial year ended 31 March 2022; INR: 0.0135 dollars
37	Hypera	672	429	n/a	1,101	45	Brazilian real: 0.1855 dollars
38	Mallinckrodt	662	1,547	n/a	2,209	-20	
39	Kalbe Farma	642	n/a	1,163	1,805	14	Indonesian rupiah; 0.00006874 dollars
40	Orion	595	459	178	1,232	-3	Euros: 1.183 US dollars
41	Adcock Ingram	526	n/a	n/a	526	6	Financial year ended 30 June 2021; South African rand: 0.0677 dollars
42	Lannett	479	n/a	n/a	479	-12	Financial year ended 30 June 2021
43	Wockhardt	439	n/a	n/a	439	14	Financial year ended 31 March 2022; INR: 0.0135 dollars
44	Amphastar	438	n/a	n/a	438	25	
45	Strides Pharma Science	432	n/a	n/a	432	-5	Financial year ended 31 March 2022; INR: 0.0135 dollars
46	Genomma	417	n/a	345	762	12	Mexican peso: 0.0493 US dollars
47	Beximco	348	n/a	n/a	348	15	Financial Year Ended June 30, 2021, BDT: 0.0118 dollars
48	Coherus Biosciences	327	n/a	n/a	327	-31	
49	Nippon Chemiphar	296	n/a	n/a	296	3	Financial year ended 31 March 2022; Yen: 0.00910 dollars
50	Natco Pharma	276	n/a	n/a	276	-5	Financial year ended 31 March 2022; INR: 0.0135 dollars

The Generic Bulletin Top 50 ranking is based on analysis of fiscal year 2021 sales data. For more information contact: David.Wallace@informa.com.

Humira Biosimilars Prepare For US Competition In 2023

Landmark LOE Opportunity Looms, With Multiple Adalimumab Launches Expected

The advent of biosimilar competition to Humira in the US in 2023 represents the largest loss-of-exclusivity opportunity ever for the off-patent industry. But with a host of biosimilar sponsors awaiting launches throughout the year, it remains to be seen how competition will play out.

BY **DAVID WALLACE,** EXECUTIVE EDITOR, EUROPE

With long-awaited biosimilar competition to AbbVie Inc.'s top-selling Humira (adalimumab) brand finally expected to hit the US in 2023, the off-patent industry is bracing for its biggest ever loss-of-exclusivity opportunity.

While Humira finally lost its crown as the world's top-selling drug last year – unseated only by Pfizer Inc./BioNTech SE's Comirnaty mRNA vaccine for COVID-19 – the brand still achieved sales of $20.7bn worldwide, with $17.3bn of this total coming from the US alone, representing growth of 7.6% over the 2020 US sales figure.

However, with multiple biosimilar sponsors already holding US Food and Drug Administration approvals for Humira rivals and awaiting launches throughout the year – along with anticipated competition from further biosimilars that are still awaiting FDA approval – it remains to be seen how competition will shake out among adalimumab rivals.

Complicating the picture are a number of different variables that could influence uptake for individual biosimilar products. As well as launch timing – dictated by a series of settlements between biosimilars sponsors and originator AbbVie that offer a variety of launch dates throughout 2023 – and price, these factors also include FDA designations of interchangeability for certain products and different concentrations of adalimumab (50mg/ml and 100mg/ml), as well as other attributes such as citrate-free and latex-free presentations.

Amgen Leads The Pack With Late-January Launch

Leading off biosimilar competition to Humira is expected to be Amgen, Inc., which saw its Amjevita (adalimumab-atto) 50mg/ml biosimilar approved by the FDA in 2016 and which has the right to launch from 31 January 2023, under a global settlement agreement signed with AbbVie in September 2017.

Amgen is expected to have almost six months with the market to itself until a chasing pack of adalimumab biosimilars launch around 1 July.

These include Organon, with its Samsung Bioepis Co., Ltd.-developed Hadlima (adalimumab-bwwd) version that is expected to be available in both 50mg/ml and 100mg/ml strengths following a recent landmark approval as well as Coherus BioSciences, Inc.,

GENERICS AND BIOSIMILARS

with its Yusimry (adalimumab-aqvh) 50mg/ml biosimilar and Boehringer Ingelheim GmbH with Cyltezo (adalimumab-adbm) 50mg/ml version.

Standing out among this second wave of adalimumab biosimilars is Cyltezo, which was the first rival to Humira to be granted an interchangeability designation by the FDA. This means that it will be eligible for pharmacy-level substitution as permitted by US state law, as well as benefiting from 12 months of first interchangeable biosimilar exclusivity, thus preventing any other 50mg/ml versions from being designated as interchangeable for a year.

Viatris Inc. is set to follow this chasing pack of biosimilars with its Hulio (adalimumab-fkjp) 50mg/ml version on 31 July, with further 50mg/ml biosimilars set to follow in the form of Sandoz Pharma Ltd.'s Hyrimoz (adalimumab-adaz) on 30 September and Pfizer's Abrilada (adalimumab-afzb) on 20 November.

However, these seven FDA-approved adalimumab biosimilars are far from being the only Humira competition on the horizon.

Alvotech And Celltrion Await Approval For High-Concentration Versions

Several major sponsors aiming to play a significant role in the US biosimilar adalimumab market have not yet seen their Humira rivals approved by the FDA.

Alvotech is currently expecting its AVT02 candidate – due to be marketed in the US by partner Teva Pharmaceutical Industries Ltd. – to be approved as an interchangeable 100mg/ml adalimumab biosimilar, with a settlement with AbbVie offering the potential to launch on 1 July, the same day as Boehringer Ingelheim's interchangeable lower-strength Cyltezo.

However, despite approvals and launches for AVT02 in other territories such as Canada and Europe, Alvotech has seen the US approval held up following deficiencies being identified by FDA facility inspections.

Meanwhile, Korea's Celltrion, Inc. is also eyeing a Q3 launch date for its own 100mg/ml adalimumab biosimilar that is also still awaiting FDA approval.

Another potential player in the market could be Fresenius Kabi AG, which is awaiting FDA approval for its 50mg/ml MSB11022 biosimilar adalimumab candidate and has an agreement with AbbVie that will allow it to launch on 30 September.

And further biosimilar variants could be in the works from some of the existing players, with firms such as Sandoz planning 100mg/ml higher-strength versions of already-approved 50mg/ml biosimilars, as well as players such as Pfizer looking to eventually secure interchangeability designations once any exclusivity periods awarded to rivals expire.

Top Attributes For Selecting Biosimilar Adalimumab

Both CHA and non-CHA institutions note payer placement and interchangeability in their top three attributes.

Mean (CHA)	Attributes (CHA)	Mean (non-CHA)	Attributes (non-CHA)
1.3	Payer placement	1.7	Acquisition price
1.8	Interchangeability	1.8	Payer placement
2.0	Autoinjector ease of use	2.1	Interchangeability
2.0	Ease of use of autoinjector	2.1	Ease of use of autoinjector
2.3	Absence of citric acid	2.3	Strength (preference for higher concentration)
2.5	Quality and extent of patient assistance program	2.3	Absence of citric acid
2.9	Acquisition price	2.7	Autoinjector ease of use
2.0	Other	2.7	Quality and extent of patient assistance program
		1.5	Other

Source: Vizient

Price, Interchangeability And Concentration

Unsurprisingly given the varying attributes of their adalimumab biosimilars, these competing US players have aired different views on which elements will be crucial to success in such a competitive landscape.

Alvotech has suggested that its anticipated combination of a 100mg/ml higher-strength version with an interchangeability designation will give it the edge in the US market.

With the firm pointing to the higher concentration version of the Humira original now accounting for around 85% of brand use in the US, the company has said that, especially given the likely presence of multiple high-concentration biosimilars in the market, "there will be no big need for the market to convert from the high-concentration back to the older product, which was a worse product."

And Boehringer Ingelheim has indicated that "the interchangeability status of Cyltezo reinforces our goal of expanding overall treatment options and contributing to the quality and sustainability of the US healthcare system."

However, Amgen – which will enjoy a significant competitive advantage as a result of its early launch date – has suggested that interchangeability is a "nice to have, not a need to have" attribute.

Similarly, Coherus BioSciences, Inc. has suggested that the significance of interchangeability could be overplayed, with the firm instead viewing "significant supply capability with low pricing [as] the primary driver of conversion."

Alluding to a competitive pricing strategy, Coherus has promised that its 50mg/ml Yusimry version will be accompanied by a "compelling value proposition" that it hopes will help it to capture market share.

> **"So 2024 is very much where we should be really thinking about."**
>
> Steven Lucio, Vizient

Vizient Survey Ranks Key Adalimumab Attributes

Offering a separate perspective to biosimilar sponsors is healthcare organization improvement firm Vizient, which recently published a report – based on a survey to pharmacy executives and professionals – aimed at assessing "factors likely to guide the utilization of Humira competition products, once available."

The report's findings on the top attributes for selecting a preferred biosimilar adalimumab rank payer placement, acquisition price and interchangeability above aspects such as the ease of use of autoinjectors, the absence of citric acid, a higher-concentration product, or patient support programs, although some difference was seen between Community Hospitals Association and non-CHA responses.

Steven Lucio – Vizient's senior principal of pharmacy solutions – said that "what we've been encouraging people to do is to go ahead and have early conversations about Humira biosimilars, now, while we're still waiting for their launch," to see "how you could engage with them to find common value and benefit from both the provider and payer perspective."

Referring to the survey's findings, Lucio said "I think this gives us a good insight as to what our audience is thinking at this point – I think it's consistent with what we've been describing [in terms of] the push and pull between the payer and the provider." Key aspects for Humira biosimilars would include "definitely the payer placement and the acquisition price," he confirmed.

Commenting further on the findings, he noted that "given how much conversation there has been about citric acid and the strength – the high concentration – I was maybe expecting that to be a little bit higher."

"The thing that surprised me," he added, "was interchangeability being as prominent as it was, because we've worked very hard to help people not misunderstand interchangeability," which in the US is a legal but not clinical distinction.

European Experience Points To Heavy Competitive Pressures

While the launch of Humira biosimilars is set to be a watershed moment for the US, the European experience of multiple simultaneous adalimumab biosimilar launches could provide a cautionary tale.

When four biosimilars hit the European market at the same time – in late 2018 – heavy price competition resulted almost immediately, with steep discounts reported as competitors battled for market share. The European market for adalimumab quickly became so competitive that even certain sponsors with approved Humira biosimilars, namely Pfizer, chose not to launch altogether, due to such "unfavorable market conditions."

However, it remains to be seen whether the specificities of the US market and the very different aspects at play for next year's cascade of US adalimumab launches result in similarly fierce price competition.

But while all eyes are on 2023 in the US, the Vizient report suggested that the true impact of Humira biosimilars in this market would only really begin to be seen from 2024.

Given that only one biosimilar, Amjevita, would be on the market from the end of January, with others following only from mid-year, Lucio observed that in terms of formulary decisions, "payers usually make their determination well in advance of the next year. So at what time those molecules could get to the respective formularies is unknown."

"So 2024 is very much where we should be really thinking about."

Driving More Effective Clinical Trials To Impact Lives

The blending of science and technology is changing the life sciences industry at an extraordinary pace. Clinical trials are getting more complex, both in design and in their conduct. Never before have we seen the growing number of systems and new technologies used within clinical research. And the need for greater efficiencies to get new therapies, whether they be medicines or devices, to patients has never been more pronounced.

SAM SRIVASTAVA, CEO, WCG

Championing An Integrated Approach

The life sciences industry has the capability to ensure the right patients, clinicians, and research sites – in the right locations – are in the right clinical trials at the right time. However, while artificial intelligence, machine learning, and other novel technologies are game changers, they alone are not a magic bullet that can be used to truly transform clinical research.

Connectivity across all research stakeholders remains critical. For sponsors to be successful in the future, Sam Srivastava, chief executive officer of WCG, highlights the need for a connected ecosystem that leverages deep expertise, services, data, and technology to create a truly high-performing clinical research network on a global scale. “In today’s environment,” remarks Srivastava, “pain points are integrated and connected, affecting multiple groups, so there is a need to break silos and connect all trial stakeholders.”

Driving this ecosystem connectivity and interoperability between often disparate electronic systems to accelerate the delivery of needed new therapies to patients, while maintaining scientific rigor and the highest quality protections for study participants, is WCG’s raison d’être.

What do clinical trials of the future look like and how do we get there? How can we be the catalysts of change that make a meaningful difference to patients across the globe? These are the questions WCG asks, Srivastava explains. “It is about optimization on both a macro and micro level.”

A Changed Mindset

One of the side effects of COVID-19 is that the global pharmaceutical industry was forced to embrace and invest in innovative clinical research methods and new technology tools. Currently, much of the discussion on these methods and tools has focused on decentralized clinical trials (DCTs).

However, Srivastava has a different view and focus, based not only on his experience at WCG, but also having spent many years on the care delivery side of the industry. He feels that the intense focus on DCTs is a limiting one. “DCTs currently represent a small portion of all the clinical trials in the marketplace.” He notes that due to the current disease burden on patients, comorbidities, and challenges of many infectious and chronic diseases, the DCT model often does not lend itself to all clinical trials. “Hybrid trials extend trial points of care beyond the site and specialist, with technology to engage, care, and provide biometric feedback remotely or in the home. They are the real key to the future and have the opportunity to transform research as we know it today.”

By using technological advances such as eConsent, remote patient monitoring, and telemedicine, the industry is poised to reach more targeted patient populations. However, Srivastava explains that more work needs to be done. “Researchers are still focused on federated point solutions. They still work on single issues and then in silos,” he says. The clinical research area is just starting to embrace integrating care with clinical outcomes.

Srivastava suggests moving away from federated silos and centralized models, and towards integrated solutions. “Such a change improves the overall experience for the participant, and the overall ability of a site, a provider, or an investigator to deliver services and research more effectively.” Under his leadership, WCG is increasing the velocity, efficiency, and effectiveness of clinical trials with such integrated solutions.

Integration And Collaboration

Srivastava sees WCG’s role not as a provider but a convener and partner to help biopharma, CROs, and sites strengthen existing systems as a drive to true interoperability between them. This is largely due to the company’s global portfolio platform of solutions, which includes ethical and scientific review services, clinical research solutions, deep expertise, data, and insights. “Through WCG’s access to 5,000+ sponsors, 4,000+ sites and networks, and dozens of patient advocacy groups globally, we realized that our role shifted from a pure-play solutions provider to a convener of stakeholders,” he explains.

The goal is to use technology, data, insights, and innovative workflows to improve efficiency and outcomes, and ultimately to change behavior. To achieve this, the needs of all stakeholders must be accounted for while collaborating. WCG, for example, has formed partnerships with entities such as Global Alzheimer’s Platform Foundation and Florence Healthcare, to actively support clinical research sites serving underrepresented communities by providing a variety of services, such as training resources, workflow support, and automation platforms.

Understanding that all stakeholders must have access and support, WCG is continuing to integrate more patients into its ecosystem, allowing for increased access to a larger patient recruitment pool for clinical studies. Besides providing needed institutional review board expertise and capabilities, WCG’s partnership with The Michael J. Fox Foundation for Parkinson’s Research also helps patients to find suitable trials, thus further demonstrating the success of its network design. This type of collaboration for a global ecosystem not only solves one issue for one stakeholder, such as a sponsor, but is able to impact many others.

Technology Isn’t Enough On Its Own

Technology is a prerequisite for this undertaking, to bring the clinical research community together, but technological solutions are not enough on their own. What is equally important, but also a potential pitfall, is expertise, Srivastava states. “I think technology solutions aren’t enough on their own. You must have expertise and data advisory capabilities to truly meet the needs of each unique trial and stakeholder.”

An example of this is WCG Investigator Space. “It’s a platform for site training, safety reporting and communication,” Srivastava explains “If we’re able to dock into multiple academic medical centers and their research investigators, we’re able to educate them quickly on protocols, inclusion criteria, exclusion criteria, etc. They’re then able to get up to speed more quickly and leverage the best possible information to ask the right set of questions and make an informed decision about whether to enroll a patient. This is an important piece to ensuring the needed flexibility and agility.”

By working with companies that are constantly evaluating new technologies and adopting them, stakeholders are continually able to be innovative, agile, and efficient. WCG is an early adopter of technology and pioneering shifts in the industry to enable interoperability between a wide range of novel clinical trial solutions. “As a convenor, we have a technological wrap around a set of experts,” Srivastava notes. “We have the ability to connect into how a sponsor, clinical research site, or organization works today.”

Equally important is expertise to review the data in an advisory capacity, that meets the needs of, and solves problems for, each stakeholder and trial. It is such flexibility, agility, and data advisory capabilities which create a successful partnership and global collaboration.

Driving Health Equity

Diversity, equity, and inclusion (DE&I) are some of the most critical topics in medical research today, yet many populations remain severely underrepresented in clinical trials. While minority communities (racial and ethnic) make up nearly 40 percent of the U.S. population, an overwhelming 75 percent of the 32,000 clinical trial participants for 53 new drugs approved in 2020 were white. This persistent lack of diversity in clinical trials means many therapies are never tested on the very patients for whom they are intended.

A trusted partner in trial participant protection for more than 50 years, WCG’s dedicated patient advocacy group and subject matter experts are working with stakeholders across the ecosystem to overcome the challenges involved in driving greater health equity. These obstacles range from a lack of physical access to clinical trial sites to a lack of trust in pharmaceutical companies and medical institutions conducting research and a lack of proper community outreach.

Leveraging its deep expertise and broad network, reaching into communities and meeting patients where they are, WCG is building a foundation for the future of clinical research, one that represents patients from all walks of life. “The next chapter of DE&I within clinical research goes beyond program management to rethinking protocols and trial designs from the ground up, around the personalization of clinical research,” Srivastava states. “Because we’ve made investments on the patient side and on working with sites more locally, across the globe, I believe WCG is uniquely positioned to understand the challenges of the social determinants of health. Because of these investments, we support those who design inclusion criteria, exclusion criteria, and clinical endpoints that serve all people, not just the majority.”

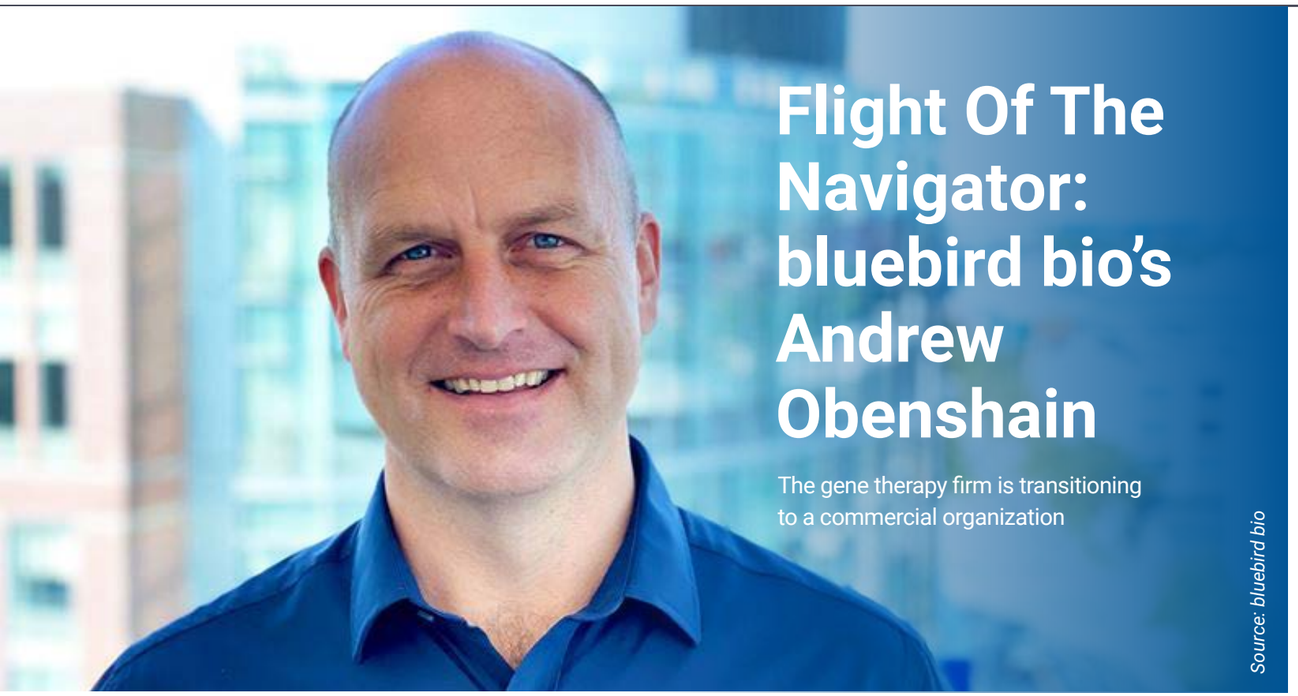
> **“You must have expertise and data advisory capabilities to truly meet the needs of each unique trial and stakeholder.”**
> Sam Srivastava, WCG

Mobilizing The Ecosystem

Clinical trials take a village. The pandemic showed what’s possible when all stakeholders come together. For its part, WCG remains focused on mobilizing ecosystem collaborators who can together streamline study operations and data collection, resolve interoperability challenges, increase diversity and inclusion in clinical research, and reduce the burden on participating patients and sites, improving the experience for them.

“Working together, we can increase access, efficiency, and the quality of clinical trials,” Srivastava notes, “not just the solution for one stakeholder, but across the industry, for the benefit of the patients we all serve.”

LEADERSHIP



Flight Of The Navigator: bluebird bio's Andrew Obenshain

The gene therapy firm is transitioning to a commercial organization

Source: *bluebird bio*

BY **JO SHORTHOUSE,** EXECUTIVE EDITOR, EUROPE

For 12 years, bluebird bio has been developing gene therapies for rare genetic disease and now, with two approvals under its belt, the company is continuing to explore uncharted territory as it brings forward innovative new treatments. Holding the map is CEO Andrew Obenshain.

When deciding on its company moniker in 2010, bluebird bio said the name exemplified its intent to set a bold new course for the future. The eastern bluebird is known to be a symbol of transition and renewal as well as a competitive and disciplined bird, it said at the time, traits that were reflected in the company's passion for transforming the lives of patients and their families.

Twelve years down the line and two therapy approvals later, the company continues to set its stall by the characteristics of transition and renewal. The last two years have been punctuated by an evolution of what the company looks like, develops, and how it works with major stakeholders. The organization has changed shape by spinning out its oncology arm, restructuring to extend its cash runway, exiting commercial activities in Europe after failing to secure reimbursement for gene therapy Zynteglo (betibeglogene autotemcel), and debuting an innovative outcomes-based contracting strategy in the US.

The other major change has been a new leader, Andrew Obenshain, who became CEO in January 2021 when predecessor Nick Leschly became CEO of the company's oncology spinoff. Not that Obenshain is a new bird in the nest, he has worked with the company since 2016 as head of Europe, and then as president of its Severe Genetic Diseases division. Having previously worked for Shire Pharmaceuticals Group PLC as general manager for France and Benelux, responsible for a portfolio that included seven rare disease products, and prior to that for Sanofi Genzyme, Obenshain has spent his career working alongside researchers, developers, regulators, and payers have pushed forward new strategies for cell and gene therapy.

His career path took him further, to becoming the leader of a pioneering company during yet another transition, this time at a fully commercial company. 2023 is set to be a huge year for bluebird, with two newly approved therapies to commercialize and a third on the horizon.

Following the August 2022 FDA approval of Zynteglo for the treatment of children and adults with beta thalassemia who require regular red blood cell transfusions, the company is progressing through launch plans and is on track for first apheresis (cell collection). It has also completed the activation of its first wave of qualified treatment centers (QTCs), expecting to scale these to 40 to 50 by the end of 2023. At the time of writing, the company had signed outcomes-based agreements with pharmacy benefit managers (PBMs) representing more than 40 national and regional plans.

> **"I believe in sweating the details of the decision because it's the decision that matters. You can't always control the outcome, even if you make a good decision."**

Zynteglo works by adding functional copies of a modified form of the beta-globin gene into a patient's own hematopoietic stem cells to allow them to make normal to near normal levels of total hemoglobin without regular red blood cells (RBC) transfusions. The functional beta-globin gene is added into a patient's cells *ex-vivo*, and then infused into the patient. Though Zynteglo is designed to be administered to the patient once, the treatment process is comprised of several steps that may take place over the course of several months.

The company will not see revenue from Zynteglo until it is infused into patients, which will take months due to the gene therapy's complex manufacturing and quality control process. The list price for Zynteglo is $2.8m, with an 80% payback option for patients who do not achieve and maintain transfusion independence in the two years following treatment. The investment bank Raymond James estimates that peak sales of the gene therapy should reach around $206m in 2027.

In September 2022, the FDA granted accelerated approval for Skysona (elivaldogene autotemcel) to slow the progression of neurologic dysfunction in boys four to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Three QTCs have been activated for this therapy, and the company anticipates commercial readiness for Skysona, with a list price of $3m, by the end of 2022. Unlike Zynteglo, Skysona is not subject to a outcomes-based payment scheme.

Bluebird plans to submit the sickle cell gene therapy lovotibeglogene autotemcel (lovo-cel) to the FDA in the first quarter of 2023 and could potentially be launched by the end of the year. Could bluebird be looking at three commercialized products by the end of 2023? "I'll leave that to the FDA," Obenshain diplomatically told *In Vivo*.

Whether 2023 brings two successfully launched therapies, or three, the grooves made by commercialization of Zynteglo and Skysona will ultimately benefit the launch of lovo-cel. It will be the same physicians using Zynteglo that will be using lovo-cel at the same transplant centers.

Obenshain is especially excited about the potential for lovo-cel's use in the US Black community, which has been "significantly underserved" and "under invested in". He said: "The potential to bring a solution to this patient community is incredibly gratifying."

Ruffling Feathers

Bold commercial decisions taken by Obenshain, and the wider bluebird team have led to this point of transition, taking the company from nest builder to fully fledged trailblazer. But those decisions have not been taken without a huge amount of consideration. "I'm a big believer that you don't make decisions in a silo, you make them with your team," Obenshain said. "I believe in sweating the details of the decision because it's the decision that matters. You can't always control the outcome, even if you make a good decision."

The company has two principles that it follows universally for making those big decisions: taking the long-term view and keeping focus on its mission. Obenshain and his team consider not just what is best for bluebird and the patients that it serves, but also for the whole gene therapy industry. While these types of commercial decisions are never easy, he says, these two principles help to clarify and points the organization toward its "true north."

Having now brought forward two of the five approved gene therapies in the US, those decisions have come to bear in a positive way, both for the company, and for the gene therapy industry. Some strategic choices are easier to make than others; bluebird's innovative outcomes-based contracting strategy with payers for Zynteglo was made based on insights from the payers themselves.

With Zynteglo, bluebird has a therapy with a high efficacy rate but a small risk of failure in its clinical data (in clinical studies 89% of patients achieved transfusion independence). However, having an endpoint that was easily measurable – transfusion independence – made the reimbursement strategy simpler, explained Obenshain. "What we learned from the payers, which actually surprised us a little bit, is they don't want to look for more than a year or two out, they want something they can measure quickly and easily, and they want to mitigate the risks," he said.

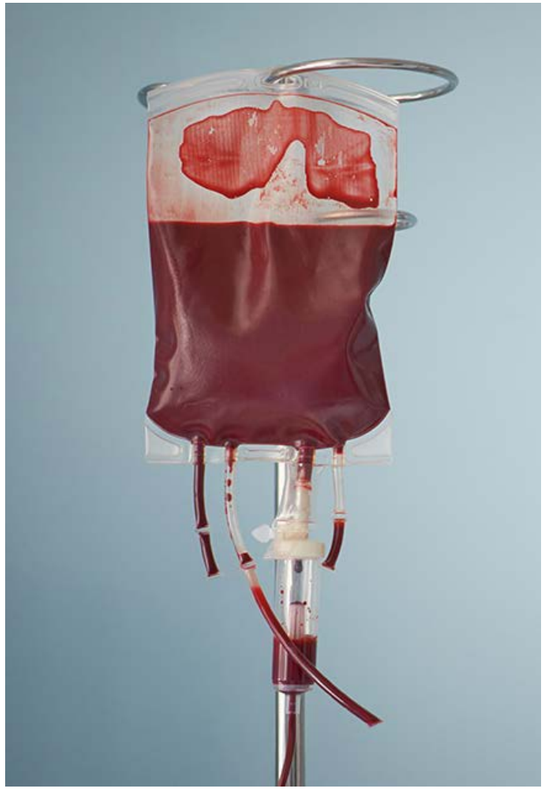
> **"The decision to leave Europe was heartbreaking."**

Rationalization aside, some decisions cut deeper than others. "The decision to leave Europe was heartbreaking," said Obenshain when discussing bluebird's 2021 exit from the continent to prioritize the US market when European payers did not recognize the value in the $3m therapy. As a child Obenshain lived in London, before moving to Belgium, then France, and finally Switzerland before moving to the US. Despite the American accent his cultural identity hangs somewhere over the Atlantic, he explains.

Despite bluebird's commitment to clinical sites, patient communities, regulators, and even governments and payers at first, there "really wasn't a decision," the CEO said. "There was only one path forward that we could have taken. So as much as we sweated, I really think that there was no other option to us. Looking on that today, the fact that we're around as a company and able to bring these therapies forward, at the very least in one geography, it owes in large part to the fact that we made those really difficult decisions then."

The value of Zynteglo has been recognized in the US, with an ICER report validating that the cost is justified up to $3m.

Bluebird is fully focused on the US, said Obenshain, to show that it can commercially scale the therapy, and take some risk and uncertainty out of the system for payers. The hope is that this, in turn, will help the gene therapy industry – and maybe, someday, bluebird – move forward not just in one country, but many markets.



A Hard 12 Months

The organization has had a particularly hard 12 months. In April, it had to lay off 30% of its workforce and deprioritize some investments to free up capital for upcoming launches, aiming to deliver up to $160m in cost savings over the next two years.

> **"I tell my team, 'You're writing a chapter in the history of medicine.' The approval of Zynteglo and Skysona are key moments in that chapter."**

Two years of taking tough decisions mean that the firm is now ahead of the curve, said Obenshain, and prepared for the macroeconomic headwinds that have been battering the biopharma industry since February 2022 when the biotech bubble burst and valuations floored.

Remember that the eastern bluebird is a competitive and disciplined creature? That still stands to this day, he said. The company has it's spend under control, it is operationally sound, and has hit all its milestones this year. It is also producing therapies that offer clinical value. "That amalgamation of an internal company that can really make hard decisions and has discipline, combined with therapies that bring value to the health care system, means that we're in a good position to get through this tough time," he said.

The tough times over the last year have been eclipsed by the first approvals in the company's 12-year history, and Obenshain's reaction to these events is visceral. He described the emotion when Zynteglo got approved, "I thought it'd be difficult to top that, then Syksona got approved," he recalls.

Having been involved in the biotech industry for over 20 years, the weight of bluebird's accomplishments to date are not lost on him. Its place in the history of medicine has now been secured and Obenshain is well aware of that. "I tell my team, 'You're writing a chapter in the history of medicine'. The approval of Zynteglo and Skysona are key moments in that chapter."

Leading The Flock

Obenshain has been involved in the gene therapy industry since he studied genetics, cell, and developmental biology at Dartmouth College, before receiving his MBA from Northwestern's Kellogg School of Management. He has worked as a consultant, a venture capitalist, and then pursued a career in pharma by joining Genzyme and Sanofi in commercial roles before leaving to work in rare disease at Shire.

Having been a bluebird for many years, Obenshain – like his company – is indicative of the firm's phenotype. He describes himself as non-hierarchical, collaborative, and mission driven. As a leader, he is clear on direction, adding that "people don't generally doubt what my opinion is on something."

A visiting CEO once advised a younger Obenshain to plant himself where he would grow. Having planted himself at bluebird in 2016, his roots are now intertwined with the success of the company, as it continues to develop budding gene therapies. Those roots have created a company that is stronger than it was 18 months ago, and it is Obenshain's leadership that will determine whether this plant now bears fruit.

Al Sandrock On His First Mission At Voyager: Cracking The Tau Alzheimer's Puzzle

Ex-Biogen Research Head Prioritizes Anti-Tau Antibody

Source: Voyager Therapeutics

BY **ANDREW MCCONAGHIE,** SENIOR WRITER, EUROPE

Twelve months on from exiting Biogen, Al Sandrock is once again leading innovation in neuroscience, and hopes to crack the tau nut in Alzheimer's and prove that Voyager's next-generation gene therapy system will be a breakthrough.

Al Sandrock left Biogen under a cloud in 2021, his 23 years in R&D leadership at the company ending abruptly amid growing controversy around its Alzheimer's therapy Aduhelm (aducanumab).

It was a disappointing end to his time at the company, where he had developed some of the most important neuroscience drugs of recent decades, such as the multiple sclerosis treatment Tecfidera (dimethyl fumarate) the rare disease antisense therapy Spinraza (nusinersen), as well as the controversial beta amyloid targeting Alzheimer's drug.

Sandrock is once again looking to bring ground-breaking neuroscience drugs to market, as CEO of gene therapy company Voyager Therapeutics, where he took the helm in March.

Sandrock is convinced that Voyager, with its proprietary TRACER capsids, has found a way to overcome one of the biggest stumbling blocks to existing AAV gene therapies reaching CNS targets – the blood-brain barrier.

"Delivery is the challenge. The only class of drugs we can [reliably] get into the brains are small molecules, but not all targets are druggable with small molecules," he said. "So, if we could solve the delivery issue with other kinds of molecules it would really open up that druggable target space, especially in CNS therapeutics. I think we're already entering a golden age [in neuroscience], but that will accelerate it even more."

A New Challenge

Leading the preclinical, pre-market biotech represents a new challenge for Sandrock, though the company is located just a few blocks away from Biogen, Inc. in central Cambridge, MA.

Just one year on from his Biogen exit and nine months into his new leadership role, questions about what went wrong at Biogen remain off limits, with Sandrock preferring to focus on the challenges that he and his Voyager team have taken on.

Founded in 2013, Voyager has suffered its own travails in recent years, deciding in mid-2021 to scrap its pipeline of AAV-based gene therapies after AbbVie and Sanofi exited licensing deals.

A pivot to its early-stage TRACER gene therapy platform looks to be paying off. These next-generation targeted AAV capsids have been shown to cross the blood brain barrier more easily than traditional capsids in non-human primates, and through a convenient intravenous administration.

This could mean that they can also reach CNS targets in humans more effectively, and without the high doses which have caused safety

issues in traditional AAV9 and AAV5 gene therapies in the field. However, the company won't begin human studies for another 12 months or more – so for now this remains only a promising concept.

Even so, Voyager has received some important endorsements from big pharma, with an opt-in from Novartis AG in March 2022 and a full commitment from Pfizer Inc. last month. Pfizer has signed up to a development alliance on a TRACER capsid for use against an undisclosed rare neurologic disease target, handing Voyager a $10m option exercise payment on top of an existing $30m upfront payment. Voyager is eligible to $290m in associated development, regulatory, and commercial milestones, plus tiered royalties.

Sandrock's first priority when he joined Voyager was to work with chief scientific officer Todd Carter to take a deep dive into the company's programs. The team took the decision to reprioritize the pipeline, and promote as its lead program a potential antibody therapy which took a new approach to tau - another Alzheimer's target with a chequered past.

"We really wanted to focus on programs that had a commercial opportunity in high unmet need, that had a rapid path to proof of biology. When you go after high unmet need, it's inherently risky, so we chose programs where we could see risk as early as possible in the clinic. And we picked targets where if we accomplished what we needed to in gene expression, we would get therapeutic benefits."

Sandrock said he was unaware of the anti-tau antibody work being done at Voyager before he arrived, but was impressed by the team's science. Crucially, the candidate targets the C epitope on tau, a different target from the N terminal that had been the target for numerous earlier anti-tau antibodies – including Biogen's gosuranemab which Sandrock oversaw – but which all failed in the clinic.

In August, Voyager presented preclinical data from four antibody candidates which produced a 70% reduction in the spread tau in the brains of rodents.

Having had first-hand experience of tau antibodies before, Sandrock believes Voyager has an opportunity to make a breakthrough, starting with a potentially rapid proof-of-concept study in humans.

"With a group of around 20 to 25 patients, you can see whether or not tau is spreading or not in a one-year study, and determine whether our antibodies block the spread of tau in humans. We think it would be tremendous if we could show that."

Behind the tau antibody, are the company's two lead TRACER programs: a GBA1 gene replacement therapy for Parkinson's disease, and a SOD1 gene silencing therapy for amyotrophic lateral sclerosis (ALS).

Biogen and partner Ionis Pharmaceuticals, Inc. recently suffered a setback with their SOD1 targeting antisense oligonucleotide candidate, tofersen, in ALS after its pivotal study produced weak efficacy data.

Commenting on the failure, Sandrock claimed tofersen still represented a proof-of-concept for targeting SOD1, and pointed again to the problems existing AAV capsids and other modalities such as antisense drugs have in crossing the blood-brain barrier.

Lending credence to its technology, Voyager recently announced it had identified a novel cell surface receptor identified as a binding receptor for its TRACER AAV capsids that is expressed by human CNS and brain endothelial cells.

"Voyager now knows how to get a capsid to cross the blood brain barrier," he said. "I'm excited about how we could leverage this receptor to get other kinds of molecules into the brain. Delivery is a key limitation for antisense oligonucleotides, siRNAs, and even proteins. So, for example, we could use [TRACER capsids] as a shuttle to administer nucleic acids."

While Voyager is conscious of the need to generate human data, it appears to be focused on optimizing and selecting its lead candidates before entering the clinic. It currently plans to identify lead development candidates for all three programs before the first half of 2023, with investigational new drug filings expected in 2024 and 2025.

This lengthy runway has not gone unnoticed. Yun Zhong, director of Biotech Equity Research at BTIG, said while other companies in the field were willing to predict their IND studies reaching human trials starting by 2024, Voyager was taking a more conservative outlook. "Management is not willing to provide a guidance on when any of the selected programs will enter the clinic. That suggests to us that the road to clinical entry may still be long," he said.

Can Voyager Buck The Gene Therapy Gloom?

The Pfizer Inc. and Novartis AG licensing deals have undoubtedly helped Voyager buck the AAV gene therapy trend in 2022, where many companies have seen share prices plunge by as much as 80% since the start of the year. By contrast, Voyager's shares are up by 70% since January.

Yun Zhong thinks Voyager's potential to deliver its gene therapy via IV infusion is an additional factor in its favor. Its immediate rivals, Passage Bio and Taysha Gene Therapies, are both developing gene therapy programs for CNS indications using direct administration into the brain or spinal canal cerebrospinal fluid respectively.

He believes the IV route could be a much more attractive delivery method, but this depends on Voyager achieving its goal of improved potency in crossing the blood-brain barrier, thereby allowing for much lower dose to be used.

Given the fallout over Aduhelm, with people looking at who is to blame – the FDA, Biogen's CEO Michel Vounatsos or Sandrock – it seems natural to wonder whether Sandrock now has something to prove at Voyager. But Zhong comments that while the FDA approval of Aduhelm were controversial, biopharma company executives should not be blamed for gaining approval within the rules.

"I don't believe Al has anything to prove at Voyager. If there is anything he needs to prove, it should be his belief that Voyager's focus on IV delivery for the CNS is correct."

BTIG asked that the following disclaimer appear in the article: BTIG LLC expects to receive or intends to seek compensation for investment banking services in the next three months from Voyager Therapeutics

Lessons From Novo Nordisk's Mads Øvlisen, The Father Of CSR

Source: Novo Nordisk

BY **JO SHORTHOUSE,** EXECUTIVE EDITOR, EUROPE

When Mads Øvlisen was persuaded by his father-in-law to join the family business, Novo Industri, in 1974 for a short stint in the legal department, little did he know it would the beginning of a lifetime of service to the company that he helped to shape into the diabetes powerhouse it is today.

Novo Nordisk A/S has appointed five CEOs in almost 100 years. It is testament to the culture in the previously family-run company that leaders have the freedom to bring their unique form of guidance and management to the Danish diabetes specialist.

The firm is understandably proud if its culture. The values passed down from its founders of honesty, ambition, accountability, and openness define the way it treats its staff, how staff treat one another, and how it innovates. While it is from the company founders that these values emanate, it is Mads Øvlisen, the company's third CEO, who is best known for articulating the founders' principles into a deep-rooted set of guiding principles such as Values In Action, and the Novo Nordisk Way, a lived version of those ethics that underpin company decisions.

"I always interview our new colleagues and ask what their first impressions are of the company. There are always some comments about our culture. The way we work together, the respect we show to each other, and for that I'm incredibly thankful of Mads for having written down these principles into a set of core values," Lars Fruergaard Jørgensen, Novo Nordisk's current CEO, told *In Vivo*.

Duty And Obligation

If a conversation with Øvlisen were a word cloud, duty and obligation would be writ large. This sense of giving back is not only a Nordic-influenced concept, but also deeply held in the heritage of Novo Nordisk. Harald and Thorvald Pedersen established the Novo Foundation in 1951 to secure the foundation of the company, but also to the many employees who had tied their destiny to Novo. "They felt that ownership did not equate to leadership, or vice versa," Øvlisen explained to *In Vivo*. He felt a responsibility to lead the company with this sentiment in mind. "My father-in-law [Novo Industri's second CEO, Knud Hallas-Møller] always said, 'Where is it written that you can start your own company and use society's talent, resources, infrastructure, to your own good? Don't you have an obligation to pay back?'

"I could only agree with that because I would not have gotten anywhere if it had not been for teachers and parents that believed in me, and gave me choices, for sending me to the US for school. You realize that you're a part of something bigger, and that you have an obligation that goes way beyond yourself. So therefore, paying back is critically important," he explained.

Øvlisen had a "normal upbringing." Born in 1940, the son of a father who worked in a lumberyard, and a mother that stayed at home with him and his two siblings in their Copenhagen apartment, Øvlisen found a passion for languages in his formative years. In high school he received a scholarship to study in Cedars Rapids, Iowa, an "incredible experience", he recalls, that made him determined to work internationally. Languages fell by the wayside and Øvlisen instead picked up his law books.

Denmark's egalitarian society has meant a lot to Øvlisen, he explained. His friends from school are still his friends now, even though he was "suddenly a CEO." It also influenced his management style. The Nordic concept of stakeholders, whereby an inclusive society is a source of success, has "been very significant in the way we tried to run our company."

Upon leaving Copenhagen University Øvlisen applied to business school in the US "partly for education and partly for an ego trip." Swayed by the palm trees outside the library, he moved his wife, Lise Hallas-Møller, and young daughter Annemette to California to attend Stanford University in 1970. In 1972, upon graduating with an MBA from Stanford, Øvlisen did the thing he swore he would never do, and joined his father-in-law's firm, Novo Industri.

"I wanted to prove I could do it on my own," said Øvlisen. "It was vanity, I wanted to fend for myself." However, his father-in-law persuaded him to join the firm on a temporary basis. "He wrote me a letter, stating that Novo was considering an IPO. The company needed somebody to work together with the company and with the family, and since I had legal background, some finance experience and knew the family, they thought I might be the one who could get shares away from the family and into the public," he explained.

Hallas-Møller, CEO from 1961-1981, had restructured the company to cope with growing sales of Lente insulins. This had created a product-oriented organization that generated further growth for Novo in the ensuing decades. In 1974, this culminated in the introduction of Novo Industri's B shares on the Copenhagen Stock Exchange. As secretary to the Board of Directors, it was Øvlisen's job to facilitate the public offering by going through the company structure. A one-year job turned into a lifetime of service to the company. Øvlisen became chief counsel and then CEO from 1981 to 2000, remaining as chairman of the board until 2006.

"In my early days, the issue of visibility was not important to me. But I was then told by our people that I should be visible. It was an educational task, getting used to being the one everybody looked at," he recalled. "I realized that it's not enough to make certain that things happen, as leader you must be the giraffe of the company."

Nordic Leadership

This modesty is representative of the Nordic leadership style, and the Novo Nordisk company values are based on the Scandinavian values of an open and honest culture that prides itself on its integrity. "Values are difficult to instill in a company because it takes a very consistent behavior of all leaders. It would be easy for this to become a cynical thing that's just spoken, but it's not lived," Jørgensen told *In Vivo*. Øvlisen agreed, "You must embody the values of the company. It's more exciting to be Caesar's wife than to be the CEO," he laughs.

Company values may seem a rather woolly priority in an industry based on cutting edge innovation and capital on the balance sheet. However, Øvlisen and Jørgensen both believe that the emphasis on ethics and values when running a business builds trust, and a sustainable competitive advantage. And it is far from easy.

"The only sustainable competitive advantage you have in our business is not patents, it's not know-how, it's the ability that all people – who *are* the company – have to learn and to change faster than others. The ability for people to anticipate change, and have the possibility of acting on it, is very important," Øvlisen explained to *In Vivo*. "To try to lead a company by values is as hard work as by any other way," he said. "You've got to make certain that the values are understood and that the company lives up to them, and it adheres to them as much as any operating budget."

Øvlisen was one of the engineers of the 1989 merger of Nordisk Gentofte and Novo Industri to become Novo Nordisk. "Mads played a key role in that merger," explained Jørgensen. "He built trust across the two companies. The CEO of Nordisk, Henry Brennum, was co-CEO with Mads for some time. It's very rare to have companies merging where there are two CEOs, that tells you a lot about Mads, he doesn't want to stand in the limelight on his own. It was really a merger of equals," he said.

The merger was one of the largest in Denmark. At the time, Nordisk had 11 foreign subsidiaries, 14 branches and 1,450 employees, while Novo had subsidiaries and representative offices in 27 countries and 5,900 employees. The merger took place despite many years of intense rivalry between the two competitors and tense relations, including court cases over patent rights from 1938 to 1941.

Today, the Copenhagen-based firm is a dominant presence in the diabetes field, producing half of the world's insulin. Almost a century old, it now works in obesity, hemophilia, and growth disorders, as well as diabetes.

Øvlisen's Approach To People

Company values include opportunities for people to realize their potential, something Øvlisen is evangelical about. "I believe that each and every person in your company has a unique potential for contributing to the progress of the company. It is the most important task of any CEO or leader to release that energy, to set that energy free," he explained. But to untap that potential, he said, there need to be some rules of the game.

Managers and the senior leadership team need to listen to employees as much as employees need to listen to their managers, he explained. In one instance, at a town hall meeting to assess the Values In Action program, the company was held to account for the way its accounts were approved by the board of directors who were appointed by the Novo Foundation which owned 68% of voting power in the company: i.e., the company was approving its own accounts. This led to a change in company grandfathering, and Øvlisen ensured the Foundation reduced its influence on the corporate board.

Around the same time, Øvlisen was concerned about the extent to which managers around the company were living up to their obligations regarding the people working at Novo Nordisk. "We would make unnoticed inspections on the quality assurance side, so why not check whether we are living up to our values around the world, too," he explained.

Øvlisen instilled "facilitators" to audit company culture around the world. These facilitators came from within the company, understood the company values and wanted to help. Once they had lived in a facility or division for a week, they would create an action plan that was followed up later. Importantly, none of these action plans were reported to superiors because that would have "cut them off at the knees," he said. Corporate management were not told of incidences, or specific behaviors, they were just handed a trends report. "The facilitation is not about finding the holes in the cheese," said Jørgensen, "it's about helping leaders make sure that we have this consistent set of values lived throughout the company."

HENRY BRENNUM AND MADS ØVLISEN, NOVO NORDISK

Source: Novo Nordisk

"You have to push decisions and initiative to the periphery of your company because that's where people really know what the problems are, that's where people know what the solutions are," Øvlisen explained. "Does that mean you make mistakes? Certainly, but smart mistakes. That's the price for progress."

Art Appreciation

Øvlisen is known not only for his corporate triumphs, but also for his love of the arts. He reportedly has the biggest private art collection in Denmark and was chairman of the Royal Danish Theatre and the Royal Danish Art Council. His renowned appreciation of art should create a dichotomy between his corporate and personal selves. However, his use of visual art as a means of communication with Novo Nordisk employees and to counter habitual thinking, "one of the biggest risks in an industry that depends on innovation," made coming to work at the company quite unique.

"I wanted something that made people stop and think. They didn't have to like the art I bought," he said, "it was a way of helping people to stop for a few minutes, to see if we could change their sense of reality, or what the real world is." The important thing in any company, he said, is to have a critical dialog. With a soft chuckle, he recalled a time when his secretary stormed into his office and demanded to know why he had placed "some kind of junk" in reception, referring to an art piece made of silicone and kitchen swabbers. "I loved it because she had stopped to look and not think about any other distractions for a few minutes. It showed her that things could be different."

Art was never hung in executive offices, only in reception and in factories, and Øvlisen had an understanding that electricians and carpenters, when visiting each office building, would move the art around to keep it fresh. "I never bought expensive art, only for investment," he explained. "I only bought art when the company was doing all right. Because nobody knows what art costs. I couldn't hang a new painting in reception if I said to a colleague that we couldn't afford to send them to a conference. All the art was from emerging artists and artists who would feel that it was a pat on the shoulder to sell to us. It was to encourage young people," he explained. The Novo Nordisk Foundation funds the Mads Øvlisen PhD scholarship within art history and practice-based artistic research every year.

Legacy

Among Øvlisen's other considerable achievements, such as being the chairman of LEGO, "again, for vanity," is the publication of Novo Nordisk's environmental report in 1994, the first in Denmark and one of the first internationally. In 1999, the company published its first corporate social responsibility report. It was also the first to publish an integrated report, where the financial, social, and environmental accounts were all included in one report as it is today. "It's really an integrated part of how we do business," said Jørgensen.

It was not just in his home country that Øvlisen was recognized for his approach to the environment. He was appointed to the advisory board of the United Nation's Global Compact, the world's largest corporate sustainability initiative, by secretary general Kofi Annan. "Corporate social responsibility is about how a company makes its money, not how it spends it," he explained.

Mad Øvlisen is the 2022 recipient of the Scrip Lifetime Achievement Award. "I'm really pleased that he gets this acknowledgement. Because he's an amazing person," said Jørgensen. While Øvlisen told *In Vivo* he would be "crawling into the smallest mousehole" on the night, his contributions toward the progression not only of the pharmaceutical industry, but to the field of diabetes, and company responsibility on a corporate, social, and environmental basis, are not to be taken lightly.

When asked about his legacy, octogenarian Øvlisen pauses: he hasn't thought about this question before. "I'm still proud of having played on the current Novo Nordisk team. The way the leadership team, since I've stepped down, has continued to develop the company both business wise and stewardship wise is admirable. I really like to say that we've been on the same team."

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Global Supply Chain Scrutiny And Investment In Domestic Alternatives For US Drug Shortages

Pharmaceutical supply chains may grow less efficient and less risk prone as US government gets more involved to ensure availability of pandemic and essential medicines. But what about pediatric oncology medicines and other treatments that save lives even though they may not be considered essential?

BY **BOWMAN COX,** EXECUTIVE EDITOR, US

Just a few months after she was diagnosed with acute lymphoblastic leukemia (ALL) Laura Bray's daughter Abby, then nine, encountered her first drug shortage.

Abby was among the 20% of ALL patients who develop allergies to E-coli-based enzymes used in the normally curative standard ALL treatment protocol to kill leukemic cells and must switch to a non-E coli-derived alternative, Erwinase.

When Bray took her daughter to the hospital for her first dose in spring 2019, she was told there was a shortage of Erwinase and they would have to go home and wait until it became available, Bray recalled during a virtual summit convened by an organization she later formed to help other families overcome pediatric oncology drug shortages.

"There was not a lot of answers about when it would be available. And then my child asked me, 'am I going to die because I don't get my medicine?' We were kind of free falling. It was very hopeless. How does someone find a drug? You know, how do you answer that question from your nine-year-old?"

Wrestling With Brutually Efficient Markets

Bray's quest to help her daughter came as thinking on pharmaceutical supply chains had begun to shift from efficiency to availability.

Many drug shortages like the one that affected Abby have been traced to brutally efficient global markets that drove prices of essential medicines, especially generic sterile injectables, to unsustainably low levels.

The neoliberal vision of a lightly regulated, low-friction free trade zone that would draw authoritarian countries like China and the former Soviet Union toward democracy instead gave rise in the 1990s and 2000s to increasingly global manufacturing enterprises that hollowed out many industrialized economies like those of the US, the UK, and the EU, which by the 2010s began fueling authoritarian political movements.

As global markets continued to deliver drug shortages, US Congress in the autumn of 2019 prepared to give the federal government more ability to police global pharmaceutical supply chains.

The Buckling Of Increasingly Brittle Supply Chains

It was the quest for the efficiency needed to compete globally that drove pharmaceutical companies to reduce their cost of goods by moving manufacturing operations to countries like India and China, which offered lower wages, lower environmental standards, and less strict domestic oversight of drug manufacturing quality.

Supply chains grew longer and more brittle, with manufacturers forgoing the expense of retaining backup suppliers and large inventories, all in the interests of efficiency.

It fell to the US FDA to impose US quality standards abroad in countries that lacked comparable domestic standards. The agency also would have to keep a close eye on domestic operations, where quality and availability suffered as manufacturers pared back investments in aging facilities and stopped producing the cheapest drugs to compete globally on price.

By the early 2010s, the system began to buckle and drug shortages soared.

After a record 250 new drug shortages hit the US in 2011, efforts by the FDA and others have tamped the annual rate of new drug shortages down to 40 or 50, according to the agency's 2021 drug shortage report to Congress.

Meanwhile, many existing drug shortages have persisted from year to year, adding 60 to 80 ongoing drug shortages, for a total of 100 to 130 in recent years.

The report noted that many of the shortages, including those of critical cancer treatments, parenteral nutrition products and blood pressure medications, pose a serious public health challenge. The suffering would not escape the attention of Congress.

The COVID-19 pandemic disrupted global pharmaceutical supply chains not only by suppressing production, interrupting distribution, and triggering demand surges, but also by inviting government intervention.

Some countries diverted resources to develop, produce or acquire COVID-19 vaccines and therapeutics for domestic use. Some hoarded APIs and drug products that other countries wanted for COVID-19 treatment.

The US government used its World War II Defense Production Act authorities to redirect ingredients and supplies from global private markets for production of the COVID-19 vaccines and therapeutics it was funding.

Abby's Angels Pull Through

As a patient's parent, Bray lacked the ability of a government or a manufacturer to control or redirect a pharmaceutical supply chain. But as a business professor, she knew that supplies don't completely disappear during shortages. To find enough Erwinase to meet her daughter's needs, she started by cold-calling suppliers' toll-free customer service numbers.

She also reached out to the 350 friends and family members who, when Abby was diagnosed, had started a webpage called Abby's Angels. It was the Abby's Angels network that found some leftover Erwinase at a hospital, enough to meet Abby's needs.

But what about other families? "I couldn't sleep knowing that there were patients all over the country who had doctors working to save their lives without the proven tools to do it," Bray said.

With some friends, she started a new webpage and an organization in December 2019, Angels for Change, to do for others what her friends and family had done for Abby. Worried parents began finding the group online and Bray and her network began to deliver results for them as well.

When Angels for Change held its second virtual summit in May 2021, Bray reported the group had found 65 lifesaving doses of medicine for the families of 43 children. "With just a phone call, or an email and your help, we've been able to get every single one of those children back on protocol," she told the summit, which brought together an array of supply chain participants working to solve the drug shortage problem.

But it still wasn't enough, she said. "It's reactive and it's not scalable."

FDA Discussion And Action

It turns out Bray in her own small way was on a parallel path with the FDA and Congress. The FDA's drug shortage staff had since 1999 been reacting to drug shortages by finding alternative supplies. Then Congress began providing tools to help the agency prevent shortages.

The FDA Safety and Innovation Act in July 2012 responded to the prior year's drug shortage crisis with new requirements to alert the agency about potential shortages.

The March 2020 Coronavirus Aid, Relief and Economic Security (CARES) Act added more requirements to the Food Drug & Cosmetic Act, most notably measures in section 506C requiring manufacturers to share more information about potential shortages and to plan on managing risks with redundant sites and suppliers as appropriate, while requiring the FDA to focus more on reviews that could mitigate or prevent shortages.

A new section 510(j)(3) provision required manufacturers to annually report active pharmaceutical ingredient and drug product manufacturing volume by facility, which could help the FDA identify weak links in the supply chain such as alternative drug product manufacturers relying on the same at-risk API supplier.

The FDA has begun to interpret the CARES Act provisions in draft guidance documents, stirring up industry opposition. Guidance on implementing the section 506C redundancy risk management plans lays out a broader vision for them than Congress required, recommending their use in additional scenarios and for more drug products.

Industry groups representing global pharmaceutical manufacturers pushed back in comments on the draft guideline, urging the FDA to stick with the narrower scope Congress gave for the program.

When the FDA hosted a webinar in September on the new CARES Act drug amount reporting requirements, participants' questions reflected two key areas of concern for industry. Prescription drug manufacturers asked how they could use their well-established processes for producing annual reports to address the new manufacturing volume reporting requirements. Meanwhile, manufacturers of over-the-counter monograph drugs, who have never had to file any kind of annual reports, were reeling from the new requirement, with several asking for confirmation that it applies to them.

"We were kind of free falling. It was very hopeless. How does someone find a drug?"

Laura Bray, Angels for Change

A List That Could Go On And On

A series of executive orders has yielded a bounty of studies and reports suggestive of the complexities that can arise when the federal government gets more involved in an industry's business.

No longer just a regulator, the US government now also promotes, demands, and contracts for domestic pharmaceutical manufacturing of medical countermeasures and essential medicines.

President Trump's Executive Order 13944, published 14 August 2020, called for the FDA to produce a list of essential medicines, medical countermeasures and critical inputs that should be manufactured domestically, perhaps with government help, which the agency published 30 October 2020.

The initial list focused mainly on emergency medicines, but EO 13944 called for the FDA to periodically update it, and those updates could expand into other categories such as, for example, the pediatric oncology drugs that concern Bray.

Already, Marta Wosinska and Richard Frank of the USC-Brookings Schaeffer Initiative for Health Policy proposed in a 24 June 2022 Brookings Institution blog post expanding the list to include baby formula due to the recent shortage as well as to include psychotropic medications and common pharmaceutical excipients like microcrystalline cellulose and magnesium stearate due to the potential impact if they were in short supply.

A Pandemic Preparedness Moonshot

President Biden called for greater public sector involvement to strengthen pharmaceutical supply chains in a pair of executive orders, one the day after he took office and the other a month later.

Executive Order 14001, issued 21 January 2021, called for a pandemic supply chain resilience strategy in 180 days. The July 2021 180-day report called for an expanded domestic public health industrial base, a greater diversity of suppliers, more extensive stockpiles, "warm" manufacturing facilities that are ready to scale up quickly, and a greater ability for the government to monitor the public health supply chain.

Over the next decade, the report envisioned the federal government making significant investments in the expansion and sustainment of a public health industrial base that the government would manage and oversee.

Executive Order 14017 on 24 February 2021 called for federal agencies to study and strengthen supply chains for pharmaceuticals and other technologies in 100-day reviews that they follow up in a year with more in-depth analysis.

A June 2021 100-day report from the Health and Human Services Department said the Biden administration was moving ahead with plans to use certain authorities under the 1950 Defense Production Act to establish a public-private consortium that would involve the government to a much greater degree than ever before in the management of supply chains for essential medicines.

A 2 September 2021 report on a whole-of-government review and update of US biopreparedness policy required by Executive Order 13987 called for investing $65bn in pandemic preparedness over the next seven to 10 years, coordinated by a "mission control" office at the HHS that would speed vaccines and therapeutics to the public like the National Aeronautics and Space Administration's Apollo program sped astronauts to the moon.

Meanwhile, a March 2022 National Academies of Science, Engineering and Medicine report that fulfilled a CARES Act commitment may have fallen on deaf ears with its caution against a "kneejerk response … to blame globalization" for supply chain hiccups and "glib on-shoring proposals" that proliferated in the wake of the pandemic.

A New Program And A New Deputy To Run It

A February 2022 EO 14017 one-year report from HHS' Administration for Strategic Preparedness and Response, or ASPR, gave more detail on plans for strengthening the public health supply chain and expanding the domestic industrial base.

ASPR said it was consolidating its industrial base expansion and Defense Production Act-related activities into a program office focused on building domestic manufacturing capacity through industrial partnerships. As part of that effort, ASPR advertised in August 2022 an opening for a new deputy assistant secretary to establish and run the ASPR industrial base expansion program office.

The deputy will work on "establishing a permanent appropriation that will be specific to onshoring strategic medical supply chain manufacturing and distribution capacities to build resilience, sustain COVID gains and strengthen the industrial base," the notice says.

The one-year report also said ASPR would:

- launch a Defense Production Act Title III program in summer 2022 to invest in sustaining critical production, commercializing products and scaling up the domestic public health industrial base's ability to respond to emergencies;
- work to secure sustainable funding from the Commerce Department's Critical Supply Chain Resilience Program to support long-term contracts and increased inventories, while ensuring access to sufficient manufacturing capacity for quick response to public health emergencies;
- work to develop and commercialize continuous, distributed, and other types of advanced manufacturing platform technologies; and
- build on the supply chain "control tower" program, established early in the pandemic to monitor distribution of more than 40 drugs for COVID-19 patients, by growing the information platform, which had been producing "reports and dashboards that provide unprecedented visibility into commercial supply chains."

BARDA Looks To Establish Industry Consortia

ASPR's Biomedical Advanced Research and Development Authority, or BARDA, requested information in November 2021 on a plan to establish a Biopharmaceutical Manufacturing Partnership, or BioMaP, consortium.

Then in August 2022, BARDA began seeking potential industry partners that could lead consortia planned for vaccines and therapeutics as well as medical devices. These consortia would provide a rapid response vehicle for medical countermeasures much as the Defense Department's Medical CBRN Defense Consortium did for Operation Warp Speed's COVID-19 vaccines and therapeutics.

A key feature is the reliance on "other transaction agreements" rather than grants or contracts to sidestep byzantine federal procurement requirements in which the pharmaceutical industry generally is not steeped.

This BARDA initiative also would involve working with commercial lenders to fund countermeasure capacity development in ways that would leverage federal tax dollars far more than grants and contracts would.

Legislation In The Works

Meanwhile, an array of legislative initiatives has been rolled up into a bipartisan Senate bill, the PREVENT Pandemics Act, which could help kick off an unprecedented expansion of the publicly funded US drug manufacturing sector.

Sen. Patty Murray, D-WA, who chairs the Senate Health, Education, Labor and Pensions Committee, introduced the bill, S.3799, on 10 March with the HELP Committee's ranking minority member, Sen. Richard Burr, R-NC.

Passage could occur during the so-called lame duck session as the 117th Congress completes its work following the 8 November election. Alternatively, the measure could be reintroduced in the 118th Congress, which convenes 3 January, but without sponsorship from Sen. Burr, who did not run for re-election.

Title IV of the bill would strengthen the supply chain for "vital medical products" such as medical countermeasures by, among other things, establishing "warm-base" manufacturing capacity that would be kept in operational readiness, perhaps with private-sector work, for pandemic response and perhaps for prevention of essential medicine shortages.

The More Things Change...

Whether the emerging public-private collaborations to reshore US pharmaceutical manufacturing would help prevent pediatric oncology medicine shortages like the one that led Bray to establish Angels for Change remains an open question.

After all, the problem of global competition driving prices to unsustainably low levels is an issue for generic drugs, not brand drugs like the Erwinase that Bray went looking for. And the reshoring efforts focused on infectious diseases and emergency medicine, not cancer. Plus, just like private multinationals, public-private collaborations can run into quality problems that cause shortages.

This happened during the pandemic when quality concerns ruined the drug substance for millions of COVID-19 vaccine doses manufactured by a public-private partnership between BARDA and Emergent BioSolutions.

And it was quality problems at a public-private venture that led to the Erwinase shortage.

In 2015, the UK's Department of Health and Social Care's Public Health England had spun out Porton Biopharma Ltd. as a private company whose shares are all held by the department to manufacture Erwinase and an anthrax vaccine at a facility that once belonged to the UK's Porton Down military research complex, originally a World War I chemical weapons research and development site in Salisbury, UK.

A US FDA inspection of the former Porton Down facility in March 2016 found that the new venture was having difficulty investigating and resolving problems with metal and other particulates in Erwinase lyophilized powder for injection. Porton Biopharma blamed a stopper supplier, but that didn't make the problem go away. The FDA sent the firm a warning letter the following January.

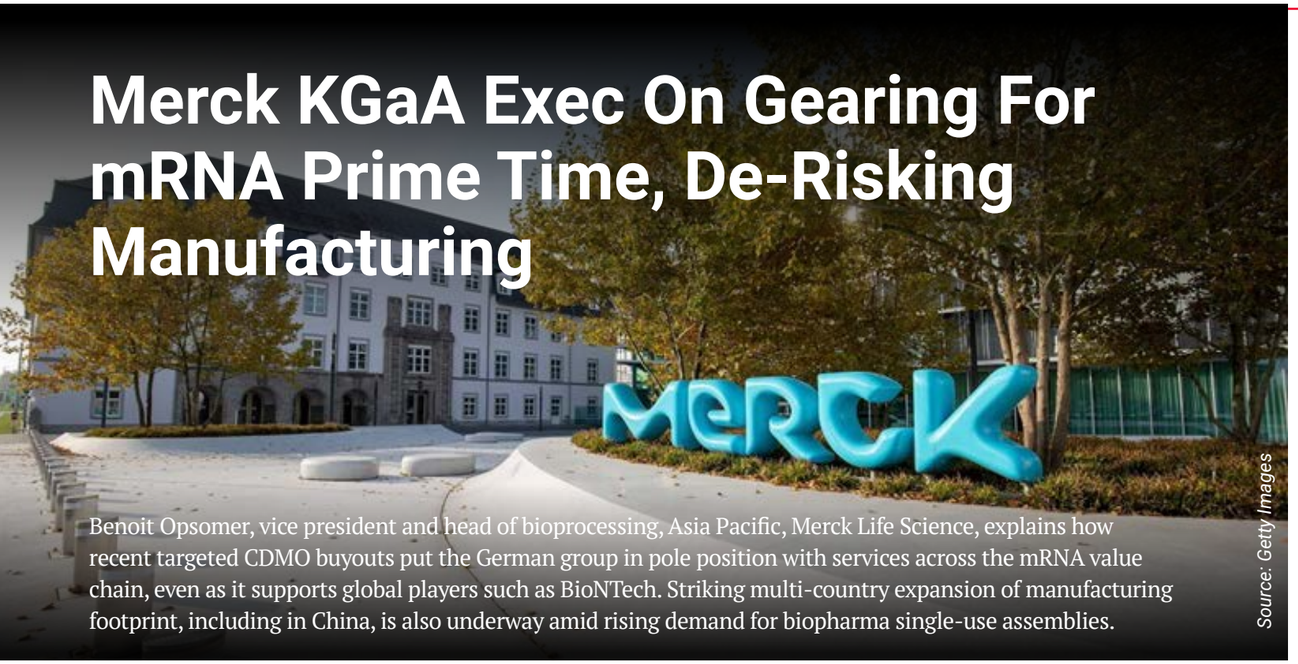
The FDA let the US marketer of Erwinase, Jazz Pharmaceuticals plc, distribute some batches with instructions for filtering out any particulates or switching to intramuscular injection. After Porton switched to a different marketer, Jazz developed an alternative, Rylaze, which the FDA approved following an accelerated review.

Although Rylaze remains available, the American Society of Health-System Pharmacists on 24 August 2022 put Erwinase back on its drug shortage list due to ongoing manufacturing issues and capacity constraints at Porton Biopharma.

On 17 September, Angels for Change held its second annual "Champions for Change" gala in Tampa, FL. Sponsors included McKesson, Vizient, Phlow, Hikma, USP and other organizations that are working to prevent drug shortages.

But as much as FDA and industry champions are changing the effort to root out drug shortages, the reliance on desperate responses to them remains the same.

Merck KGaA Exec On Gearing For mRNA Prime Time, De-Risking Manufacturing



Source: Getty Images

Benoit Opsomer, vice president and head of bioprocessing, Asia Pacific, Merck Life Science, explains how recent targeted CDMO buyouts put the German group in pole position with services across the mRNA value chain, even as it supports global players such as BioNTech. Striking multi-country expansion of manufacturing footprint, including in China, is also underway amid rising demand for biopharma single-use assemblies.

BY **ANJU GHANGURDE,** EXECUTIVE EDITOR, ASIA-PACIFIC

Merck KGaA, which has enabled important cost efficiencies and record go-to-market timelines for COVID-19 vaccines globally, is doubling down on plans for its messenger RNA (mRNA) offerings and single-use technologies.

While the German group already collaborates with frontline mRNA players and has long-standing experience in producing lipids – one of the key components for the formulation of mRNA therapeutics, including COVID-19 vaccines – it has recently expanded its horizon in the segment with two targeted acquisitions of contract development and marketing organizations (CDMOs).

In an interview with *In Vivo* sister publication *Scrip*, Benoit Opsomer, vice president and head of bioprocessing, Asia-Pacific, Merck Life Science, outlined how the company was building on core strengths and adding new capabilities, while also more widely de-risking manufacturing for single-use assemblies with an expanded global footprint.

Opsomer underscored that while the company supports global mRNA manufacturers, including BioNTech SE, to help increase speed to market, ensure safety and efficacy and reduce complexity across the entire mRNA process, facilitating accelerated delivery of vaccines such as for COVID-19, the star new modality holds huge promise for other diseases as well.

"mRNA vaccines use synthesized RNA to instruct the body to produce antigens; being a non-infectious technology, small dosage requirement, easier production in BSL [biosafety levels]-1 facility, we see tremendous potential for mRNA technology for future therapeutic purpose," the Merck executive said.

That's perhaps where the CDMO deals piece adds new dimensions to Merck's growth strategy, given the potential of the mRNA technology to transform the infectious disease treatment and be applied across a broad range of other diseases including cancer.

The group's recent CDMO acquisitions, which include the $780m buyout of Exelead this year, are expected to enable it to provide end-to-end services across the mRNA value chain, opening up significant opportunities in the high-potential market for therapies based on the novel modality.

"We want to invest in this area because we trust that this technology could be adapted for other types of vaccines. I'm sure that there will be mRNA vaccines coming for other types of disease. A lot has to be done but it has been a fantastic discovery over the past few years," Opsomer stated.

Exelead focuses on complex injectable formulations, including lipid nanoparticle (LNP)-based drug delivery technology, which is key in mRNA therapeutics, while AmpTec, the CDMO acquired last year by Merck, brought with it differentiated polymerase chain reaction-based technology said to have advantages over other technologies for mRNA manufacturing.

While the German group has long-standing CDMO experience in high-potent active pharmaceutical ingredients, linkers and monoclonal antibodies, it has indicated an intent to up its stakes in the segment. At its Capital Markets Day briefing early October, senior management said that "accelerating CDMO is a priority not only for organic investment, but also to potentially inorganic moves."

Barclays Equity Research, in a recent note, also referred to the appointment of Dirk Lange, head of Life Science Services, at Merck, earlier this year – the executive comes with over two decades of experience in the CDMO segment and was president and CEO of US-based CDMO, KBI Biopharma Inc. prior to joining the German multinational.

"Merck can maximize synergies across CTS [contract testing services], CDMO and the individual modalities. This creates a defined interface between the products business and the services business," Barclays said in an update based on the Capital Markets Day briefing.

CDMO Services For Emerging Biotech

Merck expects to further invest more than €500m ($527m) to scale up Exelead's technology over the next decade and Opsomer indicated these acquisitions will mean the German group can provide CDMO services for emerging biotech that may have in their pipeline a vaccine but lack the capacity or capabilities to manufacture such products.

BENOIT OPSOMER, VP AND HEAD OF BIOPROCESSING, ASIA-PACIFIC, MERCK LIFE SCIENCE

"We can do that for them and this is where Merck is entering. It's not only about delivering products to big companies but providing the services to manufacture for them. So that's where we are entering the game as well," he explained.

Earlier this year, a *Scrip* roundtable discussed various aspects around easing manufacturing bottlenecks to meet the potential of mRNA. Experts noted that the initial stages of commercializing COVID-19 mRNA vaccines saw BioNTech, Pfizer Inc. and Moderna, Inc. refrain from seeking CDMO alliances, largely since it was a new manufacturing process and developers were "wary of sharing the know-how for fear of leakage."

Things have since changed, however, and CDMOs have not only acquired the necessary capacity and capabilities to produce mRNA products but some have specialized in discrete areas of the manufacturing process, such as plasmas, lipids, LNPs or even analytics, a summary of the event noted.

"It really does democratize the technology," Greg Troiano, Sanofi's chief manufacturing officer, mRNA Centre of Excellence, was quoted as saying in the discussion.

Merck's Opsomer didn't want to be drawn into the wider intellectual property aspects around mRNA vaccines in the early days, but acknowledged the importance of intellectual property/confidentiality when customers ally with CDMOs. These aspects are part of a supply/services agreement that companies go through with customers as well as suppliers, though Merck's long-standing experience and industry alliances perhaps give it an edge over newer players.

"It's all about how we can trust each other from a customer to a CDMO," the Merck long-timer said.

Competition too is eyeing the mRNA niche, with some like the Indian contract research, development and manufacturing services firm Syngene International Ltd. underscoring that it has what it takes to rein in the cost element to make therapeutics based on mRNA "more dominant" across markets.

"We are set up to make some of the raw materials that are the most limiting for the supplies of what the Pfizer-BioNTech, Moderna vaccines actually use. So that is the component which we can do to bring the cost down," Syngene's chief operating officer, Mahesh Bhalgat, told *Scrip* in a recent interview.

Merck's Opsomer also noted that a key hurdle which the scientific community is trying to address is "efficiency and effective process development" of mRNA vaccines and therapies and drew attention to the company's broad lipid portfolio and custom lipid manufacturing.

"Our portfolio of lipids include synthetic lipids with higher stability, solubility, and improved handling characteristics. All of our lipids are being used in various clinical trials, and some also in marketed drug products," he added.

The success of mRNA in COVID-19 vaccine development and its promise as a treatment well beyond the infectious disease for use in therapeutic vaccines, treatments and diagnostics has catapulted the new modality into the spotlight everywhere in the world. Opsomer also noted how even governments, such as in South Korea and France, are looking at this technology to facilitate development of new drugs.

In 2022, the UK government and Moderna, Inc. firmed up an agreement under which the US company expects to build a state-of-the-art manufacturing and research and development center in the UK. National Health Service patients are expected to have access to next generation of mRNA vaccines and treatments under the collaboration, the partners said in June.

Some industry experts also pointed to Merck's own interest in the segment, on the health care side. In February 2022, Merck and eTheRNA immunotherapies NV signed a research agreement with the aim of investigating the application of eTheRNA's proprietary mRNA design expertise and LNP-delivery platforms to disease areas of interest to Merck, though the latest on the collaboration could not immediately be ascertained.

Ascent Of Single-Use Technologies

Meanwhile, Opsomer also referred to the overall trend in the industry to move to single-use technologies in parallel with the rise of biologics.

While single-use technologies have been deployed to date – they were incorporated into vaccine manufacturing processes following the H1N1 pandemic and were also widely used during the Ebola outbreak in 2014, for example – COVID-19 has accelerated further adoption given the advantages versus traditional vaccine manufacturing setups.

In line with the growing prospects in the area, Merck has invested and expanded its single-use manufacturing capabilities in Danvers, MA in the US, Wuxi in China and Molsheim in France.

"Our recent expansions in Danvers have allowed us to double our production capacity. In 2021, we moved from producing 300,000 single-use plastic assemblies to 600,000 assemblies used in the development and manufacturing of vaccines and other life-saving therapies," Opsomer said.

In April 2022, Merck said it plans to invest about €100m over six years to expand its existing Wuxi production site to bolster biopharma single-use assemblies and custom design capabilities.

"The Wuxi center will support the broad range of Mobius single-use products to support our customers in China and the Asia Pacific region, which will help in improving logistics and lead times on these products for our customers in these markets," the executive added.

Merck anticipates significant momentum over the next five years in the bioprocessing market, with growth in Asia expected to be in the mid-teens and over 20% per annum in China on average, largely led by rising demand for single-use products in advanced biopharmaceutical manufacturing, such as monoclonal antibodies, vaccines and new therapies.

Expanding Manufacturing, Risk Mitigation

Opsomer emphasized that a multi-continent manufacturing footprint also ensures risk mitigation.

"It means that Europe manufacturing could as well serve the APAC market or Wuxi can serve Europe or the US. So it's a kind of risk mitigation that will help us to better serve our customers," he emphasized.

"I think the world is moving from globalization to regionalization. So it was really important for the company to have a plant to manufacture single-use components in each of the regions."

Single-use technology came into operation essentially because it eliminated the need for large, stainless steel bioreactors to make drugs; it also does away with expensive, time-consuming cleaning steps and enhances flexibility and adaptability.

"Single-use has long facilitated the manufacture of biologics because it allows us to have better titers and reduces contamination risks. The range of single-use technologies has also increased to include high-end, disposable plastic mixing bags, storage units and tubing systems," Opsomer explained.

He added that regulatory agencies like the US Food and Drug Administration and the European Medicines Agency were looking at these technologies very closely and "are in favor" of moving to such technology.

"It's all about how can we validate and approve a process and to keep in mind that safety of the patient is at the center of any decision that is taken by a pharma company. But definitely there are a lot of advantages of single-use technology."

Supporting Vaccine Players

The COVID-19 pandemic saw Merck collaborate with multiple players across the globe to accelerate production of vaccine candidates, including with prominent participants such as The Jenner Institute and several Indian companies.

AstraZeneca PLC collaborated with the institute and the Oxford Vaccine Group at the University of Oxford to advance AZD1222 (ChAdOx1 nCoV-19), now widely known as Vaxzevria, its COVID-19 jab.

Merck's collaboration with The Jenner Institute, initiated in 2017, saw the development of a rapid, scalable platform following Good Manufacturing Practices and using disposable technologies for the institute's adenovirus platform. While initial work was conducted with a rabies vaccine candidate, the platform was then validated with different adenovirus constructs to accelerate future development and manufacturing. As a result, the partners could crunch process development time to two months from a year – a critical step to manufacturing the COVID-19 vaccine at scale.

Opsomer recalled how the partners developed the "first use scalable GMP template," reducing the time to as little as one week.

"Our role supported process development and scale up at 10 liters for downstream unit operations and preparation for further scale-up efforts and tech transfers to contract manufacturing organizations," he said.

Merck also supported key vaccine customers in India, including Serum Institute of India Pvt. Ltd., Bharat Biotech and Zydus Lifesciences Limited, among others, the executive noted.

Opsomer underscored that the "people factor" was top priority during the peak of the pandemic and also recounted how the company "analyzed, learned, and pivoted its ways of working" during the pandemic. This meant working in lockstep with local authorities and customers.

"We were able to take care of the safety of our people, but also to send them into the vaccine plants in India in order to help our customers optimize processes and to do technical transfer of technologies and vaccines that have been developed in the Western world," he explained.

"That was again a collaboration but a huge investment on people fully dedicated, I would say, to serve the world."

Globally, in partnership with life science customers and local governments, Merck is supporting more than 80 different vaccine programs, along with more than 50 monoclonal antibody and antiviral treatments for COVID-19.

Edwards Lifesciences' Mike Mussallem: Inspiring People Is A Way Of Life

Whatever The New Technology, For Mike Mussallem, It Starts And Ends With The Patient

Source: Edwards Lifesciences

Edwards Lifesciences CEO Mike Mussallem has a unique and long-standing perspective of what the medtech industry should be and do. In over two decades, he has built the structural heart disease and critical care monitoring company into one of the global medtech industry's most effective innovators.

BY **ASHLEY YEO,** EXECUTIVE EDITOR, EUROPE

BY **MARION WEBB,** MANAGING EDITOR, US

Mike Mussallem has a long memory and a hold on detail from history as if it were yesterday. He recalls the personal dilemmas he had on deciding whether or not to close research programs – some of the "smaller" decisions a CEO must make – just as readily as how he felt during the milestone moments of Edwards Lifesciences Corp.'s evolution.

Those started in 2000, when Edwards Lifesciences Corp. was spun out from Baxter Healthcare Corp. That was a ground-breaking moment for a company with "big dreams of building something special," Mussallem told *Medtech Insight*.

Another big decision came four years later, when Edwards paid $125m to acquire Percutaneous Valve Technologies. That same year, Mussallem joined the board of the Edwards Lifesciences Foundation. His industry insight and decision-making during a 43-year career to date in the medtech industry – including 21 at Baxter – have been instrumental in building Edwards into a $5.2bn revenue company (in 2021), putting it among the leading 25 medtech companies by revenues.

Not that he appears to be one to blow his own trumpet. Mussallem has many drivers and professional ambitions as CEO of Edwards, chief of which is a passion to help patients. Among other things, he prizes a corporate culture of innovation and is a champion of charitable efforts and giving back to society on professional and personal levels.

Beyond that, he has established Edwards' commitment to philanthropy and corporate social responsibility (CSR). Edwards has been recognized for six consecutive years by the Ethisphere Institute as being among the World's Most Ethical Companies. Ethisphere is an organization that defines and advances standards of ethical business practices.

Patient-Focused Innovation Strategy

Mussallem underscored his belief in Edwards' patient-focused innovation strategy when reporting Q3 2022 results on 27 October. They showed a 7% constant currency increase for the quarter. Persistent US hospital staff shortages and COVID headwinds in Japan held the revenue total back, at $1.3bn.

He also reported on recent next-generation technology and clinical trials breakthroughs, including new EU and US regulatory milestones for the transcatheter mitral repair technology Pascal Precision; and, from the transcatheter aortic valve replacement (TAVR) business, US approval to sell the aortic Sapien 3 Ultra Resilia heart valve.

Edwards expects the global TAVR opportunity to reach $10bn by 2028, and Mussallem notes that OUS penetration by the aortic stenosis technology remains "quite low."

As to the near-term outlook, he said that foreign exchange movements will keep full-year 2022 revenues at the lower end of the $5.35bn-to-$5.55bn guidance. A difficult COVID and winter flu season will have impacts into 2023.

Delivering Care: 'It Takes A Village'

COVID created tough operating conditions for the medtech industry generally, but for Mussallem, a bigger picture became clear as the pandemic underscored the vital nature of medtech for patients.

COVID was also "a great reminder that it takes a village to actually get treated," he told the 2021 MedTech Forum in Brussels.

Industry, providers, regulators and payers all came together, their collective efforts shining a strong light on health care to leave positive legacies in the adoption of telehealth, digital care and remote connectivity. The trend towards virtual proctoring to guide surgeons through complex cases from remote global locations was also expedited.

However, nothing can replace the person-to-person approach, Mussallem said, promising that Edwards will remain a "high-touch" company as far as the patient is concerned. "The pandemic taught us the value of our health, and COVID-19 will help us prioritize our health," he said. It will also drive the democratization and decentralization of care.

Edwards' operational adjustments in the wake of COVID are still ongoing, but how things work in practice for Edwards' employees on a day-to-day, routine basis, post-COVID, is not just for Mussallem to decide. The tendency as a leader, he said, is sometimes to want to grab for more control. "But in moments like this, it's almost better to trust our leaders and trust our employees to come up with the right solution."

Leadership Qualities

If this is a textbook way of inspiring staff and colleagues, Mussallem has learnt the process by heart. He gives credit where it is due, shares accolades and openly rewards effort, as he did in commending staff who put in an "extra shift" during COVID.

"If you're looking for a leader, the idea of someone who brings others along who is less focused on themselves but counts their accomplishment as those that they have brought along is very special," Mussallem said. Inspiring colleagues in this way appears to be ingrained in the Mussallem approach to management.

> **"The lure was to drive entrepreneurial innovation in a way that is not quite the same as at a number of other companies."**
>
> Todd Brinton, CSO, talks about an Edwards' philosophy

For instance, his compelling way of selling the company's innovation ambitions was the reason Todd Brinton left a long career and successful role as clinical professor of medicine at Stanford University School of Medicine to become Edwards' corporate VP of advanced medical technology and chief scientific officer in 2019.

Talking to *In Vivo*, Brinton explained: "The lure was to drive entrepreneurial innovation in a way that is not quite the same as at a number of other companies. We have a lot of opportunity for growth, and our innovation strategy is really key to executing."

Had Mussallem not come calling, Brinton might well still happily be solving the challenges a medical school poses. As it is, he now works for a company that put almost $1bn into R&D in 2022, and which has averaged R&D spending of 16-18% in the past decade.

Challenges For A Leader To Face

Marion Webb, managing editor at *Medtech Insight*, a sister publication of *In Vivo,* traveled in fall 2022 to Edwards' California global HQ to ask Mussallem, among other things, about how he makes the necessary tough decisions in the medtech industry.

Marion Webb: What have been some of your biggest challenges in leading Edwards?

Mike Mussallem: One of the greatest challenges is maintaining the innovation culture. As a board and as a company, we always talk about how to maintain the culture of staying innovative and staying patient-focused as we get bigger. As you grow, do you become more conservative and not really reach for the big innovations? Do you decrease your tolerance for failure? If you're going to be a bold innovator, then failure is part of it.

As to big decisions, I don't think that you can make them alone. I think you owe it to yourself to listen to a lot of voices – the believers and the non-believers. But personally getting involved, not delegating to somebody else but actually owning the decision, is part of it. For example, on discontinuing a program, the biggest thing is how you treat the team that was

engaged in that program. In many cases, they have put their heart and soul into that innovation. Not in any way should we have that team feel like they were failures.

What are Edwards' biggest accomplishments?
I think it starts with culture, this idea of really declaring that we're here because of patients. That's why we exist. Helping patients is our life's work. That it's always patients first, that it's our priority, is ingrained with our team, and in many cases, that's why they come to Edwards.

We have a culture that prioritizes innovation and picking chances to do something big, like changing the practice of medicine and then backing it up with evidence.

I'm so proud of what we've done, for example, in areas like transcatheter aortic valve replacement. To actually be able to routinely replace valves in under an hour and have patients go home in a day or two has turned out to be a remarkably positive development for patients with aortic stenosis.

The ESG agenda looms large for medtech. Describe Edwards's approach inclusion and diversity.
At the industry level, we're having much more conversation about inclusion and diversity. For me, it starts with the patients. We know that we're leaving a lot of patients behind. There are groups that are underserved that maybe never get access to the medical technologies.

That leads to a lot of really thought-provoking questions. For instance: What are the reasons for that? Is there something wrong with the system that serves those people? Are they being served by doctors that look like them and talk like them and with whom they're comfortable having relationships? Is there sufficient clinical data that's being generated by those groups? We probably need to improve in terms of the way that we operate.

"That it's always patients first, that it's our priority, is ingrained with our team."
Mike Mussallem, Edwards Lifesciences

Charitable activity and giving back to society is a cornerstone of Edwards' culture?
The list of all the charities that we support in the local area is quite long. The Edwards Lifesciences Foundation has gifted almost $130m to non-profit organizations worldwide. It has invested more than $30m and employee hours in an initiative called "Every Heartbeat Matters," which aims to improve the lives of an additional 2.5 million underserved structural heart and critical care patients by the end of 2025. We also work very closely with United Way and the American Heart Association.

One that I'm most proud of is Washington Elementary School (Santa Ana), where 70% to 80% of the kids are food-insecure and don't have secure homes. Our employee base has embraced them, and tries to open their eyes to a future of science, technology, engineering and math that would stimulate them to get excited.

This is a personal not only a corporate drive for you?
I just feel very fortunate to have a career where I've been able to earn money and be successful beyond what I ever imagined or ever dreamed. I'm engaged in organizations that relate to the help that I got when I was growing up, whether it's trying to do something nice for places like my hometown Gary, Indiana, or for the Rose-Hulman Institute of Technology, the college where I was able to get an engineering degree, and generally support those that have a willingness to work hard and move up and who need a little bit of a break in life.

Giving back to the communities is something that we take very seriously.


MIKE MUSSALLEM

Leadership Continuity

Under Edwards' succession planning, Mussallem announced on 8 December that he would retire as CEO and stand for election as board non-executive chairman at the May 2023 AGM. Succeeding him as CEO will be Bernard Zovighian, who has been with the company since 2015.

The full interview by Marion Webb, Getting Personal With Edwards' Mike Mussallem: Hard Work, Giving Back And Changing The Practice Of Medicine, was published in Medtech Insight on 17 October 2022.

Why Patient-Centered Care Has To Change

Going The Last Mile Is Taking Longer Than It Should

A typical word cloud for discussions around patient-centered care would feature: business model, digital health, financing, PPP, resources, data sharing, staffing and escalation of costs. But so many other words are missing, which is why patient-centricity risks getting stuck in its current incomplete form. What are medtechs to do?

BY **ASHLEY YEO,** EXECUTIVE EDITOR, EUROPE

The term patient-centricity has tripped off the tongue for a decade or more. The words have a pleasing sound and are associated with a positive impact. They describe a place where providers, the medtech industry and, it may sometimes be forgotten, the patients themselves, all want to go.

Health care goals don't get much better, but are doubts being cast on the ability of ecosystems to deliver fully on the dream of patient-centered care, as viewed though the patient's own lens?

This theme was taken up by the Asia Pacific Medical Technology Association (APACMed) during its annual medtech forum, which for 2022 was a part virtual, part in-person conference hosted from Singapore. The broad array of the immediate post-COVID and longer-term challenges for the association were explained in a podcast interview with *In Vivo* by new APACMed chairman John Collings.

The issue of how to deliver to patients the care that they want, where and when they want it was taken up by keynote speaker Becton, Dickinson and Company's chief scientific officer Joseph Smith, and revisited on many panels across the two-day format.

The consensus was that patient-centered care needs are very different, depending on the point from which they are being viewed. The industry, providers and patients do not necessarily share the same priority agenda.

For all the talk of the need for interoperability of delivery systems, patient-centered care might actually be moving further away from, rather than nearer to, reality. There is a renewed risk of silos being built around individual programs of care. Corporate investment plans are made around proprietary technologies. It seems that barriers are harder to dismantle than to erect.

GE Healthcare's Vijay Subramaniam said that persistent barriers to access to care reside in a general lack of awareness about care possibilities, affordability issues and resources simply not being available. The medtech industry's role is to put technology in the hands of providers, he said, for example the company's Vscan hand-held ultrasound for use in rural settings.

It also has a duty to partner, including with ministries of health on outreach needs, such as delivering SMS reminders to patients inviting them to get their health checks done. Private-public partnerships (PPP) have a role in helping provide essential care. GE works with both private and public companies, said Subramaniam, general manager for imaging in the ASEAN, Korea and the ANZ region.

Telehealth: Must Do Better

Medtechs also have an opportunity to open up care possibilities, especially bearing in mind current global health care resourcing and staffing issues. Familiarity with telehealth in the community rocketed during COVID-19, but GE is pressing the need to provide telehealth in the critical care setting, and to better leverage tele-ICU capabilities.

Increased access to telehealth was a fortuitous outcome from the pandemic, but it's not yet "job done." In fact, far from it. Many patients in the global arena are still not able to access telehealth, and 1.6 billion people in the APAC region have suboptimal access to care, said APACMed chief executive Harjit Gill. That is more than the individual populations of the world's two most populous countries.

The contention is that 70% of the world's population has access to telehealth, Aparna Mittal, founder and CEO of PatientsEngage, observed. "But what about the 30%. Should they just be left behind?" asked Mittal, whose Singapore-based company offers an Asia-focused online health care platform for the management of chronic disease.

Behind the headline claims, access to telehealth is disparate and diverse, and people's use of telehealth is different. "We need to look at how we can simplify and keep looking at innovation that reaches the last mile," Mittal said.

More at-home care is part the future solution for delivering effective care more affordably, but with 90% to 95% of chronic disease management happening outside the acute clinical arena, supporting all patients at home is a major challenge. Similarly, while much progress has been seen in diabetes, where at-home care has moved forward, in other areas patients might not be so ready to engage.

For all the perceived and actual advantages of home dialysis, say, some patients oppose it, as it stands as is a constant reminder that they are unwell. "Patients are not one monolithic body; different patients and different care givers have different needs, and will navigate [the health care journey] differently."

On the other hand, the pandemic showed how hard it was for patients to keep up with guidances coming from the medical and healthtech community. Kidney patients in Asia were afraid to travel into clinics for their dialysis, and but at the same time, guidance was lacking on the necessary frequency of their dialysis sessions, for instance. The real need is to filter relevant guidance "right down to the last mile," Mittal observed.

Need For Partnered Care

She added that while the industry has been talking for the past decade about the value of patient-centered care, it is "patient-partnered care" that the health care community should be moving towards. Until patients are treated as shared decision-makers, health care improvements will not accrue at the point where it matters.

Patients react to their disease differently, but we tend to treat them the same, Mittal said. "We are not seeing the patient as a person, merely in the context of their disease."

In a region like APAC, there is also a need to look at languages, socio-economic strata and socio-cultural issues. People are exhorted to get all the tests and scans available, but "just as there is a fear of missing out, there is also a fear of finding out." Mittal suggested that most people don't want to know the results of their scan. And women especially are uncomfortable about seeking a test, and moreover need to be accompanied for their scan. "It's complex."

> **"We are not seeing the patient as a person, merely in the context of their disease."**
>
> Arpna Mittal, PatientsEngage

Mittal's biggest fear is that, as technology has advanced, it has also become increasingly siloed, with doctors becoming more and more specialized.

The very bottom line is that the concept of generalized patient-centered care might even be getting harder to achieve. Some red flags were raised around this contention during APACMed's annual meeting, which was themed as "Patient Futures 2025."

That does not mean medtechs or providers are not working hard to fill the gaps. However, it is useful to look below the surface, and the APACMed forum was a chance to do just that. If patient centricity is a journey, it is proving to be a long and thoughtful one.

The Moment Is Now – But What Is True Connected Care?

Patient-centered care is by no means a new concept, but a new inflection point has been reached, which, said BD's Smith, is down to a confluence of technology maturity, heightened expectations about the way technology is used, and a slew of new proof points about digital health relating to how the pandemic was managed.

"The right time to do this is now, and I have never felt more in the moment," Smith said, referring to the tailwind behind patient-centered care.

The Franklin Lakes, New Jersey company has partnered with Singapore-based digital information safeguarding company Accredify, which specializes in verifiable data and precise automation that is "pioneering the world's transition to 'TrustTech' through verifiable data and precise automation."

Simon Gordon, the chief commercial officer of Accredify, offered a non-medtech industry view of how patient-centric care should be delivered. There is a commonly-held utopia notion of what connected care will look like, he said, but he asked: "How will we achieve true connected care?"

> **"There's a chance in the next three years of us going backwards."**
>
> Simon Gordon, Accredify

One option is to connect together all the IT systems a patient interacts with on their care journey and achieve the result of having all the data in one place. But the practical challenges make that unfeasible, he said.

BD's Smith was similarly doubtful that this paradigm of interoperability would be reached. Industry has struggled with this, he said, because there is a value to the data. Business forces can get in the way of there being real interoperability. The fear is that companies that are smoothly interoperable can become "smoothly replaceable." Interoperability also speaks to the need to build in heightened security.

Smith believes that the onus resides with the provider organizations to call for information that is sharable. Providers would thereby become the "architects of information flows" in the way that the ecosystem is demanding. "It's not a technical challenge, but it is partly a business model issue," he said.

The Patient As The Interface

Gordon suggested that the approach devised by Accredify/BD represented a very different way of tailoring health care to the individual. "Our focus is on using the patient as the interface between the different solutions – for example, to have the patient receive tamper-proof records issued by a health care professional that the patient can store and share with whomever."

This, said Gordon, is a more practical solution and a quicker way of achieving patient centricity. He continued: "It's a big challenge, and certainly by 2025 we don't expect widespread adoption of this sort of approach. But we can make meaningful progress if we look at a defined problem." Patients can share results with stakeholders who are interested in the records.

This sort of patient-centric initiative can lower costs, drive better outcomes and add value. But in the wider realm of patient-centric ambitions, uncertainty is in the air.

Up ahead, as more stakeholders implement connected care in more areas, there is a risk that, with decentralization pushing more care out to the community or the home, the net result will be more data silos rather than less.

Echoing Mittal, Gordon said: "There's a chance in the next three years of us going backwards. Without some sort of integration we'll end up with a less patient-centric position that where we are now – even with advances in technology.

Borrowing a pet expression of Edwards Lifesciences Corp.'s CEO Mike Mussallem, the Accredify CEO said that the delivery of patient-centered care "takes a village." He added: "We must pick an area to focus on and show that this sort of approach is valuable."

Coda: Industry Should Make Adoption Easier

Smith indicated that the persistently suboptimal level of patient-centricity was partly down to industry. "While we are good at addressing unmet need, we are not yet great in terms of getting adoption."

He continued: "We don't always bring all the data and we miss [the opportunity before us] by not making the right thing to do the *easiest* thing to do."

"We will fail if we create great solutions that are a little hard to get work, or if the use of which results in reimbursement going down, or that are complicated and will take some getting used to. Products must be intuitive. Ease of use, for clinicians, must mean: 'When I use it, my life is easier'."

Nevertheless, health care stakeholders stand before a unique opportunity, according to Mick Reid, the former director general of health for New South Wales and Queensland, Australia. He felt that coming out of COVID, the sector can really gain benefits, with new perceptions of the role of data, technology, research and the rapid application of innovations.

Optimistically, he noted stronger ties between governments and the private sector than in the past, and probably stronger partnerships within regions as supply chain narrows down to smaller areas with a more regional focus. It is positive perspective, he said.

It would be more positive still if the patient/consumer had a solid place in the design of health care systems and more control around their care modalities. At the end of the day, it's down to policy-makers to decide where they wish their policies and plans to be focused, Reid concluded.

Whatever they decide, dismantling barriers to true and comprehensive patient-centered care should be pushed back up to the top of the agenda.

> **"Coming out of COVID, health care can really gain benefits, with new perceptions of the role of data, technology, research and the rapid application of innovations."**
>
> Mick Reid, former director general of health for New South Wales and Queensland, Australia

Evolving Technology: Regulatory Outsourcing In A Collaborative World

Regulatory outsourcing has a long and arduous history. Going back 20 years, regulatory activity was always stringently retained in-house by organizations. For many, it was viewed as part of a core competency for organizations, and some elements of regulatory still are today. It wasn't until after technological advancements in operationalizing and digitizing activities such as regulatory communications and submissions that drug registrations were able to be performed more effectively. Basic activities such as faxing or mailing regulatory information to health authorities paved the way for sending electronic submissions.

MICHELLE GYZEN, SENIOR DIRECTOR OF STRATEGIC REGULATORY SOLUTIONS AT IQVIA

The electronic submission process is where the capabilities to outsource started to become a reality. It is through technology's advancement that the industry learned how to better operationalize to make outsourcing a viable option. As Michelle Gyzen, Senior Director of Strategic Regulatory Solutions at IQVIA, explains, "It was the earliest form of remote working in life sciences as far as I can tell, because we realized we didn't necessarily need to be sitting in headquarters anymore. We could outsource that activity to vendors in regions across the globe." At this point, China was one of the major early outsourcers, followed by India, which has since maintained its lead.

Current Processes Based On Past Experience

Fast forwarding to the present, the industry is able to outsource nearly all of its regulatory operational activity. On average, however, only about 50% is outsourced. For larger scale operations, the number increases to about 75%. By combining technology with expertise, Gyzen has seen the industry not only recognize increased automation capability for more processes, but companies have also increased their trust in vendors: "They are more willing to let go and allow a trusted partner to handle more regulatory services." COVID expedited this trend, with the regulatory outsourcing market doubling in size.

Gyzen notes that the market now includes "all regulatory activity, not just regulatory operational activity." It is clear that companies are looking to streamline their processes and operationalize regulatory activities, especially at a large scale, reducing communication delays by 20%, which ultimately reduces speed to market and associated cost. Furthermore, Gyzen highlights an additional factor contributing to the reduction to cost, "Triple the amount of vendors have entered the outsourcing market within the last seven years, which is actually driving competitive pricing in the market."

The Regulatory Strategy Challenge

Operationalizing regulatory strategies still remains a challenge for the industry, as reflected by only 25% of total regulatory strategy activity being outsourced. As of today, outsourcing is mainly in the form of consulting, either by smaller consulting firms or contract research organizations (CROs). While sponsors are seeking outside expertise in this area, they are still keeping regulatory strategy in-house. This is largely due to the challenges associated with developing independent strategies for drug products. This regulatory process development requires a thorough understanding of a company's actual business and business goals, which can be challenging for both the sponsor and the partner to outsource.

Understanding the hesitation for sponsors to outsource regulatory strategy activities, Gyzen recommends a hybrid solution, where companies still retain control in-house. "There are elements of strategy that can be operationalized, such as the analytics of regulatory precedence, global expansion, and milestones. The operational components of strategy are able to use technology to support cohesive regulatory strategic activities and regulatory intelligence." Such a solution, however, still allows companies to set and determine the strategy at a higher level, which is balanced with overall business strategy and business goals. These higher-level conversations and decisions affect regulatory and stay in-house with the companies.

Looking towards the future, Gyzen feels that the industry is going to experience the same shift in regulatory strategies as it has with all other regulatory activity. "I think sponsors will rely on experienced partners to operationalize regulatory strategy as future innovative tools are designed for just that. We are working with next generation technology to create these tools for sponsors."

Technology's Future Influence On Outsourcing

Technology is designed to streamline processes, and it currently does just that for regulatory activities. Because technology allows the industry to do more with less time and human resources, it enables sponsors and partners to work faster. Today, technology in regulatory activities focuses mainly on gathering data information, but Gyzen sees potential for growth in this area. "Technology of the future is going to be more regulatory data and intelligence gathering but combined with smart automations and predictive analytics, which doesn't necessarily exist today."

Gyzen further explains, "Rather than just inputting data and allowing us to peruse information and run reports, we are developing intuitive systems that guide the user's entire regulatory experience. What we are doing is exploring the next step of AI and automation utilization." The goal is to guide the regulatory process while reducing associated risks.

This is where past insights are crucial. All of the data and experience of working with regulators and noting what has worked in the past provides a strong foundation for the future. Gyzen notes that the ultimate goal is to create standardized regulatory systems at a global scale, to work with health authorities around the world.

"I think sponsors will rely on experienced partners to operationalize regulatory strategy as future innovative tools are designed for just that. We are working with next generation technology to create these tools for sponsors."

Michelle Gyzen, IQVIA

Collaborative Global Change

Working with health authorities globally requires change. This change, however, comes from both sides: regulators and sponsors/sponsor partners. Previously, regulatory guidance would change, and life sciences companies, along with their outsourcing partners, would be left scrambling. To keep up with the future, Gyzen points out that "both sides need to collaborate to develop more unified and integrated processes and procedures." Such collaboration is the only way to push forward into the future and streamline the process of getting critical products for patients to market quicker.

The framework for such a partnership is already in place with Project Orbis, a collaboration between the national health regulators of Australia, Brazil, Canada, Israel, Singapore, Switzerland, the UK, and the US, with countries such as Japan looking to adopt as well. These countries have come together jointly to create a standardized approval process for oncology drug products, and the outcome has been to significantly streamline the process, reducing approval times by around 28%. For outsourcing partners, Gyzen highlights that they must be aware of the global regulatory climate. Gyzen states, "When global health authorities start collaborating, it is important to not only be aware of and participate in the initiatives, but understanding that this is the last frontier and will really drive innovation to increase efficiency into the drug product approval process."

Changing With The Future

As global health authorities continue to set the framework for streamlining the approval process, regulatory outsourcing is going to be imperative to successfully work with newly created and developed initiatives. As the industry transforms, sponsors will need to also undergo a business and change management transformation. This largely entails understanding what a functional regulatory organization needs to look like for the future and making technology a priority in change initiatives. Experienced regulatory partners are able to guide sponsors with the best practices, but mostly companies must understand what their outsourcing goals are and why. As Gyzen notes, "Companies need to know whether they are looking for cost reduction, global expansion, supplementing resources, or a combination of all of the above, and their own limitations." Organizations often struggle with balancing the need for efficiency and retention of process control. Such questions need to be addressed early on, as well as setting the end goal, whether it is to manage the process in-house or to have an outsourcing partner continue managing the process.

Ultimately, Gyzen recommends that the best approach when collaborating with an outsourcing regulatory partner is one of honesty and openness. "When companies are as forthcoming as possible in terms of where they are today and what their future goals are, outsourcing partners are in a better position to provide the best guidance to benefit sponsors."

For more information, visit https://www.iqvia.com/solutions/integrated-global-compliance/regulatory-compliance/global-regulatory-affairs-services

2023: A Bumpy Road Ahead For Implementation of Medtech Regulations

Originally intended to increase medical device safety, the implementation of the EU's medtech regulation was so hampered in 2022 that it had started to look as if the new regulations were a bigger potential threat to patients than any of the scandals leading to its more stringent requirements. With the European Commission's latest plans to ease challenges around implementation, will 2023 be a more positive year for the EU medtech sector?

BY **AMANDA MAXWELL,** MANAGING EDITOR, EUROPE

During 2022, there had been little that had been straightforward when it came to the implementation of the EU's new Medical Device and IVD Regulations. Originally due to first apply in 2020 and 2022 respectively, the slow rate of preparedness of the system and of its players resulted in warnings about products having to be unnecessarily withdrawn from the EU market and continuous calls to extend deadlines throughout the year.

As 2022 was drawing to a close, the volume of noise from the industry, notified bodies and even national regulatory authorities calling for extensions in the deadlines for compliance with the MDR, or some other manageable solutions, had reached fever pitch.

The main concern was the insufficient capacity at the third-party certification organizations, the notified bodies, to assess the conformity of all devices against the MDR in time for the 26 May 2024 hard deadline for the many products that have able to make use of a so-called grace period and are still in compliance with the medical device directives.

If the capacity issues and current deadlines remained as they were, actors argued, large numbers of products would continue to become non-MDR-compliant because of the lack of availability of notified body bandwidth to evaluate them under the new regulation. And this would mean they would need to be withdrawn from the market, regardless of their safety history or of the vital contribution they may make to patient care. Indeed this worrying scenario has already been unfolding over the last couple of years.

The only thing that could stop this crisis, or put an end to the extent of the damage, was a radical decision from the European Commission over allowing legacy products (those CE marked under the context of the former medical device directives), to somehow remain on the market longer, thereby taking some pressure off the notified bodies and spreading the load over more years.

Notified Body Capacity

The extent to which manufacturers were and are still likely to be impacted by notified body overload depends on whether they were already clients of notified bodies that have already been designated, and whether their notified bodies have sufficient capacity in their particular product area.

But planning at notified bodies became a "nightmare" in 2022 the words of Françoise Schlemmer, director of the EU notified body association, TEAM-NB.

While notified bodies had some spare capacity in particular products codes, this is "definitely a moving target," she had admitted.

Problems at the notified body level have been multiple. New and changing guidances are labor intensive as the testing organizations, and indeed manufacturers themselves, try to adapt. There are also challenges recruiting and keeping notified body auditors, as well as training them.

Moreover, additional valuable time has been lost because companies' applications are often incomplete or inadequate or manufacturers make applications to notified bodies that do not offer the scope of designation needed for the companies' products.

Call For Action

The situation became so critical that stakeholders spent many months of 2022 dedicating their resources to lobbying the European Commission, members of the European Parliament and member state health authorities for a new, more positive way forward.

Hopes of new measures to support the sector and better manage this crisis, were being pinned on a meeting at the Council of Europe on 8-9 December. The meeting did not disappoint.

Despite concerns that the commission had repeatedly refused to allow any further extensions to the MDR after having already delayed (but only at the very last minute) the MDR's original date of application from 26 May 2020 by one year, it made a promising presentation to EU health ministers on 9 December at the ESPCO meeting of the Council of EU

There it proposed to defer the deadlines for MDR implementation from 26 May 2024 to 26 May 2027 for high risk, class III and IIb devices, and to 26 May 2028 for medium and low-risk devices, classes IIa, and class I needing the involvement of a notified body.

It also promised a document, which was then published almost immediately after the meeting, which explains how legacy devices can remain on the market once their former certificates have expired under the Medical Devices or Active Implantable Medical Devices Directive (MDD and AIMDD).

Hopes of new measures to support the sector and better manage this crisis, were being pinned on a meeting at the Council of Europe on 8-9 December. The meeting did not disappoint.

This position paper aims to promote a common understanding of, and a uniform approach to, the application of the MDR's Article 97 which allows member states to agree to products that are not MDR compliant (in this case because the legacy certificate has expired) remaining on the market under given conditions.

The new measures are intended to apply to legacy devices which are in transition from the MDD or AIMDD to the MDR for which, despite reasonable efforts undertaken by the manufacturer to obtain certification under the MDR, the relevant conformity assessment procedure involving a notified body has not been concluded in time.

The commission's proposals were welcomed by the health ministers at EPSCO, and more work is to follow to legally adopt the commission's proposals.

Why There Are Different Deadlines

The revised MDR date of application was 26 May 2021.

As of this date, the following devices had to be in full compliance with the MDR:

- New products.
- Products which had certificates under the former medical device directives which had expired.
- Products where there had been a significant change in the design or intended purpose.
- Class I products that are not being upclassified to need future notified body involvement.

This was a tall order. Many of the necessary documents and structures had still not been set up, making it impossible for some companies, including those with products falling under the MDR for the first time, such as Annex XVI (non-medical products, such as breast implants and dermal fillers), to be able to comply.

Many documents and structures were still being drafted and created at that stage, and indeed still are, not least the pivotal European medical device database, Eudamed. Also, the rate at which standards are being harmonized under the new regulations has been painfully slow.

Products Benefiting From The Grace Period

So much for those products where manufacturers had no other choice than to meet the 26 May 2021 deadline.

The situation for all other products that have certificates that are still valid in the context of the directives, and where there have been no significant changes in their design and intended purpose, has been that they were entitled to remain on the market until 26 May 2024 if they had met certain MDR conditions, related to:

- Post-market surveillance.
- Market surveillance.
- Vigilance.

Registration of economic operators and of devices apply already in place of the corresponding requirements in the directives.

This means products that already required the involvement of a notified body in the context of the medical device directives, i.e., of Class I sterile and measuring devices, class IIa, class IIb and class III can benefit from this grace period.

Moreover, a late amendment was made to the MDR permitting class I devices self-certified under the current MDD, but which are being upclassified under the MDR, to benefit from the grace period as well. This applied to class I reusable surgical devices; some substance-based devices, such as throat lozenges, nasal spray and inhalers, certain software, and devices with nanomaterials.

Artificial 2024 Deadline

As things stood just before the EPSCO meeting, even if the five-year certificate granted under the directives would not normally expire for legacy products until after 26 May 2024, they still had to be removed from the market on 26 May 2024 whatever the extent of notified body bottlenecks and delayed documents or structures. That is unless they have been CE-marked under the MDR.

Given the breadth of devices hitting this bottleneck in 2024 (see below), all hopes were therefore pinned on some solution allowing these products to remain on the market pending formal compliance with the MDR regardless of whether their certificates expire before or after the 26 May 2024 deadline but as long as they have already been taken on by a notified body, as the commission is now suggesting.

Notified Bodies Numbers

At the time of writing, there were 36 notified bodies designated under the MDR and just seven under the IVDR, although an eighth was due to be designated on 23 December.

These totals compare with over 80 under the former Medical Devices Directive and 22 under the former IVD Directive at one time.

A full list of notified bodies designated under the MDR and links to their scope of testing is available here.

Some may argue that the discrepancy in resources is not as severe as it may look because the larger notified bodies have already been designated and have taken on significantly more staff.

Others will counter that the MDR and IVDR requirements are much more stringent than those of the former directives and notified body involvement and level of involvement has increased so much.

Figures released in October 2022 by the EU association of notified bodies, TEAM-NB, have given the sector cause for alarm.

But the irrefutable evidence is that there is simply not enough testing capacity for the 2024 deadline.

Figures Show Impossible Situation Ahead

Figures released in October 2022 by the EU association of notified bodies, TEAM-NB, have given the sector cause for alarm.

In total at that point, 1,990 conformity assessment certificates had been granted under the MDR, compared with 8,120 applications made to notified bodies for the assessment of products under the MDR since the beginning.

Moreover, this is just the tip of the iceberg.

The following table demonstrates the scale of the certificate mountain relating to products already certified under the former Medical Devices Directive (MDD) and Active Implantable Medical Devices Directive (AIMDD), and which now fall under the scope of the MDR, and which are still on the EU market.

Number Of Current MDD/AIMDD Notified Body Certificates And Expire Dates

2022	1,387
2023	4,311
2024	17,095
Total	22,793

Source: Data presented at the recent Medical Device Coordination Group meeting on 24 October

While there are 22,793 further existing certificates under the medical device directive and active implantable medical device directives due to expire, these figures do not even include applications for the assessment of all the new products coming onto the market under the scope of the MDR.

There have even been suggestions that somewhere around a quarter of products on the market will be retired when certificates expire. But even if that were to be the case, it would still leave a mountain of over 17,000 legacy products to be recertified under the MDR in addition to totally new products too.

POLICY & REGULATION

Battle Over Patents And Drug Pricing Engulfs FDA And USPTO

President Biden and Congress are pressuring the agencies to change patent policies so brand manufacturers cannot delay generic and biosimilar competition to keep monopoly prices.

BY **BRENDA SANDBURG,** SENIOR EDITOR, US

Efforts to rein in the cost of prescription drugs took a new direction when President Biden called on the US Food and Drug Administration to communicate with the US Patent and Trademark Office about misuse of the patent system to delay generic drug and biosimilar competition.

The mandate, included in Biden's June 2021 executive order on "Promoting Competition in the American Economy," led the two agencies to enter a collaboration to develop initiatives to help facilitate access to affordable drugs.

Members of Congress followed with their own demands. They sent a flurry of letters to the heads of the FDA and USPTO asking them to take action against patent practices that extend a manufacturer's monopoly on a drug. The appeals have had an impact. The USPTO issued a request for comments on its proposed initiatives, which incorporates questions raised by a bipartisan group of Senators. (*See timeline*).

Former USPTO Director David Kappos, a partner at Cravath, Swaine & Moore, said in an interview that the pressure on the agencies to work together to change patent policies as a way to cut drug prices is unusual. "It's easy to say if not for patents, prices would be lower. But government data shows that 92% of healthcare cost has nothing to do with patents."

It remains to be seen if the actions the two agencies take will change the patent process and the number and types of patents issued. But the new role imposed on them has heightened claims that patents are tied to drug pricing and the argument over what to do about it.

"I think the PTO and FDA should each stay in their lane and focus on doing their jobs."

Irena Royzman, Kramer Levin Naftalis & Frankel

Continuation Applications And Patent Thickets

At Biden's request, then-Acting FDA Commissioner Janet Woodcock sent a letter to the USPTO acting head noting that "the impact of certain pharmaceutical company patenting practices on the pharmaceutical marketplace has attracted attention within the debate over drug pricing." She cited the practice of filing "continuation" patent applications that can allow companies to create "patent thickets" by obtaining multiple patents on different aspects of the same product within a patent application. She also noted concerns about patent "evergreening," in which changes to previously approved drug products, such as a new formulation or additional method of use, are patented.

Woodcock asked if the patent office was considering means of limiting such practices. Nearly a year later, USPTO director Kathi Vidal replied in a letter to Commissioner Robert Califf, listing numerous initiatives regarding drug pricing that the agency plans to take. On 6 July, the day the letter was sent, Vidal and Califf issued a joint blog post announcing their collaboration on planned initiatives to expand resources available for assessing patentability and addressing instances of patents being used improperly to delay competition.

The two agencies have historically worked together, particularly on determining whether a patent term should be extended due to a delay in a product's regulatory review period. They also have shared information and technology and this exchange is likely to increase. Vidal said in her letter that the patent office will provide examiners with training in collaboration with FDA on publicly available FDA resources that can be utilized in prior art searches.

Vidal also noted that the USPTO is considering whether to apply greater scrutiny to continuation patent applications in large families and/or the use of declaratory evidence to rebut an examiner's determination of unpatentability. The agency is also exploring whether any changes need to be made to the patent system regarding obviousness-type double patenting, in which a patent owner seeks a patent for an obvious variation of an innovation covered by another of its patents.

Vidal noted that under current practices, a patent applicant is required to file a terminal disclaimer so that the later patent application on an obvious variant of an earlier patented invention may not be used to extend the term of patent protection. She said that although a terminal disclaimer ensures that the later patent will have the same term as the earlier patent, multiple patents directed to obvious variants of an invention could potentially deter competition if the number of patents is prohibitively expensive to challenge in post-grant proceedings before the Patent Trial and Appeal Board (PTAB) and in district court.

Six senators raised concerns about patent thickets, which they said are primarily made up of continuation patents, in a 8 June letter to Vidal. The senators: Patrick Leahy, D-Vt., Richard Blumenthal, D-Conn., Amy Klobuchar, D-Minn., John Cornyn, R-Texas, Susan Collins, R-Maine, and Mike Braun, R-Ind. asked her to consider changes to PTO regulations and practices to improve patent quality and eliminate large collections of patents on a single invention.

They specifically asked how the elimination of terminal disclaimers would affect patent prosecution strategies and patent quality, if the filing of a terminal disclaimer should be an admission of obviousness, and whether there should be heightened examination requirements for continuation patents to ensure that minor modifications do not receive second or subsequent patents.

Vidal heeded their ideas, so much so that she included their questions verbatim in a request for public comment on the USPTO's proposed initiatives. The request, issued in a 4 October Federal Register notice, focuses on continuation applications, obviousness-type double patenting, and whether applicants need to provide more information to support certain claims.

"Recommendations to further improve prior art access would be good, but recommendations to increase the value of valid patents would be even better."

David Kappos, Cravath, Swaine & Moore

Agencies Should 'Stay In Their Lane'

Some stakeholders are concerned that the FDA and USPTO have been pulled into the fight over patents and drug pricing. Irena Royzman, a partner and head of life sciences at Kramer Levin Naftalis & Frankel, said the questions the patent office posed about its proposed initiatives are fairly focused on PTO practice and how the agency can improve the quality of patents. But she said they also seem explicitly aimed at the biotech and pharmaceutical industries where patents by and large are of higher quality than those in other technologies and fare better before the PTAB.

"I think the PTO and FDA should each stay in their lane and focus on doing their jobs," Royzman said. "The PTO's job is to produce quality patents without focusing on any particular industry or particular product and FDA's job is to make sure generic drugs and biosimilars are safe and are rigorously tested and meet the same requirements as innovative drugs."

"The focus on the number of patents is wrong," she said. "The suggestion that there should be greater collaboration

between the FDA and the patent office or that the patent office should have anything to do with pricing" is not the PTO's job.

Robert Cerwinski, managing partner of Gemini Law, questioned whether PTO's initiatives will have much impact since the patent office is not proposing to change the patent statute or the number of patents that the reference product sponsor can obtain.

"Unless you actually change the patent law, the patent office is constrained on how far they can take these initiatives," he said. "It is not until we get statutory reform that we will see the thicket strategy substantially weakened or disappear because it's working well for reference product sponsors."

Congressional Efforts

Members of Congress have introduced numerous measures over the past several years that target patent practices but they failed to clear the House and Senate.

Sen. Cornyn put the spotlight on patents at a February 2019 Senate Finance Committee hearing in which biopharma executives were grilled about drug pricing. He recommended that the Senate Judiciary Committee launch an inquiry into drug patents following an exchange with AbbVie Inc.'s CEO over the more than 100 patents on Humira (adalimumab).

Cornyn subsequently introduced legislation to curtail patent thickets and product hopping. The Affordable Prescriptions for Patients Act cleared the Senate Judiciary Committee in June 2019 after the patent thicket provision was removed. Another version of the bill prohibiting product hopping cleared the committee again in September 2021, along with bills to prohibit pay-for-delay deals between brand and generic manufacturers and the filing of baseless citizen petitions. The House Judiciary Committee also cleared companion bills.

On the other side of the debate, Sen. Thom Tillis, R-N.C. has pushed back against criticism of biopharma patents. In January, he sent a letter to the FDA and USPTO stating that a "false narrative" was being advanced that patents are being systemically used to delay generic drug competition. He cited the Initiative for Medicines, Access & Knowledge (I-MAK) as a primary source of data regarding the role of patents in drug pricing. Tillis requested that the agencies conduct an independent analysis of the sources and data being relied upon by those "advocating for patent-based solutions to drug pricing."

In an August 2018 report, "Overpatented, Overpriced: How Excessive Patenting is Extending Monopolies and Driving Up Drug Prices," I-MAK analyzed the 12 best selling drugs in the US. It found that on average, there are 125 patent applications filed and 71 granted patents per drug and that drug prices have increased by 68% with only one of the top 12 decreasing in price.

Tillis is seeking changes in the patent examination process. In August, he and Leahy introduced the Patent Examination and Quality Improvement Act of 2022, which would evaluate the need for greater clarity in what constitutes patent quality, the setting of patent quality metrics, and how the performance of patent examiners is measured within the patent office. Tillis also introduced a bill on 2 August to expand the types of inventions that can be patented. The Patent Eligibility Restoration Act of 2022, S. 4734, is intended to counter a series of Supreme Court decisions that have found certain subject matter to be unpatentable.

> **"It is not until we get statutory reform that we will see the thicket strategy substantially weakened or disappear because it's working for reference product sponsors."**
>
> Robert Cerwinski, Gemini Law

What Lies Ahead

Details on the collaboration between the USPTO and FDA and their proposed initiatives will become clearer in the coming year. The response of stakeholders to the questions posed by the patent office may deter the agency from making dramatic changes to the patent process.

But drug patents will be getting closer scrutiny. In their joint blog post, Vidal and Califf stated that the USPTO will protect against the patenting of incremental, obvious changes to existing drugs that do not qualify for patents. "This effort can lead to lower drug prices because drug companies will not be able to unjustifiably delay generic drug competition based on trivial changes to a drug product," they said.

The patent office has rejected patents deemed to be obvious as it did in declining to issue a patent on a method of dosing ImmunoGen, Inc.'s investigational antibody-drug conjugate mirvetuximab soravtansine. That case illustrates the pressure on the agency to address drug pricing.

The USPTO's Patent Trial and Appeal Board affirmed the examiner's rejection of ImmunoGen's patent claims for obviousness and obviousness-type double patenting. The company then filed suit against Vidal challenging PTAB's decision. A district court upheld the decision, granting USPTO's motion for summary judgment. But the US Court of Appeals for the Federal Circuit concluded there were disputed questions of material fact, vacated the grant of summary judgment and remanded for trial.

In an 11 July petition for a panel rehearing, the USPTO repeated the concerns raised by Vidal and Califf in their blog post five days earlier. In highly unusual language, the agency cited the "well-documented problem of drug manufacturers receiving numerous follow-on patents for trivial modifications that end up delaying generic drugs' entry to the market" and driving up the prices of drugs. Such comments in a court filing shows that the patent office has indeed been engulfed in the battle over patents and drug pricing.

Kappos said he hopes that in proposing ways to make the patent system better, the agencies acknowledge prominently that development of drugs is expensive and requires a strong patent-based incentive system. "I hope they come up with a down-the-centerline report," he said. "Recommendations to further improve prior art access would be good, but recommendations to increase the value of valid patents would be even better."

Stakeholders will get a chance to offer suggestions on the agencies' proposed initiatives at a public "listening session" to be held at the USPTO headquarters on 19 January. In a notice of the meeting, the USPTO listed questions it would like participants to address, including what policy considerations the agencies should explore regarding method of use patents and associated FDA use codes for applicants seeking "skinny labeling" and the patenting of risk evaluation and mitigation strategies (REMS).

Growing Pressure To Change Patent Policies

9 JUNE 2021
President Biden issues Executive Order directing FDA to write to USPTO about use of the patent system to delay generic drug and biosimilar competition.

9 SEPTEMBER 2021
Senators Patrick Leahy, D-Vt, and Thom Tillis, R-NC, send letter to USPTO asking it to take steps to reduce patent applicants' making conflicting statements in submissions to PTO and other federal agencies.

10 SEPTEMBER 2021
Then-FDA Acting Commissioner Janet Woodcock sends letter to USPTO citing patent practices that can unduly extend market monopolies and keep drug prices high.

16 SEPTEMBER 2021
11 Senators send letter to USPTO objecting to increase in agency's discretionary denials of inter partes review petitions.

31 JANUARY 2022
Sen. Tillis criticizes the "false narrative" that patents are being systemically used to delay generic drug competition. He asks the FDA and USPTO to conduct an assessment of the Initiative for Medicines, Access & Knowledge data.

25 MAY 2022
In letter to FDA and PTO, Senators Maggie Hassan, D-NH, and Bill Cassidy, R-LA, say the lack of coordination between the agencies has allowed companies to obtain patents of questionable validity that delay generic drugs and extend monopoly prices.

8 JUNE 2022
Six bipartisan senators send letter to USPTO asking it to address patent thickets and posing questions about possible changes to the patent process.

16 JUNE 2022
Senators Leahy, Cornyn and Tillis introduce the Patent Trial and Appeal Board (PTAB) Reform Act of 2022, which would prohibit the USPTO director from declining to institute a PTAB proceeding because there is ongoing parallel district court litigation.

6 JULY 2022
USPTO Director Kathi Vidal sends letter to FDA Commissioner Robert Califf outlining initiatives to modify the patent process.

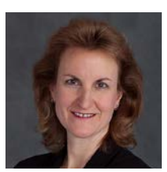
20 JULY 2022
Patent office seeks stakeholder input on the process being established for USPTO director review of final written decisions of the Patent Trial and Appeal Board.

16 AUGUST 2022
President Biden signs the Inflation Reduction Act of 2022, which lowers prescription drug prices in Medicare through price negotiation with manufacturers and imposes caps on out-of-pocket prescription drugs costs and insulin for Medicare recipients.

4 OCTOBER 2022
USPTO issues request for comments on its proposed initiatives to bolster the robustness and reliability of patents. It asks whether should be heightened requirements for continuation patents.

Reflections On The Makena, Avastin Accelerated Approval Withdrawal Hearings

Despite major differences in the sponsors, drugs and circumstances, the outcomes from the hearings on Makena's continued availability and Avastin's breast cancer indication were strikingly similar, with overwhelming votes in favor of withdrawal. In the process, however, both sponsors gained extra commercial time for their products.



BY **SUE SUTTER,**
SENIOR EDITOR, US

The dispute between US FDA's Center for Drug Evaluation and Research and Covis Pharma over the preterm birth prevention drug Makena marked the second-ever public hearing under the agency's accelerated approval withdrawal regulations, coming more than 11 years after the proceeding involving the breast cancer indication for Genentech, Inc.'s Avastin (bevacizumab).

The two hearings featured sponsors, drugs and circumstances that were very different.

Genentech is a big biopharma, oncology powerhouse. Covis is private equity-backed company with a portfolio of about a dozen small products that span therapeutic areas.

At the time of the June 2011 hearing on Avastin's breast cancer claim, the VEGF-inhibitor also carried claims for colorectal, non-small cell lung and renal cell cancers, as well as glioblastoma.

Makena (hydroxyprogesterone caproate injection, also known as 17-OHPC or 17-P) is a progestin indicated solely to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. It is the only drug approved for this use in the US and holds orphan drug designation.

CDER sought removal of Genentech's breast cancer claim because it determined that two postmarketing trials, though technically a statistical success on their progression-free survival endpoint, failed to confirm the magnitude of benefit seen in an earlier study.

In contrast, Makena's PROLONG confirmatory trial failed to meet its co-primary endpoints of gestational age and neonatal morbidity/mortality.

Despite the differences between the Avastin and Makena situations, the outcomes for the two hearings were strikingly similar, with the advisory committees rendering overwhelming votes for withdrawal. The Avastin vote was 6-0, while the Makena vote was 14-1.

Given the negative panel outcomes of the first two products to test this regulatory process, one wonders if any other sponsors will think it worth their while to pursue such a hearing in the future.

Of course, there is one very tangible thing that both sponsors gained by going through the lengthy and resource-consuming hearing process: more time on the market for the product or indication. From the date of CDER's proposed withdrawal, Avastin's breast cancer indication remained on label for about 12 months.

For Makena, that interval has now exceeded two years, and the clock is still ticking. FDA Commissioner Robert Califf and Chief Scientist Namandjé Bumpus are expected to render a final decision in 2023.

With the Makena hearing now behind us, and with the prospect of accelerated approval reform seemingly always on the legislative horizon, here are a few lessons that sponsors can take away from this admittedly small but diverse experience of accelerated approval withdrawal hearings.

Panel Composition: Does It Really Matter?

Genentech pushed for its case to be heard by experts other than, or in addition to, the FDA's Oncologic Drugs Advisory Committee.

ODAC had voted against the Avastin breast cancer indication in 2007 and 2010. For the hearing, Genentech sought "an objective advisory committee with substantial breast cancer expertise." However, presiding officer Karen Midthun convened the existing ODAC, concluding that the accelerated approval regulations do not allow for substitution of a different panel, and she rejected Genentech's request that additional experts be added to the committee.

Given the negative panel outcomes of the first two products to test this regulatory process, one wonders if any other sponsors will think it worth their while to pursue such a hearing in the future. However, one cannot overlook the extra time gained on market by going through the lengthy hearing process.

Covis' experience shows that even if a sponsor succeeds in getting a panel that could reasonably be viewed as more favorable to its cause, things may not play out that way in the end after such experts have heard detailed presentations on the available data.

Genentech subsequently complained that none of the clinical experts on the hearing panel were breast cancer specialists.

Similarly, Covis had objected that only six of 16 voting members at a October 2019 advisory committee review of Makena treated pregnant women in their clinical practice.

Nine members of that panel voted for withdrawal, while seven favored keeping Makena on the market under accelerated approval but with a requirement for a new confirmatory study. Five of the six experts with actual experience treating pregnant women voted against withdrawal, Covis said.

In the run-up to the Makena hearing, Covis requested that a significant proportion of the panel should comprise practicing obstetricians who are maternal-fetal medicine specialists. Hearing officer Celia Witten added temporary voting members to the Obstetrics, Reproductive and Urologic Drugs Advisory Committee, and the company seemingly got the type of panel it wanted, with eight of the 15 voting members having clinical expertise in MFM or perinatology.

However, this did not help Covis' case, as seven of those eight clinical experts voted for withdrawal. Covis even lost the vote of one of the MFM clinicians, Emory University's Michael Lindsay, who also participated in the 2019 meeting. In 2019, Lindsay voted to keep the drug on the market; this time around, he voted for withdrawal.

Covis' experience shows that even if a sponsor succeeds in getting a panel that could reasonably be viewed as more favorable to its cause, things may not play out that way in the end after such experts have heard detailed presentations on the available data.

In his recently published book "Drugs and the FDA: Safety, Efficacy and the Public's Trust," leukemia specialist Mikkael Sekeres, who was an ODAC member and participated in the Avastin hearing, addressed the value that the FDA's external

advisors can bring even when they are not experts in the specific disease or condition at issue.

Such individuals "have some distance from those anecdotes, those biases, those conflicts, and those memories of the awful conversations when there were no options left, and thus possibly avoid an option that offers baseless hope," Sekeres said.

At the Makena hearing, ORUDAC member Joseph Alukal, a urologist from Columbia University, offered a similar sentiment. "I'm a urologist and therefore have no clinical experience with this drug. And I think that maybe puts me on different footing than a lot of people who have weighed in. Sometimes an outsider's perspective can be useful."

Like most of the MFM experts on the panel, Alukal said the Makena should not remain on the market while a new confirmatory study is performed. "The idea that the drug is allowed to remain on the market during that window of time when we don't have data supporting a decision to do that, I find it hard to accept that," he said.

"All medications have some risk associated with them. Why are we exposing people to that risk when we can't clearly state to them this medication has benefits for you in terms of your clinical needs?"

> **"Sometimes when I see a lot of mathematical gymnastics being used to cut things in different ways and try to squeeze out a subset that has benefit ... I have concerns."**
>
> Patient representative Annie Ellis

Patient Rep's Vote Is Not A Given

More often than not, patient representatives on FDA advisory committees tasked with reviewing specific products will vote favorably for the sponsor. However, the Avastin and Makena hearings have both bucked those trends.

Natalie Compagni Portis, the patient representative on the Avastin panel, disagreed with the argument espoused at the hearing by some patient advocates and providers that breast cancer patients need "something."

"We have to give something that we know either improves the quality of life or is better than existing treatments, and the Avastin in that indication was neither," she said in a 2021 interview with *In Vivo* sister publication *Pink Sheet*.

Annie Ellis was the patient representative for both the Makena public hearing and the 2019 adcomm on the drug. In both cases, she voted for withdrawal.

Ellis described the accelerated approval pathway as conditional, based on surrogate or intermediate clinical endpoints that require a confirmatory trial. "So it's kind of like driving on your donut spare until it's confirmed, and then convert it to full approval. And nothing at this point rises to that level of evidence," she said.

Although Ellis is not a biostatistical expert, "sometimes when I see a lot of mathematical gymnastics being used to cut things in different ways and try to squeeze out a subset that has benefit ... I have concerns," she said, referring to Covis' numerous *post hoc* exploratory analyses aimed at identifying a high-risk population that might benefit from Makena.

Equipoise, Continued Marketing Are Mutually Exclusive

The accelerated approval hearing experience to date suggests that equipoise to conduct a new study for a targeted population and use, and the continued marketing of a drug or indication for that population and use, cannot coexist.

Both Genentech and Covis argued there was sufficient clinical equipoise to conduct a new randomized trial in the indications targeted for withdrawal while those indications remained on label.

In both cases, this argument failed, with the advisory committees generally agreeing that keeping the indication on label, or the drug on the market in the case of Makena, would make it more difficult to enroll the study and extend the period of time need to complete the trial, if it even could be completed.

Makena panelists were especially skeptical of Covis' argument that it would be harder, not easier, to enroll a new randomized, controlled trial if the drug were withdrawn. The company presented survey data suggesting physicians would be more likely to enroll patients in such a study if the drug were still on the market.

"If I were a patient in the high-risk group and the drug on the market with an approved indication, I would say I'm not participating in this study," said Mark Hudak, neonatology division chair at University of Florida College of Medicine.

The patients who testified during the Makena open public hearing were faceless – they did not appear on camera, and there were no photographs of them holding their preterm babies or their healthy children years after a preterm birth.

"You can't say out of one side your mouth that we don't know whether it's effective or not and therefore we need to study it in you, who are particularly at high risk, but say it's available to anybody else on the market. As the patient, I would say, no, I'll take the medication."

"It would be the rare patient, I think, that would have the equipoise to sort of read through all of this, understand the nuances involved in this and agree to participate," Hudak said. "So I think, even if we had more physicians willing to participate in trials, the rate of patient recruitment would be infinitesimal."

"Off the market, however, I think one could persuade physicians and patients to participate in the study because it is an area that everybody is saying we have equipoise, we really don't know," Hudak said. "There are some signals that it may be effective. It needs to be verified."

In-Person vs. Virtual

One major difference between the accelerated approval withdrawal hearings to date has been the format.

The Avastin proceeding was held in-person at the FDA's White Oak, Md. headquarters over two days. Due to uncertainties related to the COVID-19 pandemic, the Makena hearing was conducted virtually over two-and-a-half days.

There can be little argument the virtual format eliminated much of the emotion from the proceeding.

The open public hearing portion of Avastin was a tense proceeding, with breast cancer patients and their families testifying in front of ODAC, begging the panel to keep the indication on label. There were several disruptions in the crowded meeting room, including after the withdrawal vote when audience members started yelling at the committee. Of course, the emotional testimony and outbursts did not sway a decision in favor of Genentech, but they did make an impression on the committee members.

With Makena, the patients who testified during the open public hearing and supported the drug's continued availability were faceless – they did not appear on camera, and there were no photographs of them holding their preterm babies or their healthy children years after a preterm birth. Although the voices of some women cracked as they shared their preterm delivery experience, there was no yelling or crying, unlike in the Avastin proceeding.

Covis had sought an in-person hearing, no doubt anticipating the blunted emotional impact that a virtual proceeding would have.

Presumably, any future sponsor that requests a public hearing under the accelerated approval withdrawal regulations will also push for an in-person proceeding.

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BY **DANIEL CHANCELLOR,** THOUGHT LEADERSHIP AND CONSULTING DIRECTOR, CITELINE

Pharma Innovation: Europe Is Being Edged Into Third Place

With a declining share of global R&D and investment, Europe risks the pharmaceutical industry being increasingly molded in the image of others.

Each year, the European Federation of Pharmaceutical Industries and Associations (EFPIA) publishes an annual factbook to emphasize the tremendous strategic importance of the pharmaceutical industry to the continent. Among the key figures, European companies collectively invest approximately €40bn in R&D annually, rising at a compound annual growth rate (CAGR) of 4.0% since 2017. An impressive figure at face value, although one that the US eclipses with more than €70bn spent, with an equivalent growth rate of 8.5%.

While the trans-Atlantic equilibrium continues to tilt away from Europe and to the US, a new powerhouse in China is emerging. The local drug market has been growing at a double-digit rate for many years, and this has been accompanied by intense domestic R&D activity. EFPIA estimates that R&D growth in China is running at an impressive 12.9% CAGR. If the current trajectory is maintained, China is on course to overtake Europe within the next 10 to15 years purely in terms of spend, although other indicators point towards the crossover point being reached much earlier.

This rebalancing in Europe's position on the global stage has been a gradual process, beginning perhaps as early as the 1990s, but certainly accelerating in more recent years, as *In Vivo*'s analysis shows. While this is by no means an existential threat, biopharmaceutical industry stakeholders must be mindful of the current state of innovation within Europe. Past successes alone will not sustain the industry, and innovation is an essential component to protect Europe's future.

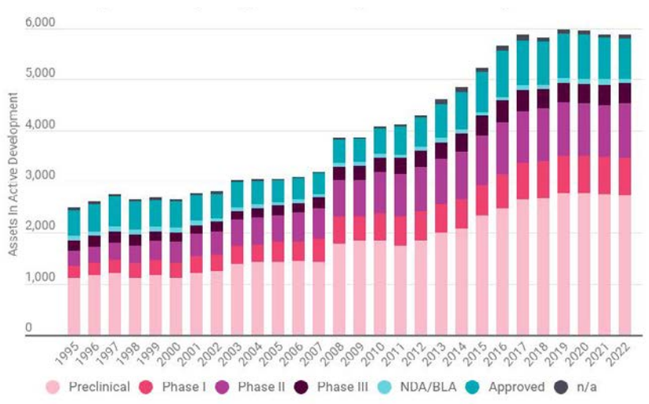
Pharma Pipelines Have Reached A Ceiling

In line with its rich heritage, European biopharmaceutical companies have discovered or developed many of the medicines that have had most impact on global health. Buoyed by successes, drug developers have continued to increase R&D spending to produce the medicines of the future. This can be viewed through the lens of Citeline's drug development database, Pharmaprojects, which has tracked industry R&D over many decades. Annual snapshots are available going back to 1995, when European biopharmaceutical companies had a combined pipeline containing 2,500 assets under active development. This number has grown steadily year-on-year, before accelerating rapidly between 2012 and 2017 to reach almost 6,000 pipeline drugs.

However, rather than continue the ascent, European drug developers have reached a ceiling at this level, whereby current levels of investment cannot sustain any further expansion. Within this pipeline, 47% of drugs are in preclinical development, while 39% are at the various clinical stages from Phase I through to pre-registration. The remaining 14% are drugs that have already been approved and are being further developed in additional indications, patient subpopulations, or new geographies.

In the years following 2017, the global pipeline has seen a notable shift. While Europe has remained stuck at around 5,900 assets, the global pipeline has expanded from 15,000 to exceed 20,000 drugs in 2022 with a CAGR of 6%. Europe's share of global R&D has plummeted from 39% to 28% in just five years.

Exhibit 1: Evolution Of European Biopharma R&D Pipeline By Highest Stage Of Development



Source: Pharmaprojects, September 2022

Exhibit 2: Drug Pipeline Growth By Company Headquarter Location, 2017–22

Country	2017	2018	2019	2020	2021	2022	CAGR 2017–22
Europe	5,877	5,824	5,981	5,962	5,884	5,873	0.00%
US	7,737	7,832	8,341	8,535	9,113	9,481	4.10%
Japan	1,553	1,532	1,568	1,552	1,513	1,453	-1.30%
China	843	1,069	1,637	2,170	2,865	3,743	34.70%
Global	14,926	15,264	16,690	17,717	19,012	20,384	6.40%

Note, drugs will be counted across more than one region if a licensee in a different geography is also pursuing development, so the totals will not sum. Snapshots are taken annually in May.

Source: Pharmaprojects, September 2022

A large proportion of the global growth has come from China, which has seen a remarkable 35% CAGR over the last five years. Starting from a small base, Chinese companies have surged from 800 R&D projects to almost 3,800 during this time. The US biopharmaceutical pipeline has maintained its upward trajectory, adding further distance to Europe in second place with a 4% CAGR. Japan, which for a long time has been a major R&D hotspot, has declined in recent years and now finds itself comfortably behind China.

Underweight In Oncology, Cell And Gene Therapy

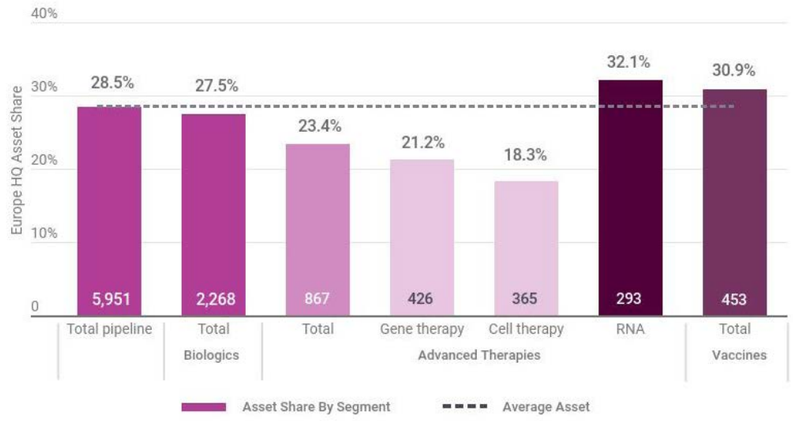
Europe's exposure to emerging science will also have long-lasting implications for its future prospects. As the industry pivoted towards biological drugs in previous decades, European companies have been well positioned with strong capabilities in antibody drug discovery. Pioneers include Cambridge Antibody Technology and Genmab A/S, while large European pharmaceutical companies have made strategic acquisitions to bolster their capabilities, such as Roche Holding AG (Genentech, Inc.) and AstraZeneca PLC (MedImmune LLC). This biotechnology revolution has also extended beyond the design of drugs, also modernizing the way vaccines can be manufactured. Europe has a long-established leadership position in the vaccines space through companies such as Sanofi and GlaxoSmithKline Pharmaceuticals Ltd.

The next wave of evolution within the pipeline is well underway, as drug developers are seeking to capitalize on new genomics technologies to create drugs and vaccines based on cell, gene and RNA scaffolds.

As shown in Exhibit 3, Europe is part of this transition, but with varying levels of exposure. With 5,951 drugs in active development as of September 2022, European biopharma has a 28% share of the total global pipeline. The proportion of biologics under development (2,268, 27%) is on par, while vaccines remain a strength (31%), although the subset of advanced therapies is notably below average. Europe possesses just 23% of the global pipeline for advanced therapies, with 867 gene, cell or RNA-based drugs in development as of September 2022. Within this, Europe is well positioned in RNA drug development (32%), thanks to innovators such as BioNTech SE and CureVac NV, in addition to acquisitive larger companies like Novo Nordisk A/S and Sanofi. Counterbalancing this, Europe is trailing rivals from the US and China in gene (21%) and cell therapy (18%), with much smaller domestic pipelines. While these are not yet mainstream drug modalities, European innovators are already giving away a large head start, which will be difficult to overturn through acquisitions alone as the technologies gain further clinical validation.

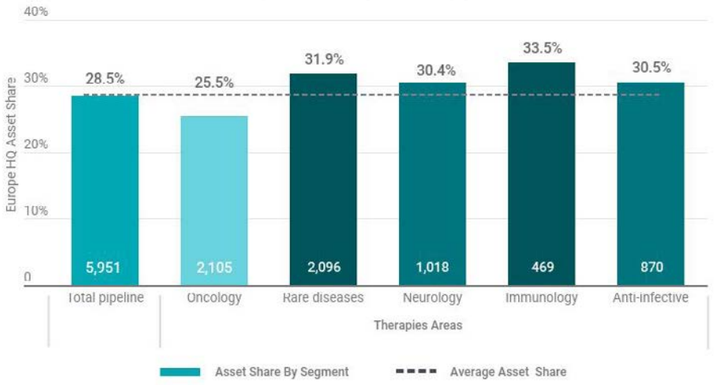
A similar analysis by therapy area shows an analogous trend, whereby Europe as a collective is underexposed to the single largest growth driver in R&D trends – oncology – but has pockets of strength in other growth drivers. Europe's share of global oncology drug development is just 25%, which leaves it underexposed to a therapy area that accounts for approximately 40% of active pipeline assets, new clinical trial starts and partnering activities globally.

Exhibit 3: European Exposure To R&D Growth Segments By Modality



Source: Pharmaprojects, September 2022

Exhibit 4: European Exposure To R&D Growth Segments By Therapy Area



Source: Pharmaprojects, September 2022

By contrast, Europe is a global leader in rare diseases R&D. Thirty two percent of global rare disease drug development is taking place within European-headquartered biopharmaceutical companies, even despite the international acquisitions of former standalone companies such as Actelion Pharmaceuticals Ltd., Shire Pharmaceuticals Group PLC and GW Pharmaceuticals plc. This position is supported by the R&D legacy of such companies, plus the strategic emphasis that larger players place on rare diseases. AstraZeneca and Sanofi are two such big pharma companies that have placed large bets on Alexion Pharmaceuticals Inc. ($39bn) and Genzyme ($20bn), respectively.

Besides oncology and rare diseases, the other prominent segments of the pipeline are neurology, immunology and anti-infectives. Europe carries an above-average share of the global pipeline in each of these areas, ranging from 30 – 34%, as shown in Exhibit 4. It could be argued that the European pipeline has better overall balance across the major therapeutic challenges. By limiting exposure to the hyper-competitive oncology drug landscape, eventual success rates and patient access may counterbalance any slower growth rates.

Healthy And Growing Appetite For Partnering Deals

European companies continue to play an active and prominent role in the global partnering landscape. Almost half (43%) of all alliances since 2015 involved at least one European company as either the licensee or licensor, which trails only the US (69%) and is a long way ahead of the nearest rival (China and Japan, both 12%).

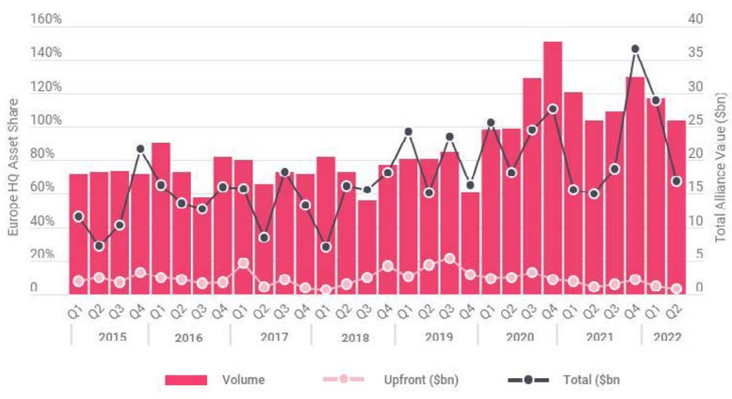
As shown in Exhibit 5, the general trend within Europe is one of increasing partnering activity, measured either as the number of deals or their value. In Q2 2022, there were an average of 115 alliances involving European biopharmaceutical companies each quarter, with combined upfront payments of $1.5bn and a total potential value in excess of $25bn. The number of deals has expanded at a CAGR of 8% between 2015 and 2021, which the total potential deal value slightly exceeds with a 9% CAGR.

Few deals will realize all the milestones required to hit this limit, so it is noteworthy that total upfront payments have declined at a CAGR of -4% over the same period. Set against the increase in the number of alliances, this reflects the growing tendencies of pharmaceutical companies to license assets at earlier stages of development and adapt typical deal structures to reflect this risk.

Despite Pandemic-Related Capital Influx, Europe Is Gradually Losing Global Share

European companies seeking to raise capital were among the beneficiaries of the pandemic, in line with broader investor interest in the biopharmaceutical sector. After several years of relatively stable levels of financing deals, 2020 saw a remarkable uptick in both the number and potential value of fundraising activities. This peaked in Q4 2020 with 64 separate financings tracked by Biomedtracker for a total value of $22bn, before gradually regressing back towards the mean. Some degree of fluctuation is inevitable, although the last

Exhibit 5: Europe Biopharma Alliance Trends, 2015–22



Source: Biomedtracker, September 2022

Exhibit 6: Europe Biopharma Financing Trends, 2015–22

Source: Biomedtracker, September 2022

full four quarters show an average run rate of approximately $4bn raised across 50 deals per quarter. It is not yet clear whether this is a new baseline level of fundraising activity, as activity is still approximately 40% higher than in the years prior to the pandemic.

However, measuring the proportion of global fundraising activities conducted by European-headquartered biopharma companies shows a gradually diminishing share. In terms of deal volumes, European-headquartered companies had a one quarter share in 2015, although this has ticked down to one in five financings on average by the mid-point of 2022. Assessing by the value of these financings, the ratio declined from one third to one quarter of all activity over the same time period.

Exhibit 7: Biopharma Financing In Europe, US, And China By Deal Type Since 2015

**includes debt, FOPOs, PIPEs, priority review voucher and royalty sales*

Source: Biomedtracker, September 2022

The chief beneficiary – or cause – of Europe's decline on this metric has been the rising attractiveness of Asian markets. China is capturing an ever-increasing portion of investment as both the domestic drug market increases in size and volume, and China-headquartered pharma companies expand their R&D capabilities to include innovative drug discovery as well as generics and manufacturing. In the meantime, the US has retained its standing as the leader in life sciences innovation and entrepreneurship.

Furthermore, investment into new companies in Europe has lagged international comparators. The balance of investment in Europe has largely been toward older companies, rather than venture financing or initial public offerings (IPOs) for companies in their earlier years. Since 2015, companies in Europe have raised a combined $34bn via these methods, accounting for just 15% of global start-up activities. This is overshadowed by the $153bn in new company financing that originates in the US, which possesses a two-thirds share of the global total. Rather than competing with the US, China is now a much more appropriate comparator, where companies have also raised $34bn via venture financing or IPOs since 2015 (*see Exhibit 7*).

In Summary

Europe may no longer be the force it once was on the global stage. While humbling to admit, the axis between the US and Europe has tilted, such that Europe now occupies less than a 30% share of the global market across various measures. This includes the scale of innovation, from pipeline size to the number of therapeutic breakthroughs, as well as commercial indicators such as prescription pharmaceutical sales and financial investment.

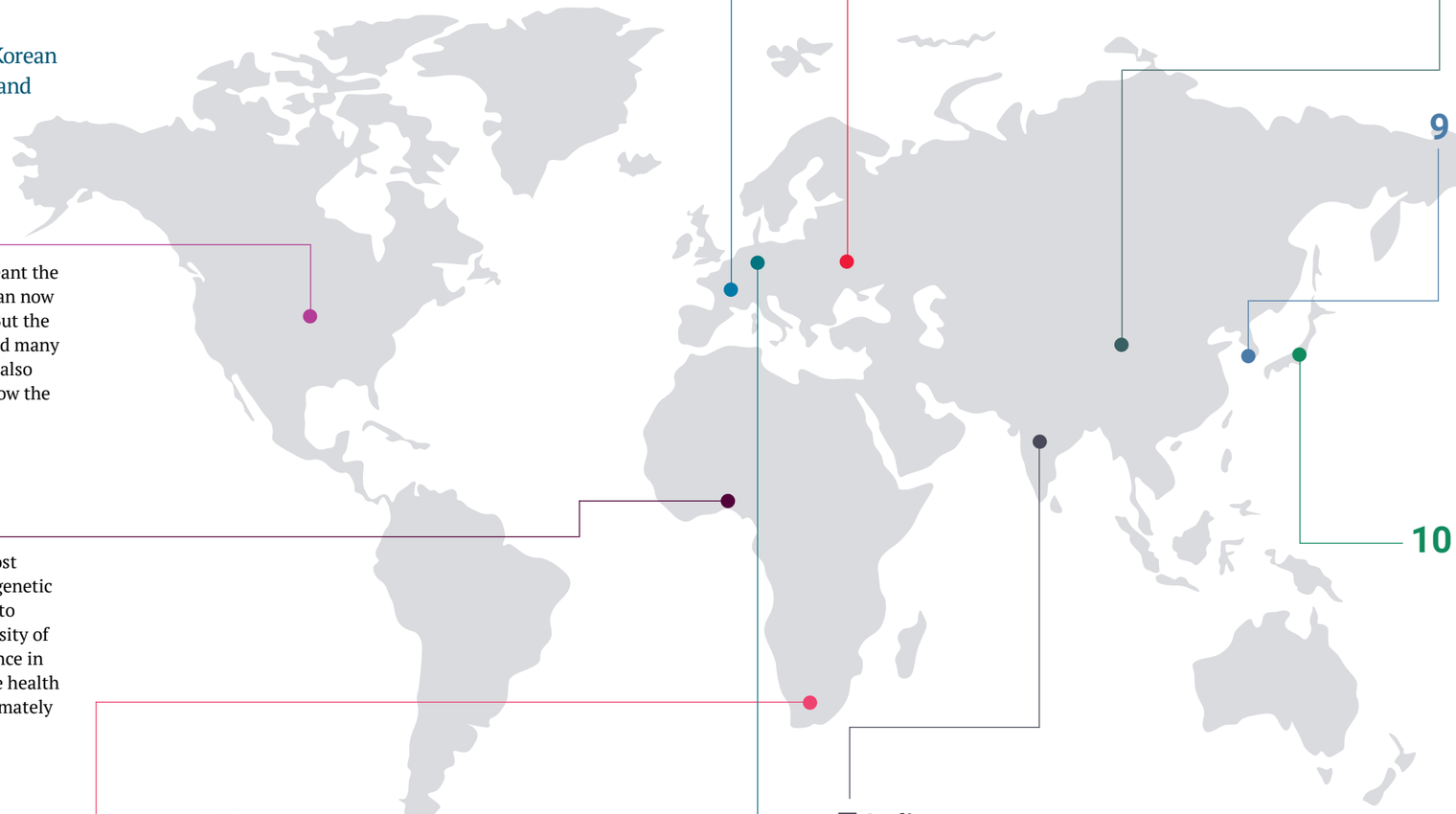
Europe's current position is still one of strength, although the rate at which its stake is declining is a concern. It is incumbent on the full range of stakeholders – drug developers, academia, investors, payers, regulators, policymakers – to set about a strategy to halt any further decline and protect Europe's standing in the global innovation ecosystem. On the part of industry players, this involves an impartial assessment of scientific strengths and technological shortcomings, prioritizing investment at the cutting edge of innovation and unmet patient needs.

This article has been adapted from a white paper, The State of Innovation in Europe, using Citeline's industry-leading datasets such as Biomedtracker and Pharmaprojects. To read the white paper in full, and to learn more about Citeline, please visit https://pharmaintelligence.informa.com.

WORLD VIEW

Exploring Life Sciences Stories From Across The Globe

Navigate through *In Vivo's* international coverage as we report on French biotech, Korean deal negotiation, Medicare developments and the ongoing situation in Ukraine.



1 United States

Passage of the Inflation Reduction Act has meant the US Health and Human Services Department can now negotiate drug prices on behalf of Medicare. But the law lacks a clear framework for the process and many key aspects are open for HHS to determine. It also means pharma has an opportunity to shape how the law becomes policy. *Read More*

2 Nigeria

Africa's 1.3bn people comprise the globe's most prolific, diverse and medically useful pool of genetic information. Now, Lagos-based 54gene seeks to apply research insights from the unique diversity of the African genome to build an African presence in precision medicine and secure more equitable health outcomes for patients, first for Africa and ultimately for the entire world. *Read More*

3 South Africa

Scientists from Cape Town-based Afrigen Biologics, which is part of an WHO-funded consortium selected to run a vaccine hub, said it had made an mRNA COVID-19 vaccine based on publicly available data from Moderna, Inc. Their success has turned out to be an exercise in addressing vaccine equity, wherever it may be. *Read More*

4 France

As the French biotech sector matures with government help, rare diseases are becoming increasingly important to firms. Orphan drug research could help carve a new niche for a country known mainly for its development of ophthalmology drugs and vaccines, suggests a report from 427 companies in the sector. *Read More*

5 Germany

Until recently, orphan drugs selling less than €50m a year escaped the normal added-benefit review that other new medicines are subjected to in Germany. However, a new law reduces that threshold to €20m and "is a turning point" for companies in the country, says Germany's association of research-based pharma companies. *Read More*

6 Ukraine

In addition to making it difficult to get marketed drugs to patients in need in Ukraine and affected surrounding areas, the war in Ukraine has affected an estimated 5% of global clinical trials. The US Food and Drug Administration has said that as many as 250 drugs and devices were being tested in Ukraine, while Citeline has identified more than 1,000 current and planned clinical trials in the country. *Read More*

7 India

Mark Cuban's online pharmacy, the Mark Cuban Cost Plus Drug Company (MCCPDC), is meant to provide patients with quality medicines at affordable prices, something that resonates with the Indian pharma industry. Will Indian generic companies ally with and use the MCCPDC channel, or will the company's possible success make the US market less lucrative for them? *Read More*

8 China

Despite a slowing economy, an aging population and the COVID-19 pandemic impact, China is continuing on its drive towards originality, advancing towards becoming a member of the world's top 10 innovator countries. In the latest 2022 ranking by the Global Innovation Index, China was ranked the 11th most innovative economy in the world overall and the most innovative among 36 upper middle-income countries. *Read More*

9 South Korea

With little mergers and acquisitions activity in the Korean bioventure industry, out-licensing deal performance is increasingly being seen by the Korea Exchange as a measure of market competitiveness when they assess IPO filings. A report by the Korea Bio-Economy Research Center suggests several factors that Korean firms need to consider before starting the out-licensing process. *Read More*

10 Japan

The "All-Genome Analysis Project" aims to build an information platform using analyses of around 100,000 genomes along with multi-omics capabilities connected to clinical information gathered from patients with refractory cancers and rare diseases. During fiscal year 2022, the government is spending $126m on programs related to the project, hoping to provide pharma firms targeting oncology and rare diseases with a new data source to boost their activities. *Read More*

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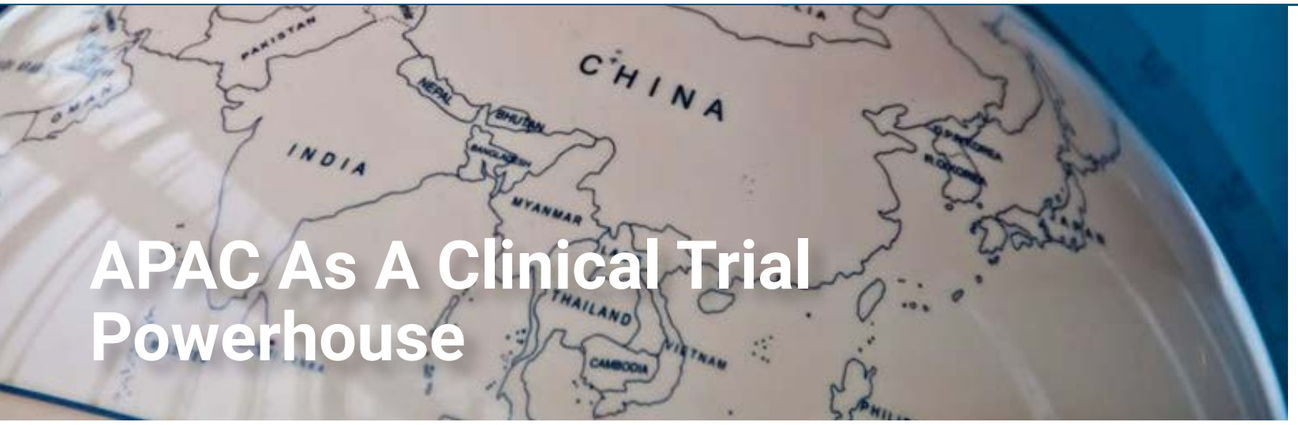
WORLD VIEW



APAC As A Clinical Trial Powerhouse

BY **ANNIE SIU,** DIRECTOR, APAC CONTENT, CITELINE

BY **ANDREW BENSON,** SENIOR DIRECTOR, TRIALTROVE

In the last 10 years, APAC has become a hotspot for clinical trials: the region contributed almost 50% of new clinical trial activity globally in 2021.

It is often said that "disease knows no borders," but is the same true for clinical development? Patient availability is a critical component for clinical trials, and so it stands to reason that clinical development should match the epidemiology of diseases. Of course, this is often not the case, with longstanding biases towards studies in the US and Europe, where health care infrastructure and the pharmaceutical market are generally more mature. However, change is underway.

The Rise Of APAC

Clinical trial activity in APAC has increased considerably over the past decade. The total number of Phase I–IV trial starts in APAC increased from 4,562 trials in 2012 to 7,718 trials in 2021, with a compound annual growth rate (CAGR) of 5.4%. Much of this growth is back-ended towards recent years. In particular, almost every year since 2016 has seen double digit increases in the number of new clinical trial initiations (*see Exhibit 1)*.

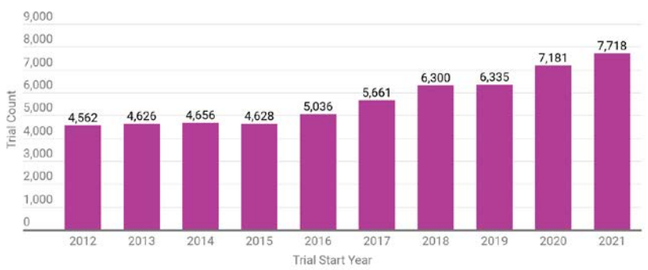
In contrast, the total number of trial starts in the rest of the world decreased at a CAGR of -0.4% from 8,080 trials in 2012 to 7,801 trials in 2021. These RoW trials are defined as studies that do not contain a clinical site in an APAC country, although it is worth noting that a portion of APAC trials will also have sites in other regions. The continuation of this trend will surely see APAC surpass RoW as soon as next year (*see Exhibit 2*). For a region that has historically trailed behind the US and Europe, this recent transformation is remarkable and shows that APAC is very much on the cutting edge of clinical research.

Pivot Towards Early-Stage Research

Throughout the last decade, there has been a gradual but meaningful shift in research priorities among APAC clinical trials. Late-stage trials (Phase III or Phase IV) dominated from 2012 to 2016, but Phase I trials have since increased their share of the total trial landscape, coinciding with the acceleration in total trials since 2016. Phase I research now accounts for around a third of clinical activity, up from just 14% in 2012 (*see Exhibit 3*).

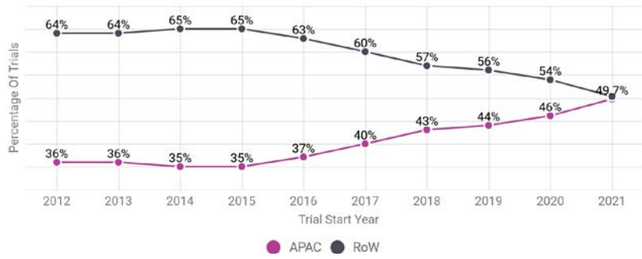
This is very much an indication of the greater levels of innovation within APAC, and particularly China. A healthy proportion of Phase I trials suggests that novel chemical or biological entities are being developed in the region, rather than

Exhibit 1: Phase I-IV Trial Starts In APAC



Source: Trialtrove, August 2022

Exhibit 2: Percentage Of Phase I-IV Trial Starts In APAC And RoW By Start Year



Source: Trialtrove, August 2022

multinational Phase III trials that satisfy global regulatory requirements, or indeed Phase IV studies of mature drugs. More drugs than ever are being discovered by companies based in this region, with China solidifying its position as the second leading location for R&D globally, and South Korea, Japan, and Australia also in the top 10.

Clinical Trial Growth In China Outstrips Peers

Where exactly is this growth in APAC happening? China has taken the lion's share of clinical activity over the past decade, with 45% of APAC trials including a Chinese site. Japan follows in second place (21%), ahead of South Korea (13%), Australia (11%), and India (10%). While these numbers sum to 100%, this is coincidental as trials are counted for each country in which a clinical site is disclosed. Notably, all remaining APAC countries combine to constitute just 10% of trials. Therefore, the top five countries – and China in particular – dictate the overall dynamic within APAC.

These five countries are following diverging growth trajectories. While 45% of all trials noted between 2012 and 2021 include a site in China, this proportion increases to 62% for studies initiated in 2021. China has sustained a 15% CAGR in annual trial initiations since 2012, contrasting a -6% CAGR decline in Japan. China first overtook Japan in 2014 and is now home to more than five times as many new clinical trials each year. South Korea has also declined modestly and ranks in fifth position for new trials, behind Australia and India.

Trends Within APAC Locations

High-Growth China Has Strong Domestic Bias For Clinical Trials

China has distinguished itself from its APAC peers on the account of the sheer scale of growth in clinical research over the last decade. China also stands out as the only major APAC location where domestically sponsored trials make up the majority. More than three-quarters of trials in China in the last decade were sponsored by local Chinese companies. In Japan, South Korea, and India we see between 56% and 67% of trials being initiated by foreign sponsors. Australia's split is striking, with 95% of the trials initiated by foreign companies.

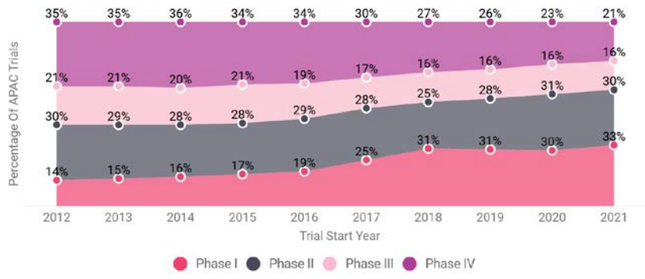
A combination of factors is nurturing China's explosive domestic growth in the pharma and biotech space. With the largest population in the world, China provides not just huge market opportunities but also a massive set of potential patients to enroll into clinical trials (*see Exhibit 4*). China's National Medical Products Administration (NMPA) has streamlined the clinical trial and drug approval process, including priority and special reviews as well as breakthrough therapy designations for innovative products that target unmet medical needs in China. The National Reimbursement Drug List is being updated more frequently and prioritizes the entry of newly approved novel drugs. Lastly, rule changes allow pre-revenue/pre-profit biotech companies to be listed in the Hong Kong Stock Exchange (HKEX) or Shanghai Stock Exchange's Science and Technology Innovative Board (STAR). Combined together, all of these factors can be seen as the "rocket propellant" for growth.

Japan Is Most Popular Trial Location In APAC For Big Pharma

Looking at the set of APAC trials according to sponsor, leading multinational pharmaceutical companies continue to have the largest footprint in Japan. Over the last decade, almost half of trials that the top 20 drug companies according to revenue conducted in APAC included at least one Japanese site. In total, 3,645 such trials were recorded in Trialtrove, compared to 2,860 in Australia and 2,610 in South Korea.

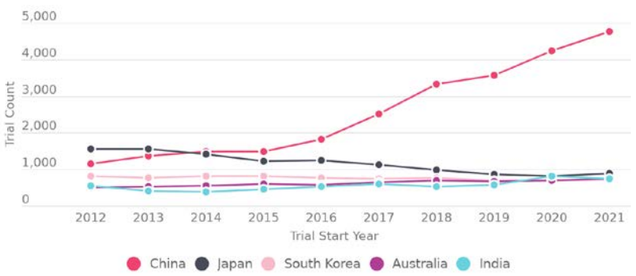
Two Japanese companies sit within the top 20 peerset, Takeda Pharmaceutical Co. Ltd. and Astellas Pharma, Inc., although even excluding these there is a strong preference for Japan. The country has an excellent reputation for clinical trials and long history in the field. Japan is also the only location in APAC that acts as a founding regulatory member (MHLW/PMDA) and a founding industry association member (JPMA) of the International Conference on Harmonization (ICH).

Exhibit 3: Clinical Trial Starts In APAC By Phase



Source: Trialtrove, August 2022

Exhibit 4: APAC Trial Starts By Trial Site Location



Source: Trialtrove, August 2022

Australia's reputation as a leading global destination for early-phase clinical trials is also well established, with a robust network of experienced specialized Phase I sites. Australia leads the APAC region in the number of first-in-human (FIH) trials, constituting 7% of its total, growing at an impressive CAGR of 15%. Interestingly, Australia has also become a location of choice for certain domestic Chinese companies looking to develop their drugs internationally, to take their drugs into FIH trials and to help accelerate global clinical development timelines. Companies including BeiGene, Ltd., Zai Lab Ltd., Akeso Inc., and Jiangsu Hengrui Medicine Co., Ltd., among others, have used this strategy for some of their FIH trials.

South Korea Leads The Way In Novel Trial Designs

One emerging trend in clinical research is the use of innovative trial designs to help answer complicated clinical questions with high degrees of efficiency. These include basket and umbrella clinical trials, as well as those with an adaptive design. These are commonplace in the personalized medicine setting, whereby patients with particular molecular or genetic signatures are matched with drugs mechanistically designed against these biomarkers. These designs are challenging from the fact that genotypic and phenotypic clinical data and genotype-phenotype associations for the population can be hard to obtain in advance at the trial planning stage.

South Korea is a regional leader in this space, with the highest percentage of umbrella and basket trials. South Korea benefits from the Korean Genome Project, a joint project by the Personal Genome Project at Harvard Medical School, the National Center for Standard Reference Data of Korea, Clinomics Inc, and the Korean Genomics Center of Ulsan National Institute of Science and Technology (UNIST). It provides access to a dataset comprising 1,094 Korean whole genomes, of which 1,007 genomes were newly generated in combination with systematically acquired clinical and biochemical measurement information from the blood and urine of the participants. With such expertise, it is no surprise that the majority of umbrella or basket clinical trials in Korea are conducted by the University of Ulsan College of Medicine.

Australia A Hub For Multi-Regional Trials And First-In-Human Studies

Across the APAC region, Australia is the leading location for multi-regional clinical trials (MRCTs). Over 4,000 MRCTs have been conducted in Australia, representing almost 70% of trials in the country. As a trial location, Australia is particularly attractive due to a streamlined regulatory framework, such as the Clinical Trial Notification (CTN) scheme, and data generated in Australian studies are accepted by the major regulatory agencies. This, coupled with the obvious close cultural and economic ties between Australia and Western countries, has led Australia to be an attractive location to include in global MRCTs for Western sponsors.

India's Contributions Towards COVID-19 Research

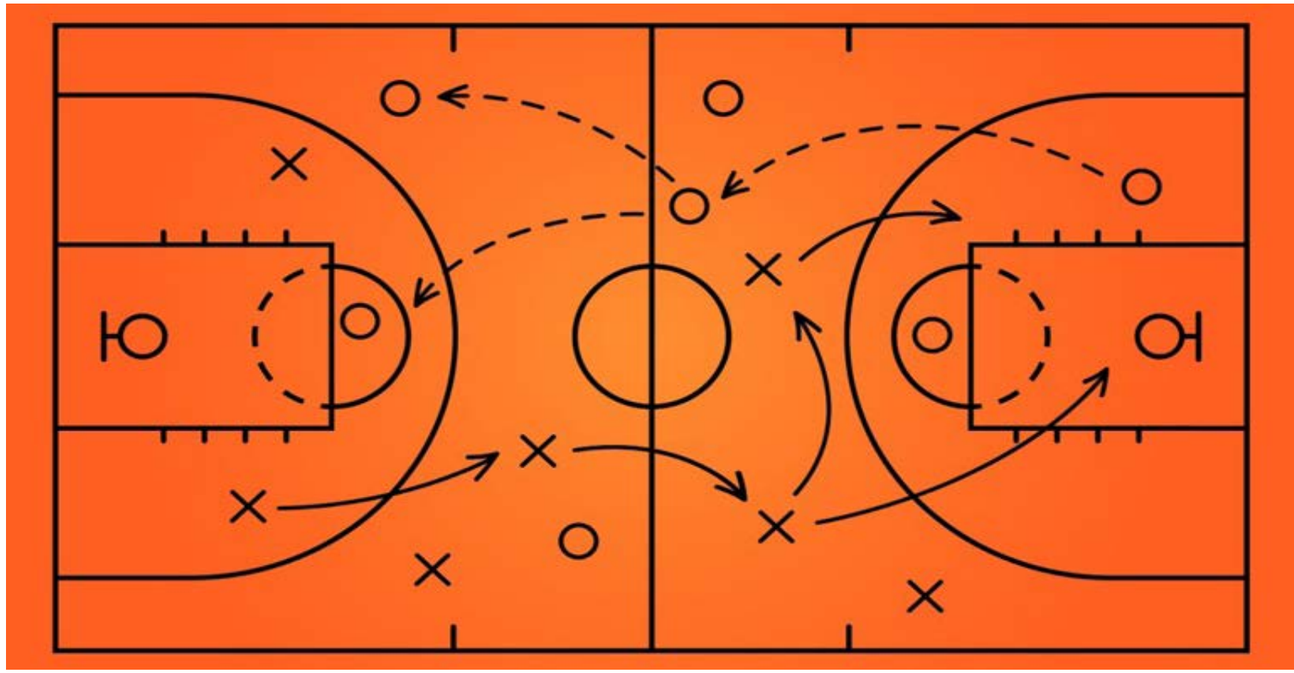
The pandemic has of course had a huge effect on the clinical research ecosystem, not least due to the rapid shift in research priorities in order to conduct the several thousand studies to date related to COVID-19. India and China have been at the forefront of APAC's contribution to COVID-19 research, with almost 500 trials taking place in each country in the 2020-21 period. Both countries contributed more than 30% each of the APAC total.

While China was the regional leader for vaccine clinical trials, on account of the large number of domestically developed candidates, India contributed more clinical trials of potential COVID-19 treatments. There was a strong bias towards drug repurposing, with large numbers of studies of the commonly mentioned oral anti-infective and anti-inflammatory drugs. Notably, India also conducted a sizable number of studies of Ayurvedic medicines, and so these were unlikely to inform treatment practices globally.

In Summary

Asia Pacific has been an important contributor to the global clinical trial ecosystem for some time, but its recent rise to become a powerhouse cannot be ignored. Half of all new trials are taking place in APAC, boosted by the growth in novel drug discovery taking place in the region, added to the background of multi-regional clinical trials by global pharma companies. China will increase its share of global activity, while each of the other major countries in APAC has defining and differentiating features that make them an attractive proposition for clinical research.

This article has been adapted from a white paper, APAC as a Clinical Trials Powerhouse, using Citeline's gold-standard clinical trials intelligence solution Trialtrove. To read the white paper in full, and to learn more about Trialtrove, please visit https://pharmaintelligence.informa.com/resources/product-content/2022/10/06/13/24/the-clinical-trials-landscape.



Big Pharma Rescripts India Playbook

Big pharma appears to be resetting operations in India, fueling some concerns of waning interest. *In Vivo* looks at what the realignment means or doesn't.

BY **ANJU GHANGURDE,** EXECUTIVE EDITOR, ASIA-PACIFIC

Foreign firms have been re-calibrating activities in India over the recent past, with some handing over marketing of mature brands to local partners and others effecting layoffs to fine-tune their go-to-market model. Divestment of non-core products and sites that have been underutilized or hit by altered market dynamics have also formed part of these reviews.

While the realignment and cutbacks have raised concerns around big pharma's waning interest in the ultra-competitive and largely out-of-pocket Indian market, most foreign drug makers have emphasized that there's no big pullback underway, at least for now.

Many instead painted a picture of sustained product launch activity, a distinct role for India in data analytics/management and using digital as a platform (*see box*) and an uptick in clinical trial activity, real and perceived barriers notwithstanding besides ongoing efforts to support the underlying innovation ecosystem, including backing start-ups.

What perhaps triggered some of the concerns was a string of headline-grabbing developments that included Novartis India Ltd.'s sales and distribution agreement for a range of established medicines with Dr. Reddy's Laboratories Ltd. that came with layoffs, as well as hundreds of field force job cuts by Pfizer Ltd. (India) as it transitions to more efficient commercial models with digitization at their crux.

Divestments by Sanofi and GlaxoSmithKline plc (including the sale of a site singed by the altered outlook for ranitidine) over the recent past and H.Lundbeck A/S's shuttering of its India operations in 2021, after it felt that its existing and future portfolio did not support "sustainable" operations in the country have also weighed on the pullback narrative.

WORLD VIEW

"Engine" Of Novartis

Novartis AS, which faced flak on social media after its listed arm Novartis India Limited (NIL) slashed 400 jobs as part of the deal with Dr Reddy's, however, asserted that its India commitment isn't fading.

The group, whose India operations goes back to 1947, noted that it has had a significant footprint in the country that today spans across drug development, manufacturing, commercial and social business services.

"India is home to one of three major Novartis global development sites and largest of five global service centers delivering high-quality business services to Novartis. Our innovative medicines division, formed by integrating our pharmaceuticals and oncology business units earlier this year, will continue to bring in innovations to patients in India," the company told *In Vivo*.

The Swiss group, which operates through three legal entities, namely, Novartis Healthcare Private Limited, Sandoz Private Limited and NIL in the country, stressed that its commitment towards building a team in India that is the "engine of Novartis" is more important than "ever before" to its global success.

"We strongly believe that the talent in India has the power to drive innovation and operational excellence necessary to reimagine medicine and to enable that we're building a culture that ensures this potential is realized to its fullest," it stated.

"We are committed to grow the presence of our iconic brands in India, while chasing the miracles of science to improve people's lives."

Sanofi India

Nevertheless, the deal with Dr Reddy's that handed over sales and distribution of certain established brands, accounting for 50% of NIL's 2020-2021 product revenues, to Dr Reddy's has been a talking point in industry and raised some questions, especially around NIL's onward trajectory.

Does it imply that most new products will launch via the group's 100%-owned unlisted entities in India and more measured commercialization efforts are in store? Novartis didn't specifically comment on the launch vehicle but stressed that it is powering the next phase of its transformation journey by "increasing efficiency and strengthening the impact of its innovative portfolio" to accelerate growth, to drive access for its innovative medicines to patients around the world, including in India.

"Like many other expedited launches of innovative molecules, we launched Kesimpta (ofatumumab; Bonspri) earlier this year for people living with multiple sclerosis. Going forward, we will continue to look at ways to best deliver for patients in India," the company said.

There is also some speculation around whether the deal with Dr Reddy's is perhaps, in some way, a precursor to potential plans down the line to move towards delisting the Indian arm – something that Novartis India has refuted in the past. Industry watchers have pointed to how several new products including Entresto (sacubitril/valsartan; sold as Vymada in India) have been routed in the past via the Swiss firm's 100%-owned entity, "diminishing the value of the listed entity making it a bargain buy-back."

Employee strength at NIL was down to 81 in 2021-22 versus 539 in 2020-21, though at the time of the deal with Dr Reddy's the Swiss group said that overall it had more than 10,000 full time employees in India. It added that since January 2020, Novartis had hired more than 1,600 employees across divisions and companies in India and expects to continue this hiring program in 2022-2023. The group had launched Novartis Biome India, its first digital innovation hub in Asia in 2020, which followed similar Biome initiatives in San Francisco, Paris and London. Novartis, though, isn't the only MNC that has tapped local partners for marketing mature brands.

Eli Lilly and Company had previously similarly transferred India rights to partner Cipla to sell, promote and distribute Humalog (insulin lispro (rDNA origin) injection) and Trulicity (dulaglutide); over 100 jobs at Lilly were reported to have been cut following the deal.

Lilly, though, clarified at the time that it will continue to maintain its "existing operating model" for the remaining portfolio of products in the country.

Industry experts said that many multinational companies are now increasingly keen to focus resources on their specialty products portfolio, keeping field force "energies" directed towards these and patented product launches. Marketing partnerships with generic companies are an increasingly viable option given the "size of the local companies' feet on the ground," one expert explained.

Pfizer Leverages Digital Core

Sales and marketing are perhaps where much of the churn is visible. 2022 also saw Pfizer Inc. axe several jobs in India as the US multinational rewired its commercialization thrust and created new roles leveraging digitization. It is thought that about 200 field force employees were let go earlier this year as the company transforms its go-to-market model and reallocates resources and capabilities.

At the time, Pfizer explained that strategic changes to the workforce were being implemented to ensure it has the "expertise and resources in place" to meet the changing needs of customers. New roles that focus on leveraging its "digital core" and increased virtual and expanded science-based engagement have been created.

"These roles are being take up by existing (where eligible) and new colleagues. We are also upskilling our commercial colleagues to take advantage of the many new functionalities being created to enhance the quality of our customer engagement. In certain cases, a fit-to-purpose approach unfortunately requires that some of our colleagues pursue their future career outside of Pfizer," the company said.

The US firm, however, underscored that India is an important market, adding that its approach is based on the fact that all parts of its portfolio – established and innovative are steadily growing and impacting a larger patient base. "For our established portfolio, our priority will be to significantly expand our customer and patient reach. For our innovative portfolio, we are investing in enhanced physician and patient experiences, global-quality content, digital platforms and subject matter expertise," it added.

"There was optimism about MNCs in India delivering superior returns to investors due to higher margin mix, better operational efficiency etc. While some of this is true, the competitive advantage is being rapidly lost."

Salil Kallianpur, former VP, GSK India

GSK has similarly cut over 150 jobs from its commercial trade channel business in India as part of a strategic review that will see the UK multinational leverage its digital reach instead.

But some experts contend that the digitization-led shifts may not be the only reasons driving right-sizing efforts in foreign firms in India. Neither are the job cuts specific to just India or pharma, with some pandemic-galvanized sectors now relatively slowing down.

More widely, a reoriented long-term strategic thrust coming from the parent companies, efforts to tackle a highly unionized workforce that is less inclined to upskilling and fatigue over India's pricing policy approach have also contributed to the local re-calibration.

"Global big pharma is keen to have local operations look at alternative promotion models that lower spends, reduce footprint from tier two, three cities and focus on the global product pipeline [which in turn needs coverage essentially in the large metros and tier one cities]," explained a senior industry executive with years of experience at the helm of a foreign firm. For instance, new oncology products may not merit a large footprint in smaller towns in interior India where sales may not match up. "The newer pipelines rarely have a primary care focus, so you don't need the kind of coverage that currently exists. It's a kind of natural manifestation of how the pipelines of companies are moving," he indicated.

Others asserted that the layoffs in the case of MNCs essentially stem from strategic decisions taken at the headquarters – such as a review of established brands and hiving off non-core businesses. Companies shed the old and focus on the new, and India has not really been a "focus market" for MNCs for a while – hence it isn't unusual to see an aging portfolio, few new product launches, and a relatively small proportion of the portfolio with patent protection, said Salil Kallianpur, a former executive vice-president at GSK in India.

"Since a larger proportion of the Indian business lies in these areas, the changes affect India more than elsewhere. Therefore, I don't think this is an outcome of digitization in pharma," Kallianpur, who now runs a digital health consultancy, then said.

Pfizer had some years ago shed certain non-core products, including the medicated soap Neko and nutritional supplement Ferradol, marketed by its global established products business in India to Piramal Enterprises Limited and also divested its rights and interests in two "tail brands" – Amisant (amisulpride) and Nebasulf (neomycin /bacitracin/sulfacetamide) – to Abbott Laboratories Limited. It had pulled the plug on two "unviable" sites in India in 2019. Last year Pfizer India transferred certain brands along with related business assets and liabilities to Viatris Inc.'s Indian arm following the 2019 Mylan-Upjohn global deal.

As of 2021-22, Pfizer Ltd., the listed entity in India, has 150 products (in 2016-17 the figure stood at 200-plus, though it may not be a like-to-like comparison given portfolio reviews) across 15 therapeutic areas in India.

Sanofi's Regular Assessments

Peer Sanofi too has pruned its portfolio over the recent past, though most foreign firms have explained that as exiting non-strategic areas to hone in on core areas where they can "win", and emerge more efficient.

Sanofi India told *In Vivo* that it regularly assesses the best ways to serve patients and customers and as a result follows a "continuous on-going process" of focusing on categories where it can have better impact for patients, health care professionals and stakeholders. "We are committed to grow the presence of our iconic brands in India, while chasing the miracles of science to improve people's lives," Sanofi emphasized but didn't specify whether we've seen the tail of the India revamp.

The company had earlier divested brands such as skin cream Soframycin and Sofradex manufactured via third-party arrangements to Encube Ethicals Private Limited and its nutraceuticals business in 2021 to Universal Nutriscience, a strategic partnership between private equity Kedaara Capital Fund II LLP and Universal Medicare. All Sanofi employees associated with the business were to transition to Universal Nutriscience. In 2020 the company sold its Ankleshwar factory and few products to Zentiva Pvt Ltd.

But the French group, which has been gearing for price control transition for its key product Lantus (insulin glargine) in India, has signaled upcoming launch momentum. While Dupixent (dupilumab) for atopic dermatitis awaits regulatory approval for launch in India, in the rare diseases space

Nexviazyme (avalglucosidase alfa-ngpt) and Xenpozyme (olipudase alfa-rpcp) are in the pipeline for launch in the next 12-24 months.

MNC Strategy Stayed Polycentric?

The launch impetus notwithstanding, experts expect multinationals in India to continue to right-size operations under competitive pressure. Abbott is the only MNC in the top 10 rankings in India (March 2022 IQVIA data) catapulted by its takeover of Piramal's domestic formulations business.

Ex-GSK executive Kallianpur told *In Vivo* that around the time of the Abbott deal in 2010, MNCs were quite bullish about India and thought they could "go glocal" by striking deals to launch generics, co-market for greater access and improve margins via local loan licensing deals. "Unfortunately, their strategy stayed quite polycentric and didn't really adapt to the competitive challenges of the country. Eventually in the last decade Indian companies that stepped up their competitiveness have all but outplayed the MNCs," he pointed out.

The executive expects more MNCs to adopt various "new ways of working", accompanied by sales force downsizing and deploying digital channels to reach HCPs. "There was optimism about MNCs in India delivering superior returns to investors due to higher margin mix, better operational efficiency, etc. While some of this is true, the competitive advantage is being rapidly lost. India will continue to be a market of interest to MNCs (research, data and manufacturing hub), just not from a market share sense," he declared.

Roche for one sees India as a "massive priority market," amid the Swiss group's Pharma Vision 2030 that hopes to provide three to five times more patient benefit at 50% cost to society by that timeframe.

India – Pharma's Data Services Hub?

Playing out alongside some of the India cutbacks is the notably upbeat tenor of MNCs like Roche, Bayer AG and Novo Nordisk AS in India, especially around the launch pipeline and amping up capacity and capabilities in the data science/services area.

Roche for one sees India as a "massive priority market", amid the Swiss group's Pharma Vision 2030 that hopes to provide three to five times more patient benefit at 50% cost to society by that timeframe.

Roche has accelerated launch timelines and has a pipeline of 20-plus new products and indication extensions planned for the next three to five years in India across oncology, hematology, ophthalmology and neurology. It has rolled out in India products like Hemlibra (emicizumab) within 14 months of the international debut, while Evrysdi (risdiplam) hit the Indian market within 10 months of the US launch. This, versus a 24-36 month India debut lag generally seen in industry about five to six years ago.

In 2020 Roche made a "big shift" in its India strategy, adopting a new cluster operating model and took "some bold steps" in its portfolio strategy with an aim to "focus on the core" and partner for the rest.

"We have made many key leadership hires in line with our operating model. Driving access to our innovations is our single biggest priority, V Simpson Emmanuel, CEO and MD, Roche Pharma India, told *In Vivo*.

On the data front, Roche has set up its second Global Analytics and Technology Centers of Excellence (GATE) in Hyderabad, the first being in Chennai. The company aims to use big data analytics to help it gain better understanding of the patient journey and partner more effectively with physicians, hospitals and other health care providers. "GATE is working on building strong knowledge of the health care landscape across different countries and utilizing its expertise in data science and advanced analytics to serve its global affiliates," Emmanuel said.

A few years ago, Bayer had similarly set up a data science analytics center in Hyderabad and has been expanding capabilities. "It's not just the data manager, the data leads, but also typically biostatistician roles, roles at senior level in the R&D structure, which are not always doing the R&D work for India, but also globally," Manoj Saxena, country division head for South Asia, Bayer Pharmaceuticals Pvt. Ltd, said at a recent industry do.

Pfizer is also engaged in data analytics, data management, and using digital as a platform; it sees significant talent available in India to engage and participate in global product development from a data and digital platform standpoint.

Ex-GSK executive Kallianpur said that it is no secret that India offers some of the world's best and low cost digital data management and analytical centers, making it a destination for most MNC off-shoring and pharma is no exception.

"India is being extensively evaluated as a possible hub for offshoring data storage, management and analytical needs. Since this is expected to be the fulcrum of the pharma industry in the future, this is likely to be pharma's IT-like moment for India."

Pandemic Drives China Surge In Asia 100 Sales

Notable new entrants moved into the Asia 100 this year, with growth catalyzed by COVID-19 vaccines.

BY **IAN HAYDOCK,**
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Looking at the top 10 rankings of APAC pharma companies by pharma sales in 2021, two things are apparent – the impact of the ongoing COVID-19 pandemic and the steady rise into the top regional echelon of pharma companies from China. In some cases, the two were related.

While Takeda held on to the top spot as the company with the largest pharma sales in Asia, helped by continued global growth for its mainstay product, Entyvio (vedolizumab) for inflammatory bowel disease, the top 10 marked the ongoing emergence of China as a pharma power.

The two new entrants this time – Sinovac Biotech and Shanghai Fosun Pharmaceutical Group – displaced China's sole representative the previous year, Jiangsu Hengrui Medicine, which slipped to 12th. Sinovac surged up the rankings from a lowly 79th in 2020 to overtake Astellas and move into second position.

Sinovac's astonishing growth was helped by the manufacturing and global supply of the inactivated COVID-19 vaccine CoronaVac, more than 2.8 billion doses of which have currently been supplied worldwide, for use in more than 60 countries. The company has built annual capacity to more than two billion doses and also saw improved sales of its other vaccines in China as the initial impact of the pandemic on doctor visits subsided.

Shanghai Fosun Pharma, meanwhile, moved up to ninth from 15th on the back of higher sales outside China, including of BioNTech's mRNA vaccine Comirnaty, to which it holds rights in selected Asian markets such as Hong Kong SAR, Macau SAR and Taiwan. It also saw new domestic launches in the oncology sector, notably the CAR-T therapy Yi Kai Da (axicabtagene ciloleucel) through the Fosun Kite joint venture.

Elsewhere in the premier league, Japan continued to field the strongest team, accounting for six of the top 10 players, although growth rates varied across the board, dependent on varying product mixes, therapeutic area presence and presence in international markets. Sumitomo Dainippon Pharma's figures were affected mostly by price cuts in Japan and lower export sales.

While it has been benefitting more recently from the growth of oncology antibody-drug conjugate Enhertu (trastuzumab deruxtecan), Daiichi Sankyo slipped from fourth in last year's rankings – hit in the period under review by price cuts in Japan and termination of a vaccine collaboration, along with forex impact.

India's largest pharma company Sun Pharma held onto its top position in that country, as did global biosimilars giant Celltrion in its home market of South Korea.

The ongoing impact of the pandemic will continue to play out across the industry both in APAC and beyond and while next year's rankings seem certain to reflect lower sales of pandemic vaccines, there should also be more of a return to business as usual in other areas, as patients resume in-person medical consultations and hospital treatments.

WORLD VIEW

Scrip Asia 100 Rank	Company	2021 Pharma Sales ($m)	Change From 2020 (% Basis)
1	Takeda	32,514	9%
2	Sinovac Biotech Ltd.	19,375	3,694%
3	Astellas	11,808	4%
4	CSL	9,980	9%
5	Otsuka Pharmaceutical	8,905	0%
6	Eisai	6,889	14%
7	Sun Pharmaceutical	5,199	15%
8	Sumitomo Dainippon Pharma	4,700	-3%
9	Shanghai Fosun Pharmaceutical Group	4,461	41%
10	Daiichi Sankyo	4,456	-51%
11	Sino Biopharmaceutical	4,165	21%
12	Jiangsu Hengrui Medicine Co. Ltd.	4,016	0%
13	Shanghai Pharmaceutical Group Co., Ltd.	3,891	13%
14	Asahi Kasei Pharma	3,789	-1%
15	Mitsubishi Tanabe Pharma	3,516	-1%
16	CSPC Pharmaceutical Group Ltd.	3,250	3%
17	Kyowa Hakko Kirin	3,209	8%
18	Aurobindo	3,173	2%
19	Cipla	2,939	15%
20	Sichuan Kelun Pharmaceutical	2,679	12%
21	Dr Reddy's	2,567	0%
22	Shionogi	2,510	9%
23	Joincare Pharmaceutical Group Industry Co., Ltd.	2,466	26%
24	Shandong Buchang Pharmaceuticals Co., Ltd.	2,444	5%
25	Santen	2,274	3%
26	Ono	2,241	11%
27	Lupin	2,191	7%
28	Zydus Lifesciences (earlier Cadila Healthcare)	2,043	0%
29	Harbin Pharmaceutical Group Co., Ltd.	1,985	27%
30	Livzon Pharmaceutical Group	1,870	23%
31	Sawai	1,766	1%
32	Meiji Holdings	1,712	-6%
33	Teijin Pharma	1,672	20%
34	Celltrion	1,671	6%
35	Glenmark Pharmaceuticals	1,665	13%
36	Nichi-Iko	1,631	-7%
37	Shijiazhuang Yiling Pharmaceutical Co., Ltd.	1,559	23%
38	Jiangsu Hansoh Pharmaceutical	1,540	22%
39	Yuhan Corp	1,475	7%
40	Zhejiang Medicine Co., Ltd.	1,415	33%
41	CR Double-Crane Pharmaceuticals Co., Ltd.	1,413	15%
42	Towa	1,411	-3%
43	Samsung BioLogics	1,371	39%
44	GC Pharma	1,344	5%
45	KPC Pharmaceutical Inc.	1,280	14%
46	Chong Kun Dang	1,174	6%
47	Kwang-Dong Pharmaceutical	1,170	11%
48	Torrent Pharmaceuticals	1,139	5%
49	Biocon	1,107	15%
50	Nippon Shinyaku	1,099	3%
51	Hisamitsu	1,095	2%
52	Hanmi Pharm	1,052	15%
53	Zhejiang Huahai Pharmaceutical Co., Ltd.	1,030	10%
54	Daewoong Pharmaceutical	1,008	12%
55	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	987	28%
56	3SBio	972	21%
57	Luye Pharma Group Ltd.	972	21%
58	Kyorin	961	0%
59	Zhejiang Conba Pharmaceutical Co., Ltd.	954	11%
60	Mochida	938	-2%
61	Piramal Healthcare	907	16%
62	PT Kimia Farma	900	30%
63	Jubilant Pharmova (earlier Jubilant Life Sciences)	829	0%
64	SK Bioscience	812	0%
65	Maruho	799	-4%
66	Dong-A Socio Holdings	771	16%
67	Shandong Lukang Pharmaceutical Co., Ltd.	758	24%
68	Japan Tobacco	732	-1%
69	Alembic	718	-1%
70	CK Life Sciences	695	92%
71	Kaken	693	11%
72	SSY Group Limited	689	25%
73	Hualan Biological Engineering, Inc.	688	-6%
74	HK inno. N (formerly CJ Healthcare)	673	32%
75	Laurus Labs Ltd.	668	10%
76	Shanghai RAAS Blood Products Co., Ltd.	665	66%
77	Jeil Pharmaceutical	661	13%
78	Shanghai Junshi Biosciences Co., Ltd.	624	170%
79	Innovent Bio	620	81%
80	Takara Bio Inc.	617	43%
81	Jiangsu NHWA Pharmaceutical Co., Ltd.	610	25%
82	Zhuzhou Qianjin Pharmaceutical Co., Ltd.	568	8%
83	Jiangsu Kanion Pharmaceutical Co., Ltd.	566	29%
84	Walvax Biotechnology Co., Ltd.	537	26%
85	JW Pharmaceutical Corporation	530	14%
86	Dongkook Pharm	519	9%
87	Sihuan Pharmaceutical Holdings Group Ltd.	510	43%
88	Kissei	493	-7%
89	Guangxi Wuzhou Pharmaceutical Group Co., Ltd.	490	-6%
90	Il-Dong Pharm	490	3%
91	Harbin Gloria Pharmaceuticals Co., Ltd.	488	10%
92	Toray Industries	483	-3%
93	Zeria Pharmaceuticals	479	70%
94	Nippon Kayaku	475	0%
95	Japan Lifeline Co., Ltd.	469	-2%
96	JCR Pharmaceuticals	465	65%
97	Xiangxue Pharmaceutical Co., Ltd.	461	3%
98	Hebei Changshan Biochemical Pharmaceutical Co. Ltd	460	34%
99	Mega Lifesciences Public Co. Ltd.	442	9%
100	Wockhardt	434	12%

The Asia 100 ranking is based on Citeline's analysis of fiscal year 2021 prescription sales data. For more information contact: Ian.Haydock@informa.com.

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