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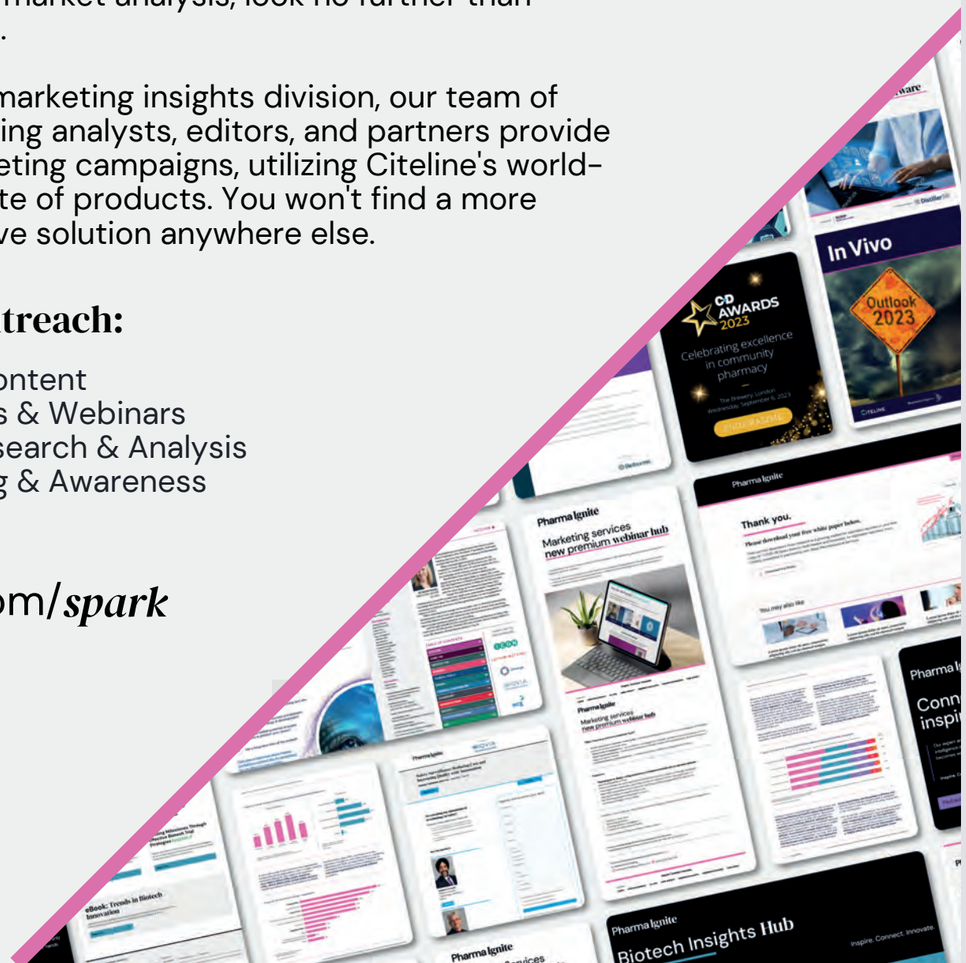

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LUCIE ELLIS-TAITT,
EXECUTIVE EDITOR

An unsteady geopolitical situation in eastern Europe, worldwide inflation and the politicization of drug pricing in the US all made their mark on 2023.

Making predictions about the biopharma world is always a tricky endeavor, but looking ahead into 2024 reveals an uptick in deal-making and perhaps the return of larger scale M&A, as big pharma feels the pressure to fill pipeline gaps at a faster rate.

2024 will perhaps be a transition year as biopharma and medtech companies get through the worst of the market turmoil.

Obesity and CNS diseases are creating fresh growth areas for big pharma. And oncology has bounced back after being overshadowed in the R&D setting by COVID-19. Technological developments hold a lot of promise, but also bring a lot of confusion about best uses. The speed of development for artificial intelligence tools is outpacing the health care sector.

For medtechs, as well as an unstable financial market, environmental demands are adding pressure. Meanwhile, health care systems are grappling with rapid change in the structure of care delivery and how to adjust payment models to facilitate the ongoing move to care delivered in the ambulatory setting and at home.

Outlook 2024 includes exclusive interviews, data, features and industry league tables for *Scrip 100, Medtech 100 and Generics Bulletin's Top 50*.

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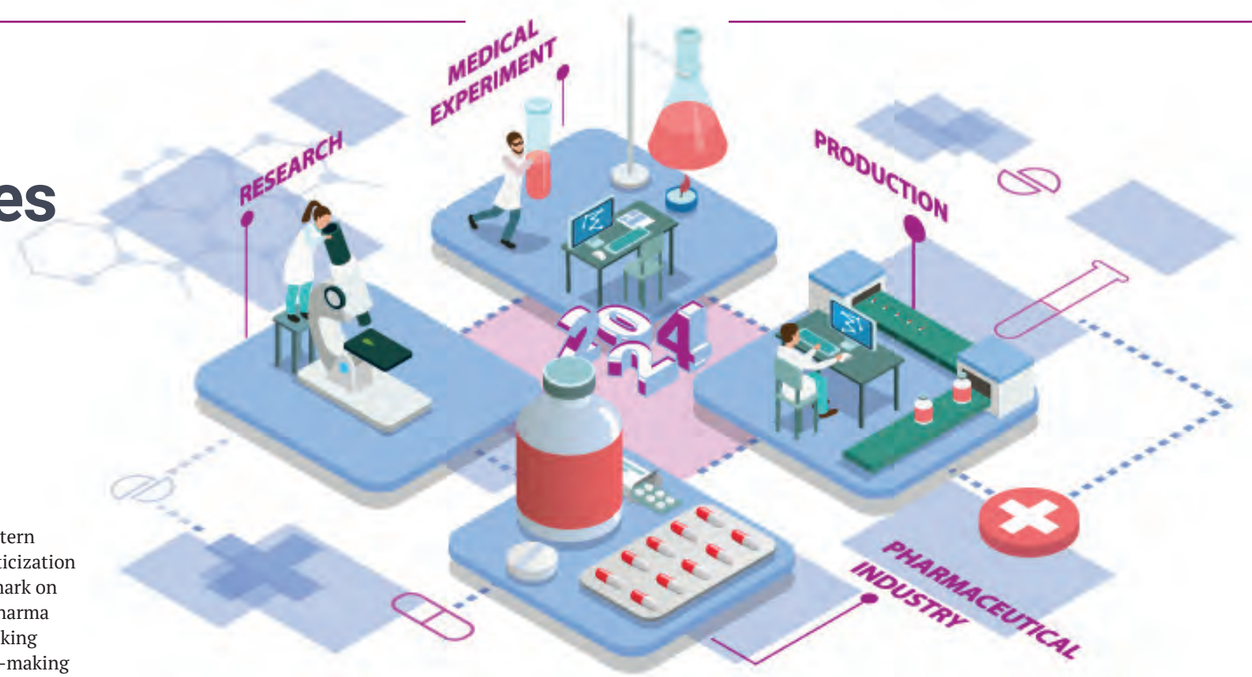
OUTLOOK

Biopharma Embraces New Markets And New Tech

New markets, a patent cliff, an M&A rebound and clinical trial catalysts. How will it all play out for the biopharma sector in 2024?

BY **LUCIE ELLIS-TAITT,** EXECUTIVE EDITOR



An unsteady geopolitical situation in eastern Europe, worldwide inflation and the politicization of drug pricing in the US all made their mark on 2023. Making predictions about the biopharma world is always a tricky endeavor, but looking ahead into 2024 reveals an uptick in deal-making and perhaps the return of larger scale M&A, as big pharma feels the pressure to fill pipeline gaps at a faster rate. The unprecedented demand for new treatments in obesity has meant a couple of companies have fuller pockets and, in turn, more cash to put to work.

The industry is moving closer to a large and extended patent cliff, a period of time from 2025 to the end of the decade when many of pharma's biggest revenue generating products are facing loss of exclusivity (*see Exhibit 1*).

While the maturation of understanding around diseases such as obesity and long-awaited novel approvals in Alzheimer's will start to fill the gap, there is not sufficient pipeline growth to make up the difference. According to Evaluate Pharma, there is $14.1bn in US sales at risk in 2024.

As well as a look at deal-making in the year ahead, *In Vivo* has highlighted a number of key development areas to watch in 2024 alongside anticipated clinical trial readouts.

Deal-Making In 2024

At November's BIO-Europe Fall conference, held in Munich, Ipsen's EVP, chief business officer, Philippe Lopes Fernandes, highlighted the challenging market in 2023. He told delegates during a panel discussion on navigating biopharma deal-making, "It has been a challenging market, especially for public companies. Thank god for the biotech CEOs they are not all public, and right now it is much better to be a private biotech than a public one. The market is crazy, but the fundamentals are right."

Bradley Hardiman, senior director, Astellas Venture Management, described the situation for companies looking for deals and raising funds as "tightly controlled at the moment."

"We hear about dry powder, venture capital funds, but there is still fear in the market and we need to flip that confidence level," Hardiman said. "Dry powder on its own is pointless, but let's make some fireworks and do some deals. Pharma is very active but there is pressure on our share price: we are not immune to what is going on in the market."

SVP, head of global business development & alliance management at Merck KGaA, Matthias Müllenbeck, noted that M&A deals had focused on "post-proof of concept" assets in 2023. But he expects more earlier stage deals in 2024. "The number of targets with totally de-risked assets is limited," he said. "You will need to move into more earlier space, you will need to take more risk, despite having all of these uncertainties in the market."

Müllenbeck was cautious about the deal-making environment in 2024. He predicts a slower rebound for the market. "It will be a tough time ahead of us. The financing environment will likely not change dramatically. We will not go back to a money-for-free set-up, which will also drive industry consolidation at all levels. If I talk with our friends at the law firms, they are pretty busy not with doing stuff for the buy side, but preparing for mergers and reverse mergers at the moment, to get the cash to the assets that people believe should be invested in."

New Growth Markets

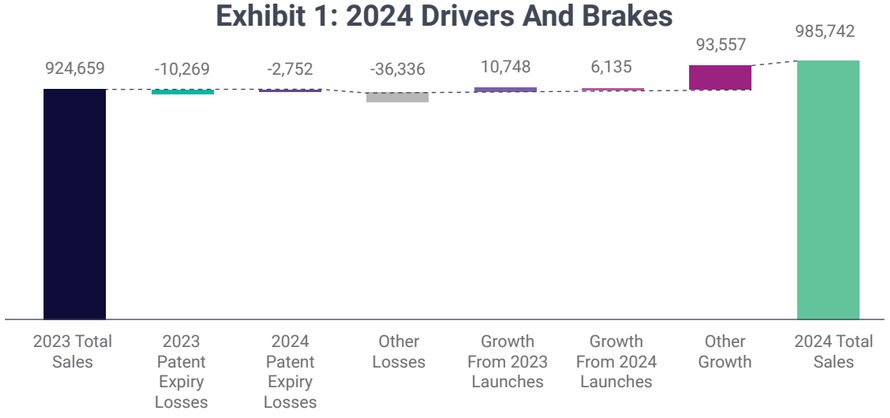
Obesity and CNS diseases are creating fresh growth areas for big pharma (*see Exhibit 2*).

In the first half of 2023, sales of Novo Nordisk's Wegovy increased by 367% to DKK12.08bn ($1.70bn) and analysts expect these figures to go through the roof in years to come, especially as Novo Nordisk expands its manufacturing capacity to address the current shortage of the drug.

At a Q3 2023 event in Copenhagen, Mads Krogsgaard Thomsen, CEO of the Novo Nordisk Foundation, said Novo Nordisk could be forgiven for not predicting such an impact as Wegovy was the first entrant into "a market that didn't exist," given that previously the only clinical option for obese people was bariatric surgery.

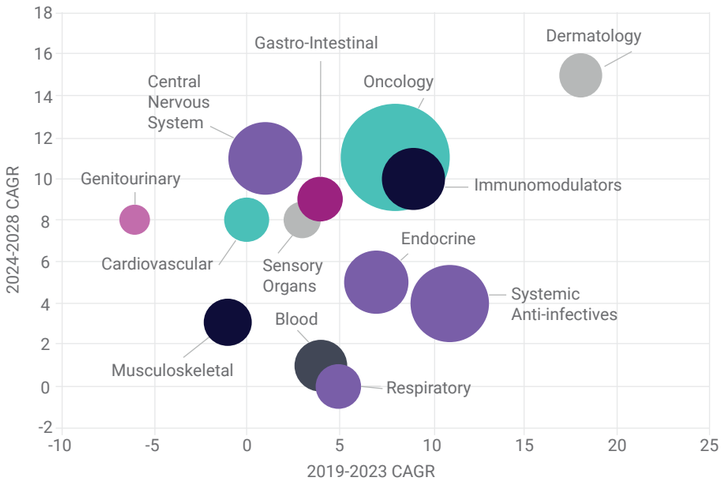
Other therapeutic options for treating obesity are emerging and the cardiovascular-metabolic (CVM) space has been reinvigorated in recent years. According to recent data presented at the Sachs Biotech in Europe Forum, clinical-stage cardiometabolic assets account for around 7% of the overall industry R&D pipeline. The top five diseases by number of studies under the cardiometabolic R&D umbrella are diabetes, NASH, hypertension, obesity and heart failure, which collectively represent about 50% of the clinical-stage CVM pipeline.

Exhibit 1: 2024 Drivers And Brakes



Source: Evaluate Pharma

Exhibit 2: Therapy Area Growth



Source: Evaluate Pharma

Novo Nordisk is also expanding its CVM pipeline. In October 2023, the company announced it was acquiring ocedurenone for uncontrolled hypertension, with potential application in cardiovascular and kidney disease, from KBP Biosciences for up to $1.3bn. Ocedurenone is an orally administered, small molecule, non-steroidal mineralocorticoid receptor antagonist that is being tested in the Phase III CLARION-CKD trial in patients with uncontrolled hypertension and advanced chronic kidney disease. Novo Nordisk expects to initiate Phase III trials for ocedurenone in additional cardiovascular and kidney disease indications in the coming years.

In the year ahead, a number of clinical trial readouts are expected for drugs targeting Alzheimer's disease (AD). CNS diseases have seen renewed interest following the approval of new treatments for Parkinson's and Alzheimer's disease. The unmet need in is huge, as is the market potential for drugs able to demonstrate a slowing of progression in symptoms or those able to tackle underlying causes of CNS conditions.

> **"Dry powder on its own is pointless, let's make some fireworks."**
>
> Bradley Hardiman,
> Astellas Venture Management

The landmark, yet controversial, US approval of Biogen and Eisai's anti-amyloid antibody Aduhelm came despite Phase III clinical trial data resulting in one positive and one negative study. In its announcement of this groundbreaking approval, the US Food and Drug Administration (FDA) acknowledged there was some uncertainty around the data, but reiterated that the treatment was the first to show a benefit in amyloid plaque reduction, thus targeting the underlying disease pathology rather than masking symptoms. The FDA's accelerated approval of Aduhelm based on amyloid reduction rather than cognitive improvement lowered the bar for approval, though market access barriers remain.

In July 2023, Eisai's Leqembi (lecanemab) became the first anti-amyloid antibody to gain full approval from the FDA, after receiving accelerated approval from the agency in January the same year. Though competitor Eli Lilly's donanemab may have a slight efficacy advantage, physicians may favor Leqembi's better safety profile. A traditional approval decision for donanemab is expected by the end of 2023. Despite uncertainties around efficacy and barriers to access, the high unmet need may ultimately create a lucrative market for anti-amyloid antibodies. If positive, data from subcutaneous formulations of anti-amyloid antibodies may generate excitement about a more desirable formulation coming down the pipeline.

Datamonitor Healthcare analyst Pamela Spicer told *In Vivo*, "Eli Lilly's next-generation plaque-removing antibody remternetug targets the same pyroglutamate residue as donanemab but is designed to avoid the level of anti-drug antibodies." Lilly has initiated the Phase III TRAILRUNNER-ALZ 1 study evaluating a subcutaneous injection and an intravenous infusion of remternetug. A subcutaneous formulation of Leqembi is also being developed.

Spicer highlighted biomarker results presented from a Phase I/IIa study of Biogen's BIIB080 in patients with mild AD as "the most exciting data to emerge from 2023." BIIB080 is an antisense oligonucleotide designed to reduce concentrations of MAPT messenger RNA and thus reduce the production of all tau species within the CNS. During the study, patients on placebo maintained relatively stable levels of CSF tau, whereas patients on BIIB080 demonstrated a dose-dependent reduction in CSF tau over the three-month treatment period. In the two highest dose cohorts, CSF tau continued to decrease after treatment was discontinued, though patients on the lower doses saw a rebound in their CSF tau levels once treatment stopped. With regard to the tau PET imaging results, which reflect aggregated forms of tau in the brain, patients that received placebo demonstrated a slight increase from baseline in tau across the majority of brain regions assessed. This is consistent with natural disease progression. For treated patients, those on the highest dose showed a slight reduction in tau burden across all brain regions.

Although tau tangles, along with beta-amyloid plaques, are considered hallmark pathological features of Alzheimer's disease, tau-based strategies remain underrepresented in the late-phase clinical pipeline.

Cancer Retakes Top Spot

Each year in its Clinical Trials Roundup, Citeline's Trialtrove team analyzes the top 10 diseases for clinical trial activity to get a view of where research efforts are taking place. The most recent dataset looks at all trials in the full year of 2022. After a two-year reign, COVID-19 finally gave its number one spot back to an oncology disease (unspecified solid tumor, 566 trials), though it continues to exert its presence in a close second place (563 trials).

Looking more broadly at therapeutic areas, oncology continued to be the top-ranking development area with a clear lead, even though its trial initiations were down by 10%.

Within oncology, bladder, prostate and ovarian cancers will potentially gain more attention in 2024. Datamonitor Healthcare analyst Millie Gray told *In Vivo* that although bladder cancer is a very difficult disease to treat, "there has been a hub of research around this indication and the work is finally coming to fruition."

She noted that in 2023, Merck & Co.'s Keytruda (pembrolizumab) plus Seagen's Padcev (enfortumab) met its primary endpoint in the Phase III EV-302 trial, becoming the first targeted combination therapy to show an overall survival benefit over the current first-line standard of care, carboplatin or cisplatin in combination with gemcitabine. "This will become the new standard of care and will change the treatment paradigm," Gray said.

In prostate cancer, there is excitement around Novartis AG's radioligand therapy Pluvicto (lutetium vipivotide tetraxetan) and its use in wider prostate cancer indications. The product won its first US approval in March 2022 for the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) patients who had previously been treated with both androgen-receptor pathway inhibitor (ARPI) therapy and taxane-based chemotherapy, based on the VISION study. Data are expected in the first half of 2024 from the Phase III PSMAddition trial, which is looking at Pluvicto in the metastatic hormone-sensitive prostate cancer indication (mHSPC). This lucrative setting is mainly comprised of *de novo* metastatic prostate cancer patients, and is heavily dominated by hormonal therapies such as Xtandi and abiraterone. "Competition here will be fierce but an approval will widen Pluvicto's reach in prostate cancer, bringing it a step closer to being ubiquitous across prostate cancer settings," Gray said.

Another key readout from the PSMAfore trial, looking at patients in the pre-chemo setting, will likely lead to a pre-chemo (but post next-gen hormonal therapy) approval sometime in 2024, further expanding Pluvicto's reach.

Also, a well-established standard of care, Xtandi, is expected to gain approvals in the high-risk biochemically recurrent setting based on data from the Phase III EMBARK trial. Gray noted that a regulatory nod for Xtandi in this setting "could change how a large proportion of prostate cancer patients are treated."

Datamonitor analyst Ellie Davenport also spotlighted the first-line advanced ovarian cancer setting as an area likely to gain prominence in 2024. This indication is expected to see PD-1 and PARP inhibitor combinations gain approvals from 2024. The Phase III DUO-O trial investigating Imfinzi plus Lynparza is the only trial to read out so far, but more are expected in 2024. Currently, only PARP inhibitors, bevacizumab and chemotherapies are treatment options for untreated advanced ovarian cancer. "The launches of PD-1/PD-L1 inhibitor combinations have the potential to shift the first-line treatment paradigm through the introduction of new options for patients without a BRCA1/2 mutation or HRD deficiency," Davenport told *In Vivo*. (*See Table 1 for late-stage cancer trial data expected in 2024.*)

Table 1: Select Oncology Trial Readouts To Watch For

Drug/ Developer	Clinical Trial	Analyst's Comments
Enhertu/ Daiichi Sankyo	Phase III DESTINY-Breast06	HR+/HER2-low breast cancer patients who have progressed on endocrine therapy in the metastatic setting. Positive data will cement its use as the leading ADC for HR+/HER2-low breast cancer, where it already has an approval based on the Phase III DESTINY-Breast04 trial.
Imfinzi/ AstraZeneca	Phase III NILE	Imfinzi in combination with standard of care chemotherapy and Imfinzi in combination with tremelimumab and standard of care chemotherapy versus standard of care chemotherapy alone in patients with unresectable locally advanced or metastatic bladder cancer. Keytruda is currently leading ICI in this setting.
Krazati/ Mirati	Phase III KRYSTAL-12	Krazati and JDQ443 are being tested in patients with previously treated KRASp.G12C-mutated NSCLC. Patients with KRAS-positive NSCLC were previously deemed 'undruggable' and responded poorly to immunotherapy treatments. If either Krazati or JDQ443 can demonstrate a survival benefit in a Phase III trial, they will likely become the treatment of choice.
JDQ443/ Novartis	Phase III KontRASt-02	See above
Jemperli combinations/ GSK	Phase II/III COSTAR	GSK is testing a triplet of cobolimab in combination with Jemperli and docetaxel, as well as a doublet of Jemperli plus docetaxel, against docetaxel alone in the Phase III COSTAR Lung trial in patients with advanced NSCLC whose disease has progressed on previous PD-1/PD-L1 inhibitor treatment. The post-immunotherapy setting is a setting of high unmet need and represents a large commercial opportunity as there is currently no standard of care, and often patients are treated with chemotherapy.

Drug/ Developer	Clinical Trial	Analyst's Comments
patritumab deruxtecan/ Daiichi Sankyo	Phase III HERTHENA-Lung02	The HER3-directed ADC patritumab deruxtecan is the first anti-HER3 monoclonal antibody in development for the treatment of NSCLC. Daiichi Sankyo is investigating patritumab deruxtecan in the Phase III HERTHENA-Lung02 trial in patients with EGFR-mutated advanced or metastatic NSCLC whose disease has progressed following treatment with a third-generation EGFR inhibitor. Tagrisso, a third-generation EGFR inhibitor, is estimated to capture 60–70% of the first-line advanced or metastatic EGFR-positive NSCLC market, and a standard of care treatment following disease progression is yet to be determined. Typically, patients are not retreated with EGFR inhibitor monotherapy, meaning chemotherapy is often the choice of treatment and these patients are lacking an active and tolerable targeted treatment.
Opdivo/ BMS	Phase III CheckMate 9DX	Testing Opdivo in the adjuvant setting for the treatment of early-stage HCC. Currently, early-stage HCC patients are primarily treated with liver transplants or surgical resection, or with locoregional therapies if they are not candidates for surgery.
Imfinzi/ AstraZeneca	Phase III EMERALD-2	Testing Imfinzi with or without bevacizumab as an adjuvant therapy in patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation. As with Opdivo, there is an unmet need for an efficacious but tolerable therapy for these early-stage HCC patients.

Closing The Door On COVID?

For many people, the pandemic is being placed firmly in the past as new worries take precedent – the challenging economic climate, upcoming election years and tougher regulation, as a few examples. However, winter of 2023 will be a key test for countries that have seen declining levels of COVID-19 following successful vaccine programs. The biopharma sector is demonstrating a mixed response, with some companies investing in advanced vaccine options while others step away from COVID R&D.

With the Omicron variant now the dominant strain globally, accounting for >99% of new cases in the US and Europe, efficacy against this strain is paramount to long-term commercial potential. So far, Pfizer/BioNTech's Comirnaty and Moderna's Spikevax have shown the most robust efficacy data against the Omicron variant, with vaccine efficacy of ~90% against hospitalization and death after a third booster dose, though protection wanes considerably after four months.

Inactivated vaccines have played a crucial role in primary vaccination series in China, India, Russia, and other emerging markets. However, as domestically produced vectored, protein subunit and recently mRNA vaccines reach emerging markets, inactivated vaccines are expected to progressively lose market share.

Many pharma companies appear to be moving away from COVID R&D. Assessing the clinical trial landscape for industry-sponsored trials shows that in 2022 the number of trial initiations decreased by 7% overall. However, when excluding COVID-19 trials from this analysis, this reduces to a 4% decline, reflecting the industry's survival mode since 2021.

"We have been seeing significant pipeline attrition as minor players have reallocated resources to other, more profitable indications from approximately 2021 onwards," noted Datamonitor Healthcare analysts Natasha Boliter and Charlotte Holmes. "This phenomenon is particularly encouraged by the speed of COVID-19 mutation, demanding annual, variant-specific vaccines, and the excellent efficacy results (exceeding 90%) of currently marketed assets. However, we are also seeing pipeline discontinuations from larger vaccine manufacturers. This was heralded by Sanofi in 2021, which suspended development of its own mRNA vaccine, despite reporting positive Phase I/II results, stating that the program was no longer commercially viable given the dominance of the other mRNA vaccines." (*see Exhibit 3*).

There is uncertainty even for giants in the COVID-19 vaccine industry. Pfizer, for example, is encountering constraints in the COVID-19 market, with predicted revenues for 2023 less than 60% of the preceding year. "In light of this, Pfizer has announced an 'enterprise-wide cost realignment program' in response to the unpredictable demand caused by the transition from the government-sponsored pandemic phase to the privately or individually funded endemic phase," Boliter and Holmes highlighted. "Currently, it is uncertain what this will mean for its pan-respiratory programs or its future seasonal, variant-specific vaccines."

There is still R&D interest in COVID, but the pipeline today consists of mainly next-generation mAbs, variant-specific adaptations of currently marketed vaccines and the pan-respiratory combination vaccines.

Looking ahead into the first half of 2024, AstraZeneca is expected to announce efficacy data from the Phase I/III SUPERNOVA study for its next-generation mAb AZD3152. Similarly, Invivyd is expecting primary endpoint data from the Phase III CANOPY trial of its next-generation mAb VYD222 by early 2024.

Generative AI

Artificial intelligence was a buzzword in almost all panel discussions at the November 2023 BIO-Europe conference. There is a lot of promise, but also a lot of confusion about best uses. The speed of technology development in AI is outpacing biopharma.

Generative AI, building upon advances in deep learning, is both a promising and a concerning technology. "If harnessed securely and ethically, leveraging multi-modal data, such as text, images, and videos, generative AI can help pharmaceutical companies identify unmet clinical needs and expedite clinical planning and execution strategies," said Luca Parisi, Citeline's director of clinical analytics and data science. In both drug discovery and repurposing, generative AI can play a role in respectively devising novel molecules and elucidating relationships that may inform drug repositioning.

"Generative AI-powered drug repurposing efforts may include both approved drugs in certain indications and help in capitalizing on those drugs that did not make it through Phase II studies in some indications but could be better suited for treating other indications," Parisi said.

He also highlighted the potential of leveraging real-world data, especially electronic health records and medical images. Here, generative AI "can help to titrate treatments on a subject-specific basis, accelerating the transformational paradigm of personalized medicine and the impact it can bring to providing subject-specific, lifesaving or life-enhancing treatments faster."

Despite the potential uses and clear excitement around generative AI tools, there are challenges for using the technology in a health care setting. "It is crucial to ensure HIPAA, GDPR (where applicable), and GxP compliance by design, thus leveraging appropriate infrastructure and technologies to guarantee that data security and confidentiality, and patient privacy are adhered to," Parisi warned. "Furthermore, considering the scale of the data required to train such large generative AI models, appropriate analyses to detect and minimize biases and ensure representativeness in the underlying data are of paramount importance to provide clinically relevant, accurate and reliable recommendations to design more recruitable, diverse, inclusive clinical trials, and inform operational workflows throughout the clinical trial lifecycle objectively."

The key challenges ahead towards a fruitful, sustainable adoption of generative AI tools are:

1. data quality, given the scale of the data required;
2. achieving a seamless integration of such advanced technologies in clinical workflows;
3. tackling ethical considerations by design;
4. ensuring replicability and reproducibility at all stages;
5. clinical validation of the outputs derived from these technologies.

The main expectation for the biopharma sector is to accelerate the continuum of the drug development pipeline and clinical trial lifecycle, increasing both time and cost savings.

A Health Care Metamorphosis

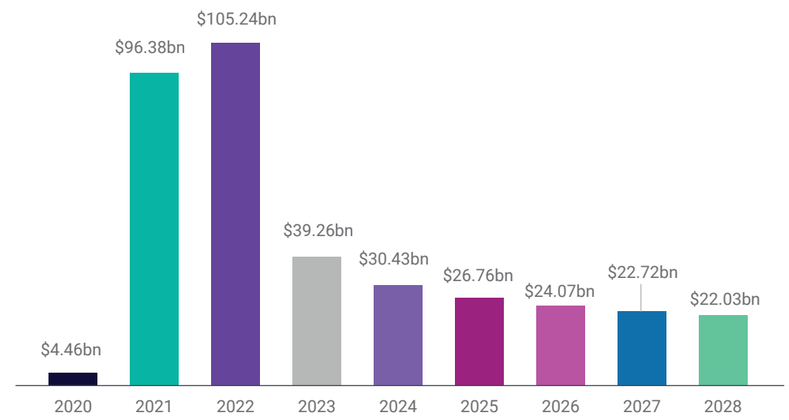
Biopharma is on the edge of a new era driven by the need to replenish pipelines and the evolution of technology. In 2024, the sector will see 70 key launches from around 65 drug brands. A notable proportion of these launches have the potential to shift treatment practices. AstraZeneca's Imfinzi is just one example, with five label expansions expected in the coming year.

After a period of easy fund raising and busy deal-making in 2020-2021, tough times have hit the sector. But there is positivity for the volume of M&A deals to rise again, even if the financial markets do not bounce back as quickly as some might hope in the coming 12 months.

Regulatory changes will have an impact from 2024 into the coming few years, in the form of both intentional and unintended consequences.

Astellas's Hardiman summarized the state of the sector: "We have seen a myriad of challenges over the course of time. As a testament to our industry, we always overcome these – I am confident and optimistic that we can again."

Exhibit 3: Worldwide Sales For COVID-19 Treatments And Prophylaxis



Source: Evaluate Pharma

Shaping A Medtech Environment Where Technology Leads The Way

Health Care Delivery Transformation And Sustainability Modeled As Opportunities For Innovation

BY **ASHLEY YEO,** EXECUTIVE EDITOR

Environmental demands, the evolution of care models, new delivery technologies and AI tools are influencing how medtechs must approach innovation.

April 2024 sees another milestone in the fast-developing environmental compliance agenda for medtech and health care products suppliers. That is when the UK's National Health Service ratchets up its Net Zero Commitment (NZC) requirements on suppliers, bringing into scope procurement contracts worth under £5m ($6m).

Suppliers in this bracket will have to demonstrate a commitment to net zero and comply with Carbon Reduction Plan demands. Since April 2023, the NHS has required contracts valued over £5m to publish a CRP for their Scope 1 and 2 emissions. Very small contracts remain out of scope.

It underlines how the environmental sustainability stakes – and costs – are rising for medtech manufacturers. The debate on how or if medtech manufacturers can pass on any of the additional costs is in full swing, but there is no obvious or easy answer. Compliance with sustainability needs remains voluntary for medtechs, but it is also non-negotiable.

Scope 3 Will Need A Lot of Work

The Commonwealth Fund reports that the US has set a 2045 net zero emissions target for certain health-related government facilities and buildings, but it is the model of NHS England (NHSE) that has set the standard in becoming the first health system to introduce Scope 1, 2 and 3 compliance targets for all suppliers.

Specifically, 2040 is the year by which NHSE's own carbon emissions must reach net zero, and 2045 is the deadline for net zero carbon compliance across the provider's entire supply chain. The supply chain accounts for 62% of NHS's GHG emissions.

"There is lots of work needed to get there," said NHSE head of sustainable procurement Alexandra Hammond. Her remit at the national provider extends to net zero, social value and the modern slavery agenda. Within the GHG footprint that the NHS does not directly control, 10% of emissions come from medical equipment and 20% from the pharma sector.

From 2030, only those suppliers who can demonstrate progress through published reports and continued carbon emissions reporting will qualify for NHS contracts. Interim sustainability performance thresholds until 2030 are being applied under the NHS supplier roadmap.

The compliance momentum is speeding up and circularity – "designing out waste" – has taken a seat at the medtech R&D table. ESG strategies have rapidly become indispensable for medtechs that intend to continue operating freely in the global market – be it attracting investment, working with partners, luring future talent or responding to the evolving customer preference and market trend.

Accordingly, many medtechs with long experience of embedding Corporate Social Responsibility commitments into their operating rationale were beginning to factor "E in ESG" principles into future business strategies before the UN's 2015 Paris climate agreement set wider society a target of limiting global warming to 1.5% this century.

But where CSR has been open to greenwashing, the more data-driven and business compliance-oriented ESG principles cannot ethically or actually be circumvented.

What Medtech Leaders Are Saying – And Doing

In Vivo's "E in ESG" series has sampled the different approaches that a selection of the industry's leaders employ – Royal Philips, Johnson & Johnson, Thermo Fisher, GE HealthCare to name just a few – and has documented the sector's burgeoning scientific standards and compliance reporting needs.

Each player in the fragmented medtech ecosystem will experience different pressures in how they achieve sustainability and compliance with the various internal goals they set for themselves in what is at present still classed as self-regulating activity. There is no "cookie cutter" way of approaching sustainability in such a varied industry, although the principles are enshrined.

Sustainability's demands were at first perceived as a constraint on medtech innovation, but things have actually worked the other way. That is the view of Philips' global head of sustainability Robert Metzke. He said Philips' R&D department was motivated by the challenge of meeting heightened environmental goals.

Circularity can – in fact must – create value for medtechs to remain competitive in the sector. Thermo Fisher's global head of sustainability and CSR Meron Matthias set the tone, telling *In Vivo*: "There's so much potential for innovation across this space, and also many gaps to fill to allow us to reach our goals faster."

She is sure that there is a major innovation boom ahead. "There are technologies we need that do not exist yet," she said in May 2023.

But compliance must be watertight, because ESG litigation is already on the rise. Life sciences and healthtech companies must ensure tight management of risks to avoid any potential for regulatory enforcement, civil litigation, criminal sanctions and reputational harm. Shareholder activism and ESG due diligence are prominent litigation risks.

Recent history shows that, in environmental and social matters, Europe tends to lead the agenda.

In early 2023, the European Commission released the Net-Zero Industry Act as part of its Green Deal Industrial Plan for scaling up manufacturing of clean technologies in the EU. Its provisions and recommendations are designed to help the EU achieve its 2030 climate and energy targets.

The EU Corporate Sustainability and Due Diligence Directive (CSDDD) will start to be put into place in EU member states as of the second quarter of 2024, and will have a two year or so lag before coming into force.

Precisely when the CSDDD will apply to companies of different sizes and differing nature of activities is the subject to ongoing debate at EU institution level, legal firm CMS told the industry in fall 2023. The directive will introduce a new basis of civil liability.

Not directly related, the European Health Data Space initiative, a regulation governing the use of electronic health data, will be implemented across the EU in two or so years. This is another area where the EU has a strong advantage.

'New Approach' To MDR Sought

But the enthusiasm with which medtechs have embraced the sustainability challenge is all but absent when the global industry reflects on the major ongoing compliance shift of recent years: the requirements of the EU medical device regulations.

Here, it remains a case pragmatism, paying for compliance, defending technical files, and, in many cases relinquishing safe and effective products and portfolios that the heightened compliance specifications – coupled with lack of system readiness – have rendered non-financially viable.

Many companies have dropped portfolio staples, frustrated by the costly requirement to revalidate tried and trusted products under the EU Medical Device and IVD Regulations. Germany's medtech industry told *In Vivo* during Medica 2023 that it believes that by the time regulatory change has bedded in, some 30% of products will have been dropped and 10% of companies will have closed.

June 2024 sees the European Parliament elections, and the industry is keen to present its case for a more pragmatic MDR well in advance of the new intake of MEPs assuming their seats in Strasbourg and Brussels.

Industry association MedTech Europe's scathing view is that the MDR has not achieved the EU's goal of delivering a transparent, predictable and sustainable regulatory framework that supports innovation and the growing use of AI. That was its position in fall 2023, on issuing a position paper.

Calls for a single EU authority to designate and oversee notified bodies have not gone away. Some medtechs suggest the European Medicines Agency should have a bigger role in medtech. Many companies call for the early technical and clinical conversations on innovations between with regulatory stakeholders that the US FDA system provides.

EU innovation has begun to vote with its feet. Companies that once prioritized the EU for device launches are now increasingly taking the commercial decision to focus resources on the US market.

But two countries on the fringes of the EU, whose major export markets are the EU, have been able to take matters into their own hands. Their local medtech industries are seeing the future possibilities.

Being outside the single European market was not what medtech businesses in the UK and Switzerland would have chosen. But now, a sense of goal-oriented purpose is evident relating to the in-development UK medtech statutory instruments and Switzerland's readiness to open the door to FDA-approved medtech innovations.

The political and regulatory developments in both

countries will be worth tracking in 2024, as much for the way the national regulatory codes and markets are reshaped as for how these breakaway initiatives are perceived in the – much larger – EU 27 market.

One big prize for the UK would be EU mutual recognition, but in the meantime, its program of statutory instruments as the basis for its sovereign, post-EU, medtech regulatory system should be ready for parliamentary debate in late 2024 ahead of planned system readiness in 2025.

Notable has been the readiness of the UK to embrace the IMDRF, international regulatory recognition and reliance, and potentially MDSAP. The use of FDA-approved devices in Swiss patients would not happen for a few years, but the parliamentary wheels are in motion, and when it happens, questions will be asked as to why the EU allowed its regulatory system to become innovation-unfriendly.

Shift In Health Care Delivery Gathers Pace

Health care systems are grappling with rapid change in the structure of care delivery and how to adjust payment models to facilitate the ongoing move to care delivered in the ambulatory setting and at home.

Germany, Europe's largest medtech market and industry base, is introducing hybrid diagnosis-related groups as a means to fund more care outside the hospital. At the same time, it is overhauling its two-decades old system of DRGs with changes starting in 2024 that will replace flat rate, case-based payments for inpatient care with a combination of funding from a provisional payment pot as well DRGs.

Hospitals will be relieved of the pressure to generate more income by maximizing procedure volumes. That is the theory, but the hospitals are first demanding a law that tackles underinvestment in hospital resources by the federal states.

Globally, as care delivery evolves, medtech innovation will increasingly be adopted in community and primary care settings, particularly with the advent of wearables, remote technology and telemetry.

Companies will require sound data infrastructures, and developers of artificial intelligence-based products will require multimodal data sets. Providers will have to respond accordingly. NHS England has set up a secure data environment (SDE) as a data and research analysis platform to give approved researchers and projects secure access to pseudonymized health care data.

Reacting or even leading the digitally enabled shift to ambulatory care will call for a different risk appetite and require a different kind of workforce capability.

At the same time, the trend towards lower availability of healthcare professionals to serve the growing demand for care in the post-COVID era has put pressure on providers to the extent that the embedding of interoperable AI capabilities clinical and operational workflows – especially in cardiology and radiology – is becoming a fact of life.

AI In Health Care

So it is no surprise that AI's approval ratings were at an all-time high in 2023. Philips' annual Future Health Index revealed that 39% of health care leaders are already investing in AI for critical decision support and 37% intend to invest in AI for automating documentation, scheduling patients or other operational efficiencies.

AI is a tool that, for the present, is desired and feared in equal measure by HCPs, and the mantra that it will not replace clinicians and will act as only as second pair of eyes for radiologists may well all be true.

But OpenAI's ChatGPT, released in 2022, took the debate to another level in 2023 when it became crystal clear that generative AI and its ability to create (almost) human texts, deliver answers, advise and produce realistic images of fictional people, setting and events was moving in one direction only.

Medtech can exploit AI's value in supporting innovative and targeted health care technologies, like the digital twin. Siemens Healthineers' managing board member Elisabeth Staudinger is an enthusiastic proponent of digital twinning, a technique that integrates data sources to model a digital representation of an individual.

The enthusiasm surrounding the potential for AI to produce markedly better patient outcomes is dampened by impending regulatory structures yet to be put in place in the EU. The EU AI Act – the world's first comprehensive AI act – is a horizontal cross-industry regulation.

It has sparked frustration among an industry that fears in the worst of all scenarios a system of double regulation for medical devices – the MDR and the AI Act. In the run up to Medica 2023, German medtech capital equipment manufacturers' association ZVEI dismissed the need for another layer of – potentially conflicting – AI regulation for medtech in the EU.

Technology Is The Answer

The AI Act gained support from the German, French and Italian governments in late November and is on a pathway to adoption. How disruptive it will be to medtech innovation is a wait-and-see issue, even with its concept of regulatory sandboxes for innovators of AI-enabled technologies.

Durable – up to a point – the medtech industry learns to live with such thorny issues. Manufacturers are still counting their wounds from recent experiences, ranging from COVID-19 to geopolitical conflicts, supply chain disruption, rising inflation and the increasing shortage of skilled staff.

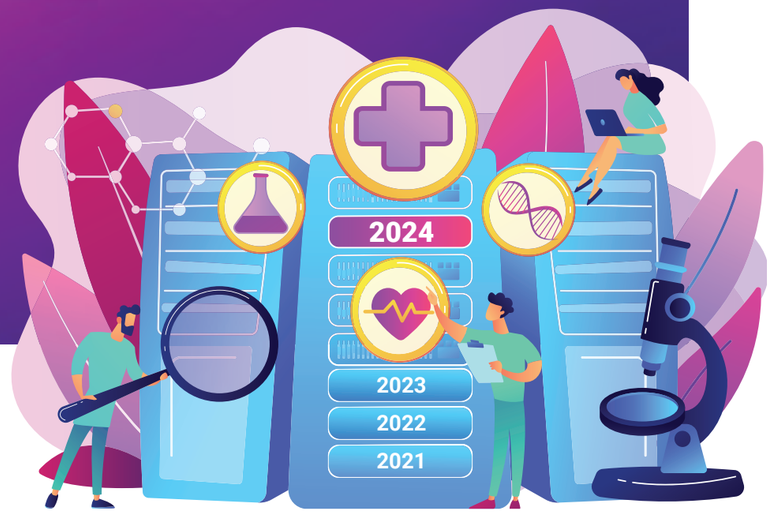
The ongoing challenges of health system transformation, the need to factor in digitally enabled remote diagnosis and therapy, reimbursement shifts, the consumer device and wearables revolution and personalized and convenient care have also become fixtures on the agenda.

The MDR (and IVDR) has been the standout bête noire for many years, but it has a rival now in sustainability compliance.

Market access barriers and challenges will certainly push medtech manufacturers to the limit again in 2024. Industry's trump card is, as ever, innovation, aided by big data, cloud computing and augmented reality-based surgical platforms designed with AI and machine learning.

Medtech must adjust to changing environments, but technology innovation is always the common denominator.

Worries And Hopes For Health Care Delivery



Industry experts from Norstella, whose data and technologies support decision making from R&D through to market access, shared their worries going into 2024.

BY **LUCIE ELLIS-TAITT,** EXECUTIVE EDITOR

From less tolerance for failure as pressure mounts on pipelines to ongoing consequences of regulatory changes, such as the introduction of US Inflation Reduction Act, life sciences companies will face a number of challenges in the coming year. Precisely *how* health care systems deliver novel medicines is also high on the list of concerns.

Industry experts from across the wider Norstella business shared their predictions going into 2024.

Ashley Schwalje, senior director of Clinical Solution Consulting at Citeline, told *In Vivo* she was expecting less tolerance for clinical trials that are not producing results. "Every trial is of increased importance," she noted. Big pharmas are approaching a lengthy patent cliff, where best-selling brands will face heavy generic competition. This is driving a "fail fast mentality," Schwalje said.

The longer that investment remains at suppressed levels, the more attritional the industry will be. "This is not necessarily a bad thing," said Daniel Chancellor, thought leadership and consulting director at Evaluate, noting that few drugs that enter clinical trials eventually gain approval. "Concentration of investment around fewer companies, platforms and assets that are more differentiated is better for long-term innovation. Nevertheless, picking the winners from the losers at early stages of R&D is as much luck as calculated risk. While an overfunded industry during 2020-2021 undoubtedly created some bloat, we are now seeing an overcorrection and that risks some ideas going underfunded."

At the individual biotech level, a clear vision is required on how to create value for the end customer, whether that is patients, potential partners or investors. "Pharma is unequivocal in looking for assets that are first-in-class or best-in-class, with a measurable patient impact, so adopting a development roadmap with this shared mindset is essential," said Chancellor. In the absence of this, raising capital will be a challenge considering the huge number of other companies vying for investment, he noted. "This must also occur alongside careful consideration of costs and alternative means of funding such as partnerships."

At the same time, industry is also witnessing innovation outpace the rate of health care delivery system evolution, experts from The Dedham Group warned. "Without recognition of insufficiencies and openness to change across payer and provider channels, novel testing and treatment options will continue to face limitations reaching patients," said James Pisano and Jen Klarer, both partners at the specialty consulting firm.

The Dedham Group highlight three key challenges in 2024 for access to medicines in the US:

1. Sustained, Insufficient CMS Reimbursement: Provider sites are increasingly strained by insufficient government reimbursement, limiting patient access to appropriate care. CMS reimbursement is also slow to change and lacks recognition of its inability to adequately accommodate novel treatment options.

2. Constraints In Offering Novel Treatments: Provider sites are struggling to evolve treatment capabilities at a pace which matches novel product releases (e.g., psychiatrist observation for psychedelics, inpatient bed availability for patient-specific treatment with cell-based therapies).

3. Slow, Inconsistent Payer Coverage Of Genetic Testing: As opportunities for personalized medicine evolve, payers are unable to develop clear, comprehensive, and consistent coverage policies for novel patient identification techniques, even when targeted treatment options are available.

Amidst these challenges, "some provider sites and payers are staying ahead of the curve with increased resource allocation and forward-looking consideration of needs to enable access to emerging innovation," Pisano and Klarer noted. Also, biopharma companies "are increasingly allocating resources toward market access to anticipate patient access challenges and develop stakeholder education plans, resources and patient services to address needs," they added.

New Tech And Patient Goals

On a brighter note, industry spectators are watching a few important trends as we head into 2024, particularly the greater use of artificial intelligence to speed up decision-making.

Also, with a renewed focus on health equity after the worldwide COVID-19 pandemic, experts expect that there will be a stronger emphasis on diversity in health care in the coming years. Looking at clinical trials specifically, Schwalje said, "Rubber will meet the road on diversity in 2024." Final guidance on DEI in clinical trials is expected from the US Food and Drug Administration in 2024 or the early part of 2025. "Pharma companies will tap deeper into real-world data to understand patient behaviors and social determinants of health to craft clinical trials that fit the needs of patients and create omnichannel, more personalized patient engagement strategies," she noted.

> **"Trial diversity is part of a bigger picture related to health equity."**
> Ashley Schwalje, Citeline

"Clinical trial diversity is part of a bigger picture related to health equity – this will become a major part of the conversation," Schwalje predicts.

Alongside a focus on diversity and inclusion, Schwalje expects an increased emphasis on clinical trial patient experience in 2024. Some companies have already made waves in this area. Moderna, as an example, has a team dedicated to site and patient experiences.

AI tools will play their part in helping biopharma companies reach the right patients. Companies are starting to use AI to augment decision making and make smarter, more refined decisions related to:

- Building more precise, measured patient cohorts/segments;
- Designing clinical trial protocols with greater confidence; and
- Selecting the best sites and investigators (based on more sophisticated data models).

Despite the increased use of AI, other digital tools are falling out of favor. Schwalje expects the interest in decentralized clinical trials to "die down" in 2024. Virtual trials were ramped up in the midst of COVID, but the need for DCTs has calmed as the world moves on from the pandemic.

AI is spilling into other areas of health care, such as managed care. "Payers experience significant infrastructure challenges so one might imagine them to be slower adopters to technological innovation," said Dinesh Kabaleeswaran, senior vice president of consulting & advisory services at MMIT. He noted that events across other industries had encouraged payers "to have conversations within their organizations on the applications of ChatGPT and AI to their day-to-day activities."

Innovation At A Cost

"Increasing R&D costs, while great for bringing new therapies to the market, also pass on a percentage of these costs to patients through payers imposing higher premiums and stricter restrictions in access," Kabaleeswaran warned. "As costs tend to increase, we should not lose sight of the most important stakeholder in the industry – the patient."

The introduction of the Inflation Reduction Act in the US will also have an impact on the cost of innovation. "What assets will be cut because companies cannot afford the R&D investments?" asked Citeline's Schwalje. According to a 2023 survey by PhRMA of its member companies, 78% of respondents expect to cancel early-stage pipeline projects that no longer make sense given the short timelines before medicines could be subject to government price setting.

Experts from Panalgo also highlighted the IRA as a critical issue in 2024, noting that "CMS is becoming the *de facto* US health technology agency."

Chancellor noted that pharma has so far been powerless to shape the IRA. Although, with numerous challenges in play it will be interesting to see whether any legal arguments hold water. "Regardless of outcome, R&D and commercial decisions taken today must reflect the reality that the pricing environment in the US is getting tougher, and the IRA may just be the tip of the iceberg."

Each new high-cost drug launch puts strains on budgets and can lead to increased premiums. In 2024, the conversation must shift towards value for money. "This will play out in real-time considering the eye-wateringly high revenue forecasts for the GLP-1 class," Chancellor gave as an example. Looking just at Novo Nordisk's glucagon-like peptide 1 agonist Wegovy (semaglutide), approved for the treatment of diabetes and obesity, the drug is expected to see worldwide sales of around $8.6bn in 2024.

Exploring Use Cases For Tokenizing Clinical Trials

By Melissa McDonald, Director of Operations, eClinical Development and Delivery, Clinical Trial Tokenization, ICON plc

In drug development, Pharmaceutical and Biotechnology organizations are leaning into data-driven insights to aid decision-making and lower the burden on physicians and patients to conduct and participate in clinical research. The paradigm has shifted even more since the global pandemic to adopt more decentralized methods of data generation versus traditional clinical study methods. Traditional clinical studies can be costly, time consuming and burdensome on patients and sites. As a result, researchers are looking for new and innovative solutions to answer challenging research questions.

One of these solutions is Clinical Trial Tokenization. The adoption of using real world data (RWD) and enhanced insights through analytics and artificial intelligence (AI) is rapidly increasing and in the United States (US), the 21st Century Cures Act encourages use of RWD or medical data in generating evidence or Real World Evidence (RWE) in regulatory submissions. Tokenization is the production of a unique encrypted token, or de-identifier in the place of Personal Identifiable Information (PII). It is already used in many industries, such as real estate, commercial analytics, finance and banking to gain insight into consumer behaviors. When employed in the life sciences, tokenization can be used for clinical research and development to enhance evidence generation.

Streamlined And Efficient Approach To Generating Evidence

Clinical trials already play a crucial role in advancing drug development by evaluating the safety and efficacy of new treatments. However, one aspect that often presents a challenge is the generation of longitudinal data showing what occurs for participating patients before, during and after the clinical study concludes. By harnessing the power of tokenization, drug developers can adopt a secure and efficient method to evaluate the long-term safety and effectiveness of treatments. Clinical trial tokenization is revolutionizing long-term participant monitoring even when patients move, change care practices, have study fatigue or discontinue study participation.

By tokenizing participant PII for consented patients, and matching to a unique identifier, researchers can link to patient records in a privacy-protected manner. These records may include medical claims data, electronic health records, laboratory data, treatment and follow-up records. Tokenization ensures that data remains accessible for long-term analysis. There could be a possibility to eliminate some of the cumbersome paper-based systems, and/or reduce the number of study site visits. By aggregating tokenized patient data within a proven privacy protected framework, researchers achieve a streamlined and efficient approach to generating enhanced clinical evidence. This approach can be particularly helpful where the research requirements include regulatory-mandated long-term follow-up portion of up to 15 years for treatments such as gene and cellular therapy products.

Tracking Effectiveness And Safety Of Treatment In Long-Term Follow-Up Studies

Long-term follow-up in clinical trials is essential for tracking the effectiveness and safety of treatments over an extended period. Tokenization enables the creation of unique tokens for each participant, which can be used to track and monitor their health outcomes in a decentralized manner. Researchers can efficiently collect and analyze long-term data, identifying any potential trends in adverse events, disease progression or concomitant drugs administered. When longitudinal real world data is accessible, visibility of events that may have gone unnoticed during the trial phase, or happened long after the study concluded, can be analyzed. For example, tokenized data can capture an adverse event (AE) occurring in the study population years after the investigational drug is approved and on the market. In addition, researchers can evaluate the patient population taking the investigational treatment through the RWD capture and compare this to the general population not taking the drug.

Enhancing Evidence Generation With Clinical Registries

Traditional registry and natural history studies, whether publicly or privately funded, support the development of improved treatments for patients. These often-lengthy studies are a key initiative for collection and storage of real world information pertaining to a specific disease. A potential benefit for inclusion of tokenization in registries is the provision of de-identified trends and additional enhanced evidence that may answer research questions in a specific patient population. Through tokenized data, researchers can compare patients with a given diagnosis or patient profile to the general population by looking at concomitant medicines, AEs, procedures, and diagnoses codes. RWD may lend insight into diagnosis patterns, pre-existing conditions or risk factors. This secondary evidence generated can lead to more treatments and understandings surrounding a specific condition. Through analytics and reporting over the larger patient population, we can further extrapolate insights that occur in a specific gender or age (i.e., .025% of the pediatric female population has a comorbidity of type 1 diabetes).

Supporting Regulatory Discussions On Post-Marketing Commitments

Regulatory agencies (e.g., FDA, EMA) will sometimes request or mandate a post approval surveillance study (PASS) or require additional safety and efficacy studies for an approved product. Although many factors are captured in the drug approval process, there may be additional evidence gleaned about real world treatment patterns after the clinical controlled environment has ceased. There is a benefit in evaluating the safety and effectiveness of treatments on patients taking approved drugs. Tokenized data can further enhance evidence and generate support for safety and efficacy. This is particularly important in cases of pediatric or vulnerable patient populations. Sponsors may use RWE to support discussions with regulators, as this data supports and can increase significantly the sheer volume of data to be considered.

Tokenization enables the creation of unique tokens for each participant, which can be used to track and monitor their health outcomes in a decentralized manner.

Balancing The Risks And Benefits

Sponsors conducting any type of study, including long-term follow-up studies, must also delicately balance risks and benefits when using new innovative technologies in clinical trials.

Some risks to be considered and managed include:
- Ensuring appropriate patient consent, privacy and data security
- Increased financial costs to implement novel technologies
- Inadvertently unblinding a clinical trial
- Lack of adherence to Good Clinical Practice (GCP

However, the potential benefits of deploying clinical trial tokenization are far reaching:
- Capability to leverage insights for product development, positioning and performance
- The ability to support launch strategies with deeper understanding of product value
- Supplementary data for regulatory discussions/ submissions
- Increased insight and ability to assess diversity, equity and inclusion (DEI) goals in clinical trials

Summary

Clinical trial tokenization has the potential to revolutionize long-term study participant follow-up in medical research. By leveraging the power of this technology, tokenization offers streamlined data management, enhanced privacy and security, efficient tracking of long-term outcomes, lessens the burden to sites and patients and facilitates collaboration among researchers.

When considering including Clinical Trial Tokenization to research efforts, it is important to collaborate with a trusted partner who understands the rigor of research and development within the framework of GCP and regulatory parameters. It takes more than a token to lead to meaningful evidence generation. Deploying Clinical Trial Tokenization requires an expert in consent and patient privacy, clinical technologies, GCP, General Data Protection Regulation (GDPR), security and compliance guidelines. As this innovative approach continues to gain traction, it holds the promise of transforming the way clinical trials are conducted, benefiting both researchers and participants in the quest for better health care solutions.

For more information on how to deploy clinical trial tokenization in your study, please contact www.ICONplc.com/tokenisation.

Industry Leaderboard Gains And Dips Were Still Marked By COVID-19

Pfizer held the number one spot on the Scrip 100 on the strength of its COVID-19 products, while some others faced challenging financial comparisons in 2022 because of COVID-19 headwinds.

BY **JESSICA MERRILL,** SENIOR EDITOR

BY **EDWIN ELMHIRST,** DATA JOURNALIST

Pfizer dominated the Scrip 100 rankings of the top pharmaceutical companies in the world based on full year 2022 pharmaceutical revenues, driven by its COVID-19 success, but Merck & Co., AstraZeneca and Novo Nordisk each rose on the leaderboard, powered more generally by business fundamentals.

It remained an atypical year for the pharmaceutical industry as some big pharma companies continued to generate unusual growth in 2022 from the sale of COVID-19 vaccines and treatments, and others faced challenging comparisons against the prior year as the pandemic phase of the COVID-19 outbreak wound down.

Ten of the companies in the top 20 pharmaceutical rankings in the Scrip 100 sold COVID-19 products that either padded the top line or chipped away at growth in 2022. Across the Scrip 100, total pharmaceutical revenues reached $1tn.

Pfizer remained the biggest winner on the COVID-19 front, with sales of its vaccine Comirnaty, shared with BioNTech, and antiviral Paxlovid driving unprecedented growth for the company. Pfizer's 2022 biopharmaceutical sales grew 24% to an astounding $98.99bn, but excluding sales of Comirnaty and Paxlovid, the company's top line only grew 2% operationally.

Other big sellers for Pfizer included the Prevnar franchise of pneumococcal vaccines, which continue to be a steady earner. June 2021 saw the first approval of Prevnar 20, which lifted the franchise sales by around $1bn in 2022. However, potential competition for Pfizer in the pneumococcal vaccine space has been emerging – particularly in infants – from the likes of Merck and Vaxcyte. However, the April 2023 approval of Prevnar 20 in infants may allow Pfizer to continue to dominate the market which it has held for so long. Ibrance, Pfizer's CDK 4 & 6 inhibitor, was also a major contributor to the 2022 sales total, pulling in over $5bn. According to Evaluate consensus forecasts 2022 was the last year before the drug begins to see a decline in its sales - losing out to competing products such as Lilly's Verzenio and Novartis's Kisqali.

Now Pfizer is facing an even more challenging comparison in 2023 as demand for COVID-19 vaccinations and treatments has continued to decline. Pfizer recently lowered its financial forecast by $9bn, citing lower than expected sales of Comirnaty and Paxlovid, and implemented a $3.5bn cost reduction program.

The company's revised guidance foresees 2023 revenues of $58bn-$61bn, a dramatic decline from the COVID-19 high of 2022, but still well above the company's pharma revenue base before the pandemic. Pfizer ranked seventh in the Scrip 100 in 2021, on 2020 pharmaceutical revenues of $41.9bn, after spinning out its established products business into a new company that is now Viatris.

A big question on the minds of Pfizer investors is how the post-pandemic COVID business will eventually settle out and what annual demand for boosters and treatment will look like long term. That could make a difference for Pfizer as it heads toward a patent cliff in the middle part of the decade like many of its peers.

Other companies across the pharmaceutical sector were also impacted by gains and dips driven by the sale of COVID-19 products. Those include vaccine makers like BioNTech and Moderna, and to a smaller extent Johnson & Johnson and AstraZeneca, as well as manufacturers of antivirals like Gilead Sciences and Merck & Co. and developers of monoclonal antibody treatments like Eli Lilly & Co., Regeneron Pharmaceuticals, and GlaxoSmithKline.

Gilead, for example, was negatively impacted in 2022 as use of its antiviral Veklury (remdesivir) tapered off later in the pandemic as newer antiviral alternatives like Paxlovid reached the market. The company's FY 2022 revenues were flat at $26.98bn and the company held steady on the Scrip 100 at number 13. Excluding Veklury, Gilead's product sales increased 8%.

Lilly experienced a smaller headwind from the sale of its COVID-19 antibodies which boosted revenues in 2021 and 2022 but were less effective against newer variants of the virus that emerged in 2022, which correlated with revenues tapering off. Lilly's 2022 pharmaceutical revenues grew 1% to $28.54bn, as COVID-19 antibody sales declined 10% for the year and 96% in the fourth quarter. Lilly's ranking on the Scrip 100, like Gilead's, also remained steady versus the prior year at number 12.

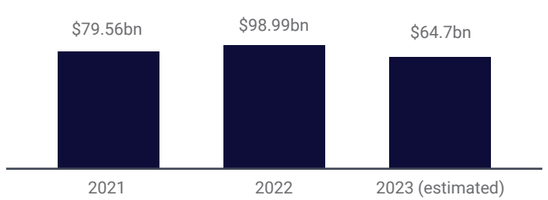
Rounding Out The Top 5

AbbVie: 2022 represented the peak of Humira's sales – bringing in over $21bn, just over a third, of Abbvie's sales. The anti-TNFa antibody is currently the biggest selling drug of all time having made $219bn in sales from its launch in 2003 to the end of 2022. However, after an exceedingly long lifetime, Humira came off patent in the US in January 2023. Although the patent may have expired and Humira is forecast to lose a third of its sales in 2023 it still maintains a commanding grip on the US market. Current consensus forecasts predict the drug will pull in over $14bn in 2023 – retaining its position as Abbvie's biggest seller.

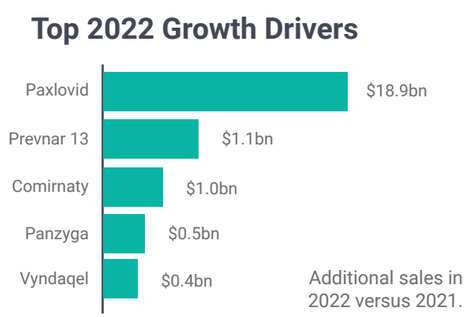
Skyrizi was Abbvie's second largest seller over the course of 2022 and also the company's largest growth driver. The psoriasis drug generated $5.1bn in sales in 2022 with $2.2bn of that representing new sales over 2021's annual tally. Rinvoq, another autoimmune agent, also counts among Abbvie's top growth drivers. Unfortunately for Abbvie Skyrizi and Rinvoq had disappointing starts to 2023 with both drugs missing their first quarter estimates. However, both of these products have seen label expansions recently, including Crohn's disease for Rinvoq in the US and Europe in Q2 2023.

Looking ahead to 2023's top-line pharma sales predictions for Abbvie reveals that current consensus is a fall of around $4bn from the 2022 total to $54bn. The loss of exclusivity on its flagship asset is a huge blow to Abbvie and its sales line. Whilst this loss is being partially offset by the growth of new immunology products investors are continuing to ask questions about potential M&A targets to try and boost performance.

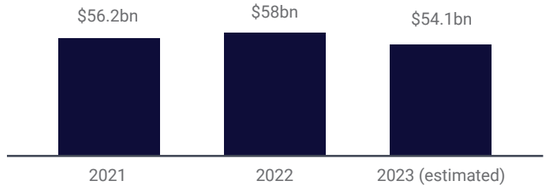
Pfizer's Pharma Sales



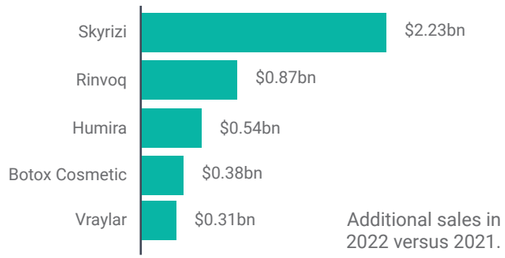
Top 2022 Growth Drivers



AbbVie's Pharma Sales



Top 2022 Growth Drivers

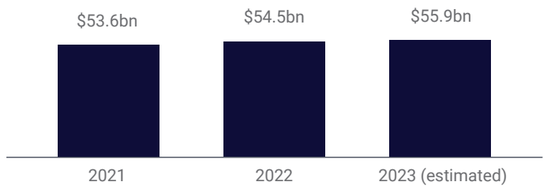


2022 Sales Portfolio Breakdown

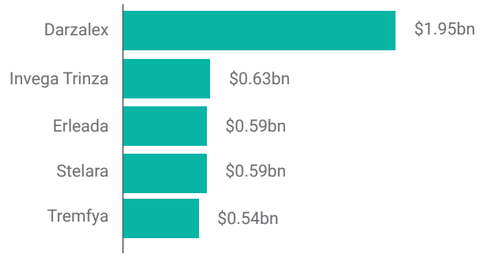
Product	Indication	2022
Humira	Arthritis, rheumatoid	$6.7bn
	Crohn's disease	$6.2bn
	Arthritis, psoriatic	$2.1bn
	Psoriasis	$3.9bn
	Ankylosing spondylitis	$1.1bn
	Ulcerative colitis	$1.2bn
Skyrizi	Psoriasis	$4.6bn
	Crohn's disease	$0.1bn
	Arthritis, psoriatic	$0.5bn
Imbruvica	Non-Hodgkin lymphoma (NHL)	$0.9bn
	Leukaemia, chronic lymphocytic (CLL)	$2.3bn
	Waldenström's macroglobulinaemia	$0.2bn
Botox	Overactive bladder	$0.6bn
	Cervical dystonia	$0.6bn
	Hyperhidrosis	$0.3bn
	Migraine	$1.2bn
	Muscle spasticity	$0.1bn
	Facial wrinkles/Nasolabial folds	$2.6bn
Rinvoq	Arthritis, rheumatoid	$2bn
	Eczema/Dermatitis	$0.2bn
	Ankylosing spondylitis	$0.1bn
	Ulcerative colitis	$0.1bn
	Arthritis, psoriatic	$0.2bn
Other	Other	$16.8bn

Source: Scrip 100; Evaluate

J&J's Pharma Sales



Top 2022 Growth Drivers



Additional sales in 2022 versus 2021.

2022 Sales Portfolio Breakdown

Product	Indication	2022
Stelara	Psoriasis	$3.4bn
	Crohn's disease	$3.8bn
	Arthritis, psoriatic	$0.1bn
	Ulcerative colitis	$2.4bn
Darzalex	Multiple myeloma	$8bn
Invega Sustenna	Schizophrenia	$3bn
Tremfya	Psoriasis	$2.7bn
Xarelto	Thrombosis, deep vein (DVT)	$1bn
	Stroke prophylaxis, secondary to atrial fibrillation (AF)	$1bn
	Stroke prophylaxis, secondary to acute coronary syndrome (ACS)	$0.5bn
Other	Other	$24.3bn

Source: Scrip 100; Evaluate

J&J: remained steady moving from 2021 into 2022 – seeing a modest $900m growth in top line pharmaceutical sales to bring it into third place. J&J appears to have a slightly more diverse top end portfolio compared to Pfizer's reliance on COVID-19 and AbbVie's aging Humira. The psoriasis antibody Stelara and multiple myeloma drug Darzalex were J&J's two biggest earners over 2022, bringing in $9.7bn and $8bn respectively.

Stelara's patent is expected to expire around 2025 and the sales are forecast to continue to climb until then. Along with Xarelto and Imbruvica (partnered with Bayer and AbbVie, respectively), Stelara has made it onto the 2026 price negotiation list for the IRA. However, as can be seen by looking at J&J's drivers over 2022, Darzalex is shaping up to be a fine replacement lead asset. The anti-CD38 antibody grew by nearly $2bn over 2022 and current forecasts show that growth rate continuing for at least another five years. In fact, Darzalex is currently predicted to be the fifth bestselling drug in the world come 2028, according to Evaluate.

Johnson & Johnson is, according to consensus, due to have another year of growth in 2023 – with estimates showing around $1.5bn in new sales. This increase is largely driven by the growth of Darzalex but also from continued increase in sales from products such as the anti-psoriasis injectable Tremfya and prostate cancer hormone treatment Erleada.

Merck & Co: the company benefited from sales of its COVID-19 antiviral Lagevrio in 2022, but to a lesser extent than Pfizer did from sales of Paxlovid, which quickly emerged as the market leader in the US.

Lagevrio generated $5.68bn in 2022, delivering a substantial boost to the company's pharmaceutical revenues, which grew 22%, to $52bn. The company also had a solid performance within its base business. Excluding Lagevrio, Merck's consolidated sales, including animal health, still grew 12%, on the continued strength of the oncology cornerstone Keytruda, which grew 22% and the vaccine Gardasil, which also grew 22%, rebounding after vaccinations had waned during the pandemic.

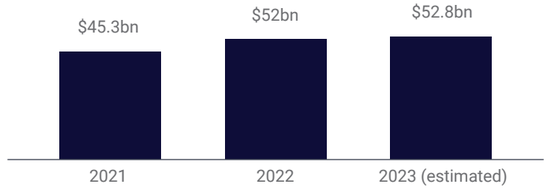
That solid performance pushed Merck into the number four slot on the Scrip 100, leapfrogging Bristol Myers Squibb, Roche and Novartis, from its number seven ranking last year. The jump represents Merck's highest rank on the leaderboard since 2018, when it also ranked fourth, and the company appears well positioned for another year of solid growth in 2023.

Keytruda continued to deliver success for the company in 2022 and shows no sign of slowing down as it smashed its second-quarter expectations in 2023. The PD-1 inhibitor raked in almost $21bn in sales over 2022 and with the reducing demand for COVID-19 products will likely retake its crown as the best-selling drug in 2023. Merck's go-wide strategy with Keytruda has certainly paid off as the drug was, at the end of 2022, approved across 38 settings. This continued expansion allowed for Keytruda to remain one of Merck's biggest growth drivers adding a further $3.8bn of new sales in 2022.

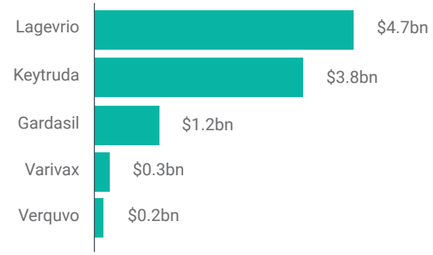
The HPV vaccine Gardasil has also turned out to be a major asset for Merck. The vaccine brought in nearly $6.9bn in 2022 – a 23% increase from 2021. Gardasil was also reported to be outperforming guidance in the Q2 2023 results. These sales are largely driven by increased demand from outside the US. In particular there has been a surge of sales in China.

Despite the better-than-expected performance for Merck's top products current forecasts for 2023 show that in terms of top-line pharma sales next year may bring modest growth for Merck. The company is predicted to post around $52.8bn in pharma sales. As with many other companies making sales from COVID-19 related products the reduced demand for these assets will impact Merck. Lagevrio's sales are expected to fall by $4.7bn next year – which is the biggest brake for Merck's sales. In addition, forecasts show sales losses of around 30% for both Januvia and Janumet.

Merck & Co's Pharma Sales



Top 2022 Growth Drivers



Additional sales in 2022 versus 2021.

2022 Sales Portfolio Breakdown

Product	Indication	2022
Keytruda	Non-small cell lung cancer (NSCLC)	$10.1bn
	Melanoma	$2.3bn
	Head & neck cancers	$1.8bn
	Renal cell carcinoma (RCC)	$1.6bn
	Bladder cancer	$1.3bn
	Breast cancer	$1.1bn
	Gastro-intestinal adenocarcinoma	$1.1bn
	Colorectal cancer	$0.9bn
	Oesophageal cancer	$0.3bn
	Pancreatic cancer	$0.2bn
	Hodgkin lymphoma	$0.1bn
	Neuroendocrine tumour	$0.1bn
	Uterine cancer	$0.1bn
	Cervical cancer	$0.0bn
	Hepatoma, liver cancer	$0.0bn
	Squamous cell carcinoma	$0.0bn
Gardasil	Cervical cancer prophylaxis	$6.9bn
Lagevrio	COVID-19 treatment	$5.7bn
Januvia	Diabetes, type 2	$2.8bn
Janumet	Diabetes, type 2	$1.7bn
Other	Other	$10.0bn
	Ulcerative colitis	$0.1bn
	Arthritis, psoriatic	$0.2bn
Other	Other	$16.8bn

Source: Scrip 100; Evaluate

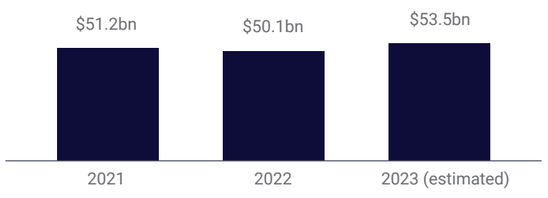
Novartis: of the top five Scrip 100 companies by pharma sales Novartis has most diversity in its sales - the Swiss company's revenue is not as dominated by one or two products. At the end of 2022 it highlighted eight core drugs marked for multi-blockbuster potential. Two of these, Cosentyx and Entresto, are already its top-selling drugs, each making up around 9% of total sales.

Cosentyx, the anti-IL-17 monoclonal antibody, brought in $4.8bn over the course of 2022 and was Novartis's biggest earner. Nevertheless, the immunosuppressant does not feature in the top growth drivers for 2022 – the company stated that growth for Cosentyx was partly offset by high US revenue deductions. However, current consensus forecasts show a return to growth for Cosentyx in 2023.

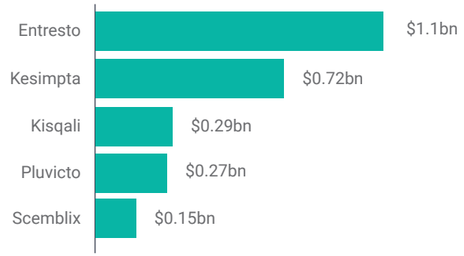
Novartis's second biggest seller for 2022 was the chronic heart failure drug Entresto. Entresto earned $4.6bn over the year and was also the company's biggest growth driver, adding $1.1bn in new sales. According to Evaluate data Novartis is forecast to be 2023's top company in the cardiovascular space by sales, bringing in $8bn, of which $6bn are derived from Entresto.

Kesimpta was another high-growth product for Novartis over 2022. The multiple sclerosis drug, launched in September 2020, saw growth of $700m during 2022 and is also forecast to

Novartis's Pharma Sales



Top 2022 Growth Drivers



Additional sales in 2022 versus 2021.

2022 Sales Portfolio Breakdown

Product	Indication Level 3	2022
Cosentyx	Psoriasis	$3.6bn
	Ankylosing spondylitis	$0.6bn
	Arthritis, psoriatic	$0.6bn
Entresto	Chronic heart failure (CHF)	$4.6bn
Promacta	Thrombocytopaenic purpura, idiopathic (ITP)	$1.2bn
	Hepatitis C induced thrombocytopaenia	$0.9bn
Gilenya	Relapsing-Remitting MS (RRMS)	$2.0bn
Tasigna	Leukaemia, chronic myeloid (CML)	$1.9bn
Other	Other	$24.8bn

Source: Scrip 100; Evaluate

be one of Novartis's biggest growth drivers for 2023 with an annual growth of 83%.

2023 is currently forecast to be a year of large growth for Novartis with pharma sales of over $55bn predicted. This lift, driven by many of the products already mentioned, will push the company up the rankings and into the top three as things stand. Novartis has, in the past few years, had to battle investor concerns over impending patent expiries but seems to be coming out the other side with a broad pipeline of innovative medicines promising growth.

Still, the company's pharmaceutical business is poised to become even smaller going forward with the recent spinout of its Sandoz generic drug unit into a separate company, which will leave Novartis positioned as a leaner innovative biopharma.

Sandoz generated $2.3bn in 2022, so the separation could leave Novartis facing another decline on the leaderboard the following year. Sandoz was spun out of Novartis in October 2023 as a standalone generics and biosimilars specialist.

Climbing The Leaderboard

AstraZeneca was another standout on the Scrip 100, moving up one spot to number eight on the leaderboard on 18% pharmaceutical revenue growth, with growth coming partly from a full year of sales from Alexion Pharmaceuticals added to the top line. Alexion sales were added to AstraZeneca's revenues for the first time as of July 2021, following the completion of the acquisition. AstraZeneca's COVID-19 vaccine, Vaxzevria, while not authorized in the US, was still used in other markets and added $3.92bn to the balance sheet in 2021, so a tapering off in 2022 remained a headwind – as seen with other COVID-19 vaccine developers.

Novo Nordisk was one winner that moved up the leaderboard from number 16 to number 15 without any COVID-19 presence to impact sales. The company's strong double-digit growth came solely from business fundamentals, driven by its strength in diabetes and obesity. Unable to keep up with the demand for its semaglutide franchise – branded as Ozempic and Wegovy – the company appears on track to continue the climb up the leaderboard in the years ahead.

Moving Down

Merck's rise to number four pushed Novartis, Roche and BMS each down one slot to number five, six and seven respectively, on the Scrip 100. The change reflects a gradual descent for Novartis and Roche, which ranked as the number one and two biggest pharmaceutical companies in the world, respectively, on the Scrip 100 two years ago. Last year, they ranked fourth and fifth respectively, as Pfizer and AbbVie assumed top spots.

All three companies have experienced slower growth recently, with Roche and BMS being impacted by the loss of exclusivity of big-selling brands like Roche's Avastin and Herceptin and BMS's Revlimid and Roche also experiencing a headwind in 2022 from lower sales of Actemra, which was used during the pandemic to treat severe COVID-19.

The Next Leaderboard

A look at the top 10 prediction for full year 2023's pharma sales shows there is little shake-up. Pfizer is still predicted to lead the market – although the gap is closing from 2022. Whilst positions two to five are still occupied by the same companies as in the 2022 rankings there has been some shuffling as to who comes in where.

Novartis is predicted to take third place whilst Merck, although owning the biggest predicted drug in 2023, may potentially fall back to fifth. However, many eyes are now on the two companies at the bottom of this top 10. Novo Nordisk and Eli Lilly are experiencing massive growth due to demand for their type 2 diabetes and obesity drugs and they may well feature much higher come 2024 and beyond.

See more data online
https://invivo.citeline.com/outlook/scrip-100

Outlook 2024

The Scrip 100 universe gathers 2022 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 2022

Combined Pharma Sales

Number Of People Employed By Top 20

1,224,693

Combined Pharma Sales Of Top 20

$755.0bn

Combined Pharma Sales Of Top 100

$1,036.1bn

Pharma Sales Ranking	2020	2021	2022
1	Novartis	Pfizer	Pfizer
2	Roche	AbbVie	AbbVie
3	AbbVie	J&J	J&J
4	J&J	Novartis	Merck & Co
5	Merck & Co	Roche	Novartis
6	BMS	BMS	Roche
7	Pfizer	Merck & Co	BMS
8	Sanofi	Sanofi	AstraZeneca
9	GSK	AstraZeneca	Sanofi
10	Takeda	GSK	GSK

COVID-19 Boost

Pfizer dominated the Scrip 100 rankings of the top pharmaceutical companies in the world based on full year 2022 pharmaceutical revenues, driven by its COVID-19 success.

Count Top 20

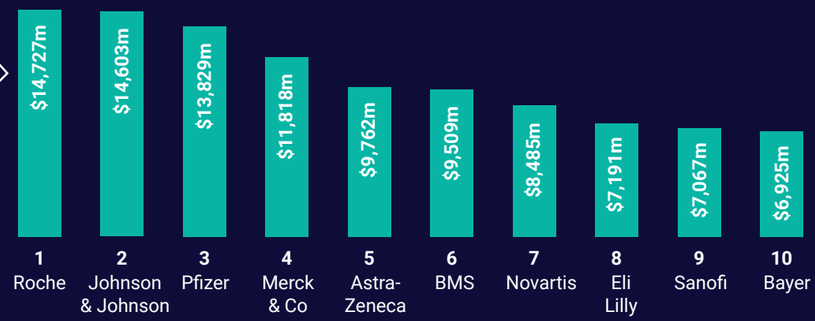
Asia	1
Europe	9
RoW	0
US	10

Count Top 100

Asia	45
Europe	30
RoW	3
US	22

Top 10 Companies By R&D Spend

Roche remains top of the table for another year, but it spent less on R&D compared to FY 2021.



Sumitomo Dainippon Pharma, GSK and AbbVie dropped out of the top 10 list.

SCRIP 100

Scrip 100 Ranking	Company	Country	Pharma Sales ($m)
1	Pfizer	United States	98,988
2	AbbVie	United States	58,054
3	Johnson & Johnson	United States	52,563
4	Merck & Co	United States	52,005
5	Novartis	Switzerland	48,274
6	Roche	Switzerland	47,745
7	Bristol Myers Squibb	United States	46,159
8	AstraZeneca	United Kingdom	44,351
9	Sanofi	France	39,956
10	GlaxoSmithKline	United Kingdom	36,274
11	Takeda	Japan	30,842
12	Eli Lilly	United States	28,541
13	Gilead Sciences	United States	27,281
14	Amgen	United States	26,323
15	Novo Nordisk	Denmark	25,065
16	Bayer	Germany	20,287
17	Boehringer Ingelheim	Germany	19,454
18	Moderna, Inc.	United States	18,435
19	BioNTech SE	Germany	18,241
20	Viatris	United States	16,218
21	Teva	Israel	14,925
22	Regeneron Pharmaceuticals	United States	12,173
23	Astellas	Japan	11,629
24	Biogen	United States	10,173
25	CSL	Australia	10,136
26	Vertex Pharmaceuticals	United States	8,931
27	Otsuka Pharmaceutical	Japan	8,714
28	Fresenius SE & Co. KGaA	Germany	8,272
29	Merck KGaA	Germany	8,261
30	Bausch Health	Canada	8124
31	Eisai	Japan	5,701
32	Sun Pharmaceutical	India	5,512
33	UCB	Belgium	5,416
34	Grifols, S.A.	Spain	5,275
35	Servier	France	5,138
36	Abbott Laboratories	United States	4,912
37	Shanghai Fosun Pharmaceutical Group	China	4,569
38	Sino Biopharmaceutical	Hong Kong	4,284
39	Sumitomo Dainippon Pharma	Japan	4,254
40	Mitsubishi Tanabe Pharma	Japan	4,100
41	STADA	Germany	4,001
42	Shanghai Pharmaceutical Group Co., Ltd.	China	3,983
43	CSPC Pharmaceutical Group Ltd.	Hong Kong	3,908
44	Asahi Kasei Pharma	Japan	3,805
45	Jazz Pharmaceuticals	Ireland	3,659
46	Horizon Therapeutics plc	Ireland	3,629
47	Incyte	United States	3,394
48	Ipsen	France	3,188
49	Jiangsu Hengrui Medicine Co. Ltd.	China	3,139
50	Dr Reddy's	India	3,131
51	Aurobindo	India	2,983
52	Cipla	India	2,898
53	Chiesi	Italy	2,897
54	Sichuan Kelun Pharmaceutical	China	2,815
55	Lundbeck	Denmark	2,584
56	Joincare Pharmaceutical Group Industry Co., Ltd.	China	2,552
57	Ferring Pharmaceuticals	Switerland	2,399
58	Samsung BioLogics	South Korea	2,331
59	Endo International	Ireland	2,319
60	Ono	Japan	2,259
61	Shandong Buchang Pharmaceuticals Co., Ltd.	China	2,226
62	Zydus Lifesciences (earlier Cadila Healthcare)	India	2,219
63	Amneal Pharmaceuticals	United States	2,212
64	Baxter International	United States	2,126
65	Santen	Japan	2,074
66	Lupin	India	2,072
67	Genmab A/S	Denmark	2,067
68	Harbin Pharmaceutical Group Co., Ltd.	China	2,055
69	BioMarin Pharmaceutical	United States	2,047
70	Hikma Pharmaceuticals	United Kingdom	2,043
71	Seattle Genetics Inc. (Seagen)	United States	1,962
72	Recordati	Italy	1,953
73	Kyowa Hakko Kirin	Japan	1,944
74	United Therapeutics	United States	1,936
75	Mallinckrodt	Ireland	1,914
76	Livzon Pharmaceutical Group	China	1,880
77	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	China	1,865
78	Swedish Orphan Biovitrum AB	Sweden	1,865
79	KRKA	Slovenia	1,809
80	Grunenthal	Germany	1,791
81	Celltrion	South Korea	1,774
82	Glenmark Pharmaceuticals	India	1,654
83	Topcon Corp.	Japan	1,651
84	Exelixis	United States	1,611
85	Towa	Japan	1,599
86	Sawai	Japan	1,534
87	Meiji Holdings	Japan	1,511
88	Leo Pharma	Denmark	1,507
89	Sinovac Biotech Ltd.	China	1,493
90	Neurocrine Biosciences, Inc.	United States	1,489
91	Biocon	India	1,410
92	CR Double-Crane Pharmaceuticals Co., Ltd	China	1,406
93	Jiangsu Hansoh Pharmaceutical	China	1,397
94	Yuhan Corp	South Korea	1,379
95	GC Biopharma (Green Cross)	South Korea	1,329
96	Beigene	China/Cayman Islands	1,255
97	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	China	1,235
98	KPC Pharmaceutical Inc.	China	1,233
99	Zhejiang Huahai Pharmaceutical Co., Ltd.	China	1,219
100	Torrent Pharmaceuticals	India	1,215

The Scrip 100 ranking is based on Citeline's analysis of fiscal year 2022 prescription pharmaceutical sales data for the top 100 biopharmaceutical companies. For more information contact: Lucie.Ellis@citeline.com.

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Our focus is on delivering Healthcare Intelligence to customers to address the full spectrum of clinical development challenges, not just point-of-service delivery. The synthesis of our experience, expertise, best practices, technology and data provides patient centric processes, commercially optimised for global success, and is driving transformation of trials to improve R&D ROI. ICON has established relationships with a majority of the world's top pharmaceutical and biotech companies, offering:

Globally scaled expertise and solutions for all customers and patients. ICON is:

- World leader in Functional Service Provision (FSP)
- Global number 2 in full-service Ph 2/3 Clinical Research
- Global number 2 in Early Phase Clinical Research
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Clinical focus: no ownership from parent organisation and no distractions from 'near adjacencies', means we are completely committed to customers' clinical development programmes.

Flexible partnership models and governance structures ensure transparent communications. Regardless of the size of your organisation or your project, we work your way.

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We commence client engagements with a strategic consultation, delivered by our team of over 700 consultants, to identify custom solutions, eliminate process white space and identify efficiencies and savings. This delivers across three areas:

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- A network of international experts delivering superior regulatory and quality assurance strategies, submissions, and support to expedite drug and medical device development and manage ongoing global compliance.
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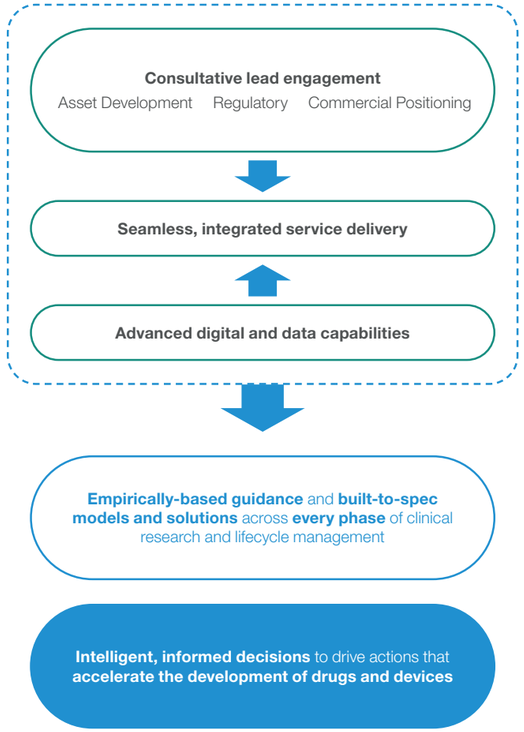
This consultative-led approach, the breadth of our capabilities and advanced digital and data capabilities enables us to deliver seamless, integrated services.



Decentralised clinical trial: Clinical research should engage with patients wherever they are. ICON has all the service components to deliver DCTs and the experience and expertise to provide integrated, customised solutions. Our integrated decentralised clinical trial solutions can help customers to achieve better outcomes, while maximising recruitment and retention of diverse patient populations.

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Advanced digital and data capabilities: Innovation at ICON is focused on the factors that are critical to our clients. Investing heavily in AI, machine learning and RPA capabilities, our portfolio of digital solutions and platforms are specifically developed for the needs for clinical research. Our enterprise clinical informatics framework ingests, integrates and interrogates the full spectrum of data sources, and assets for rich, real-time data-visualisation and actionable insights to significantly enhance the efficiency and productivity of clients' development programmes.

Data insights can include experiential data paired with external data, benchmark data on different models of research, predictive algorithms and continuous performance evaluation, whilst tokenisation of data extends reusability.

ICON is driving transformation of trials to improve R&D ROI and support a future landscape of many more trials delivered in shorter timeframes, but conversely of greater operational and scientific complexity. We strategically and proactively solve today's challenges without losing sight of their impact tomorrow.

Government **Biotech** **Pharma** **Medical Device** **Public Health** **Consumer Health**

Longitudinal Global Biopharma R&D Productivity And Growth Ranking

Markus Thunecke, Erika Kuchen and Alexander Wallroth

Longitudinal Study Background

Since 2014, Catenion have annually assessed R&D productivity and corporate growth of the top biopharma companies, assembling a unique dataset to address fundamental questions around performance and success models.

While our annual review focuses primarily on the performance of individual companies, in this analysis we dissected the patterns that have played out over longer periods of time identifying groups of companies that belong to similar performance phenotypes.

To provide the full longitudinal view, this study only includes companies that were consistently in our top 30 rankings over the past 10 years.

Six Different Performance Phenotypes Identified

Our longitudinal analysis uncovered six different performance phenotypes (*See Exhibit 1*). To evaluate the impact of these phenotypes on company performance, we created an exchange-traded fund (ETF) for each phenotype, giving equal weight to each company (*See Exhibit 2*).

Almost all ETFs achieved an upside compared to the start of our rankings in 2014 with significant gains over the Standard & Poor's (S&P) 500 pharma index, which failed to increase value over the 10-year period. The value increases per ETF reflect our ranking and phenotypes, with the strongest performance observed for the clusters 'League Of Its Own' and 'Turn-Arounds'.

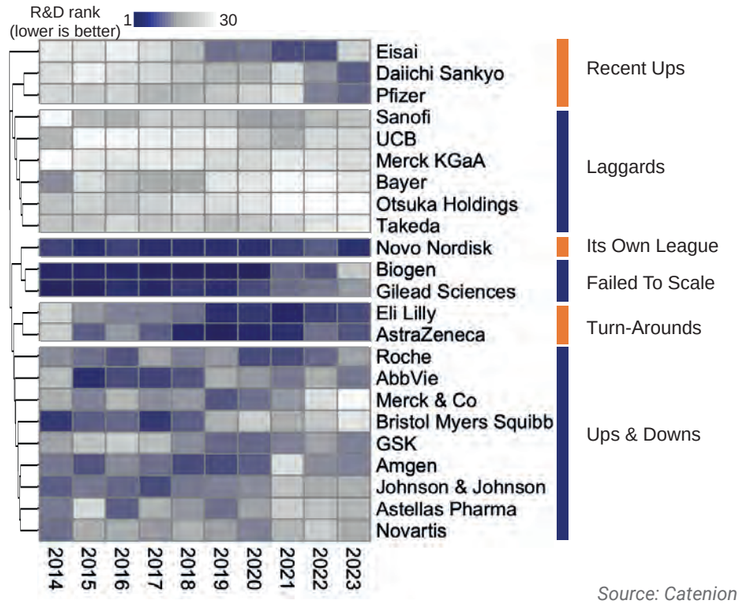
Novo In A League Of Its Own

Novo Nordisk is the only company that consistently featured in the top five since 2014, as such defining a league of its own. Novo was in the right place at the right time with its focus on diabetes and peptide-based drugs, in an era where diabetes and its co-morbidities have reached epidemic proportions.

Novo is also the company that has historically relied the most on internal strengths. Internally developed assets such as semaglutide and its various formulations account for over 90% of value. The glucagon-like peptide-1 (GLP-1) agonist class is the gift that keeps on giving. After type 2 diabetes mellitus and obesity, there has recently been a Phase III win in chronic kidney disease that could have a huge impact on how it is treated.

We wait and see whether this unprecedented run of success can outlive Novo's hypergrowth, as Novo is expected to double in size from 2022 to 2026. One thing is guaranteed: Novo will not end up as a takeover candidate, as the majority of voting shares are owned by Novo Holdings A/S that itself is owned by the non-profit Novo Foundation. Despite failures to enter new therapeutic areas (TAs), Novo keeps trying new things illustrated by recent significant mergers and acquisition (M&A) deals, including RNA company Dicerna for $3.3bn in 2021 and small molecule-focused Forma Therapeutics for $1.1bn in 2022. Investments in Novo stock back in 2014 would have generated a return of 563% until now (*See Exhibit 2*).

Exhibit 1: Performance Phenotypes Based On Catenion's Longitudinal R&D Productivity Rankings



Source: Catenion

Big Pharma Turn-Arounds: AstraZeneca & Eli Lilly

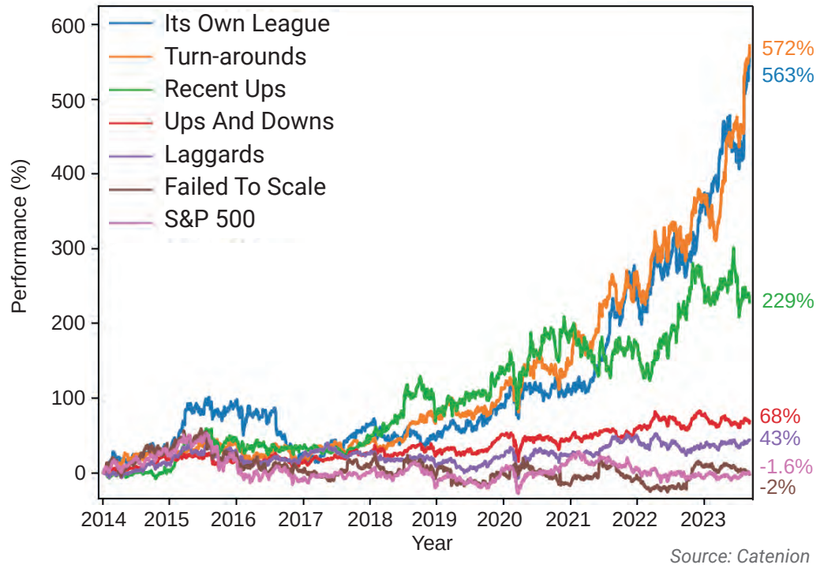
In the start of our ranking, both Eli Lilly and AstraZeneca (AZ) were underperforming big pharma companies with an uncertain future. The fate of AZ changed around 2017 when it broke into the top 10, culminating at #1 in 2019. For AZ, the solution had not only been a strong re-focusing on a few TAs, such as oncology, cardio-metabolic and respiratory – and recently rare diseases through the Alexion acquisition – but an equally strong focus on governance and decision-making. Its 5R decision framework has since served as a template for many other struggling large pharma organizations.

AZ is also a prime example of a company that never completely gave up on internal research, while emphasizing deals and M&As in parallel. Both high-value assets Tagrisso and Imfinzi have not been in-licensed.

The solution for Lilly has been its focus on metabolic diseases and creating an industry-leading GLP-1 agonist franchise, competing with Novo. Ironically, Lilly's success can be attributed to indications that were viewed as financially toxic by investors just a few years ago, such as obesity and Alzheimer's disease.

Investment in both companies in 2014 would have returned an astonishing 572% by now (*See Exhibit 2*).

Exhibit 2: ETFs Of Performance Phenotypes Anchored At The Start Of Catenion's Longitudinal Analysis



Source: Catenion

Failed To Scale: Gilead & Biogen

The 'Failed To Scale' phenotype includes Gilead and Biogen, but one could also add Celgene, as without the acquisition by Bristol Myers Squibb (BMS), Celgene would have faced the same challenge. All three companies had a very focused model at one point that led to their success. Gilead focused on virology, Biogen on multiple sclerosis (MS) and Celgene on hematologic cancers.

After contributing to curing hepatitis C (HCV) through drugs such as sofosbuvir, Gilead started to seek growth in the oncology area, and embarked on expensive acquisitions, including Kite Pharma for $11.9bn in 2017 and Immunomedics for $21bn in 2020. Simultaneously, it faced increasing growth challenges in its core business of human immunodeficiency virus (HIV) and HCV. The company contributed to the fight against COVID by launching the nucleotide analogue remdesivir, but sales are declining rapidly as COVID has become endemic.

Biogen also wanted to diversify beyond its historic focus on MS into Alzheimer's disease. After some missteps, it finally found its stride with the approval of lecanemab. The more interesting strategic question is: why is it so hard to scale R&D productivity when companies go through periods of hypergrowth? Some answers lie in the fact that creative functions often suffer as organizations grow larger and require more bureaucracy and processes. Additionally, decision-making relies more on "aligned" and highly polished views as companies add hierarchical layers.

The Recent Ups: Daiichi Sankyo, Eisai & Pfizer

For Pfizer, the recent upsurge after many years of underperformance is almost entirely driven by COVID and the success of its messenger RNA (mRNA) vaccine Comirnaty with BioNtech and its own protease inhibitor Paxlovid. Considering dwelling COVID sales we do not expect Pfizer to keep its position. Pfizer is an example of how difficult it is to scale innovation, itself being the result of decades of mega M&As. The comeback of Eisai is almost exclusively driven by Alzheimer's, where the sustainability remains.

Strategically, the most interesting company of this group is Japanese Daiichi Sankyo whose success is almost entirely down to one drug class – antibody-drug-conjugates (ADCs). The success of Enhertu and the massive deal Daiichi struck with AZ on the asset speak for itself. Further validation recently came from Merck & Co, who picked up three ADCs for a $4bn upfront payment. Of the three companies in the "Recent Ups" phenotype, Daiichi is the one most likely to remain in a top position over the next few years.

The Largest Group Of All: Ups & Downs Throughout The Years

A disappointing performance comes from Novartis, demonstrating again the challenges of maintaining top performance and innovation at that scale. When Novartis first set up shop in Boston with its Novartis Institute for Biomedical Research back in 2002, it claimed that it had "re-invented the grammar of drug discovery." Twenty years later it is fair to say that these attempts have proven unsuccessful.

Roche chose a different path compared to its Basel rival and decided to maintain two separate Research and Early Development organizations, one consisting of the former Genentech R&D organization, the other representing the former Roche. The decision not to integrate the two may be questioned by proponents of synergies, however economies scale do not really exist beyond a small threshold in creative functions.

Since 2014, Roche had a much better overall performance compared to Novartis with even a few showings in the top 10 of the yearly R&D productivity ranking. Investment into an equally weighted ETF of this phenotype would have achieved a modest +68% over the 10-year period, though still superior to the S&P pharma index.

The Laggards

Despite comparably poor R&D productivity, several companies in this group nevertheless had a satisfactory company growth performance and the 'ETF' of these companies still delivered a +43%. There are a few factors that can help sustain performance in the absence of superior R&D productivity such as a resilient portfolio of marketed products consisting of biologics and products that have a 'second life' in emerging markets, cost-cutting with or without M&A, and a diversified business base.

Common Factors Of Outperformers

The factors that most strongly correlate positively with R&D productivity in our longitudinal study are a high degree of therapeutic focus and a strong share of organically developed assets (*See Exhibit 3*). Irrespective of the TAs chosen, a high degree of focus lays the foundation for good science by allowing R&D teams to build deep and competitive expertise. This expertise not only supports the development of organic assets but also the evaluation of external opportunities.

Growth potential and focus can be achieved along several dimensions, such as TA, specific indications, modalities, and/or successive improvements on existing product families. A model of successive optimizations has been successfully adopted by Novo in the endocrine space. Focus on selected indications was demonstrated by Celgene (multiple myeloma), Gilead (HIV and HCV), Biogen (MS), and even Roche (breast cancer).

The choice of modality also plays its part in value generation. Our feature analysis shows that new biological entities (NBEs) are more positively correlated with success compared to small molecules. NBEs are more resilient compared to small molecules as they suffer less from genericization and tend to be in high-priced specialty markets. Additionally, in clinical development, NBEs have a superior probability of success (PoS), a key dimension for improving R&D productivity.

Focus on defined patient populations and stratification biomarkers is another lever to boost PoS. With more defined patient pools, rare diseases are frequently sought for initial proof of concept, generally offering a higher PoS, smaller and less costly trials, as well as faster cycle times. However, despite all the enthusiasm about rare diseases, most recent successes in large indications such as obesity and Alzheimer's fly in the face of that widely adopted logic.

Common to almost all outperforming companies is what we call the 'hybrid R&D model'. This model relies on a good mix of internal and external assets. Typically, 50% of clinical pipelines stem from external sources and 50% have an organic origin. Organic development is not just a liability. In our analysis, it is also one of the key drivers of success, having created massive value for companies such as AZ, Lilly, Novo and Daiichi.

Strong organic development is inherently linked to a high therapeutic and modality focus. If successful, organic assets will generate superior value compared to external assets, avoiding high deal payments. External sourcing, however, not only allows for risk mitigation and manifesting one's position within the area of expertise but also provides an opportunity to acquire new potential for organic innovation in the form of new platforms, explore new modalities and TAs or to access new markets.

In particular, the US market continues to account for a large proportion of the global pharmaceutical profit pool. Headquarters or a significant commercial presence in the US is invaluable. A lot has been said in the last years about cost-control in the US and the Inflation Reduction Act (IRA) is certainly moving in this direction but in terms of pricing in a global context, the US is still far and above all other countries.

External sourcing can take on multiple shapes, from mega-mergers of mature companies to smaller strategic string-of-pearl acquisitions to sporadic deals. The acquisition of Celgene by BMS for $74bn and Shire by Takeda for $62bn both in 2019 are the two biggest M&As during our longitudinal study. Neither of these deals have improved the companies' R&D productivity due to the substantial costs involved. Mega-mergers cost companies typically at least two years in R&D productivity due to integration effort, pipeline pruning and people focusing on job security rather than innovation. However, mega deals can have commercial benefits in leveraging synergies and cost-cutting measures.

Our analysis shows a positive contribution of early rather than mature-stage acquisitions to R&D productivity. In addition, regular in-licensing instead of sporadic deals ensures that critical skills such as deal sourcing, opportunity evaluation and due diligence are well honed and represent a competitive advantage.

Employee number correlates negatively with R&D productivity (*See Exhibit 3*) and most top performing companies are mid-size. Due to their R&D success, these companies are bound to go through periods of hypergrowth, facing a strategic conundrum. The critical creative functions within R&D do not benefit from economies of scale beyond a certain point, since increasing hierarchy, bureaucracy and process focus, coupled to frequent strategic re-focusing stand in the way of creative discovery. The 'Failed To Scale' phenotype is an example.

Mid-size companies who are outperforming should find a model that supports both economies of scale in functions such as chemistry, manufacturing and controls (CMC), clinical operations or commercial and creativity in functions such as research, translational medicine and clinical development. Large companies that outperform such as AZ or Lilly show that it is hard but possible.

Closely linked to the successful scaling of R&D productivity are the topics of governance and culture. AZ's 5R framework has provided a template for underperforming big pharma companies to turn around performance through strict TA focus, governance and objective portfolio decision-making. In 2011, AZ set out to boost its below-average PoS by advancing only the most promising drug candidates as determined by a priori set thresholds, earlier safety tests and deep scientific understanding. Organically developed Tagrisso was a result of these efforts, catapulting AZ from R&D productivity rank #22 in 2014 to #1 in 2019.

Outlook – Key Questions For The Future

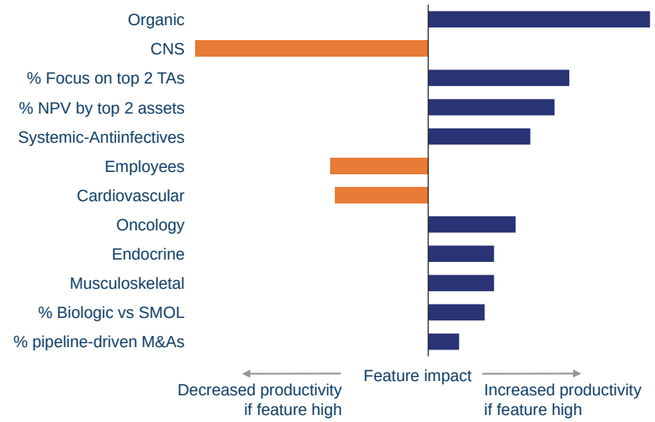
How will companies fare that only recently entered our ranking, such as Moderna and BioNtech? Will we discuss both companies as additional examples of the 'Failed To Scale' phenotype in a few years due to the decline in COVID sales? Or, will they bridge the growth gap by, for instance, demonstrating a use case for genetic medicines such as mRNAs beyond infectious diseases in the form of cancer vaccines or tolerizing agents in auto-immune diseases?

How will the current metabolic disease outperformers fare with their promise of anti-obesity? Will Lilly become the first $1000bn market cap pharma company, and how will the neck-to-neck race of Lilly and Novo for dominance in obesity play out? Will Biogen be the comeback kid and re-surface as an outperformer (driven by success in Alzheimer's disease and a general pipeline renaissance)?

Which role will China play going forward? Historically, China focused on 'me-too' innovation or 'first-in-China'. Will they start to innovate for the global markets and take on target-level risk? Companies such as Hengrui that topped our ranking a few years ago could become the first truly global innovators originating in China.

Whatever the answers, the next years will certainly be as tumultuous as the last few from a macro-economic perspective with global uncertainty high. Those companies that have a solid R&D engine and can innovate effectively will continue to outperform, as our experience shows that even in difficult times true innovation continues to be rewarded.

Exhibit 3: Feature Analysis Of Factors Contributing To R&D Productivity



Source: Catenion

METHODOLOGY

R&D productivity ranks were extracted from Catenion's annual top 30 R&D productivity rankings published in *In Vivo* between 2014 and 2023. For ETFs, daily stock prices were extracted from Yahoo Finance starting from 6 Jan 2014. A machine learning model (XGBoost) was trained on 10-year company data to predict R&D rank. Feature importance was extracted using Shapley additive explanations (SHAP).

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The Biggest M&A Announcements Of 2023 Show Deals Are Getting Bigger

M&A activity in 2023 began with March's $43bn mega-deal for Seagen, but only one other eight-figure takeout had occurred in the first three quarters. Still, the values are higher overall than seen in 2022 and indicate a gradual return to larger deals into 2024.

BY **JOSEPH HAAS,** SENIOR WRITER

As 2023 began, biopharmaceutical industry observers predicted an increase in both merger-and-acquisition activity as well as the return of some larger transactions similar to the occasional mega-mergers seen before the COVID-19 pandemic. During the first quarter, this expectation was realized as Pfizer sought to bolster its cancer biologics portfolio with the $43bn acquisition of the antibody-drug conjugate specialist Seagen.

However, an ensuing wave of larger M&A deals did not arrive and M&A activity slowed down during the second and third quarters in terms of aggregate value.

But in recent years the fourth quarter has seen some of the biggest M&As, such as Amgen's $27.8bn acquisition of Horizon in December 2022 and CSL's $12.2bn takeout of Vifor Pharma in December 2021, each the year's largest M&A deal by dollar value. So far, two of 2023's five largest M&A deals – based on upfront US dollar value – have occurred since 1 October, with the Bristol Myers Squibb/Mirati Therapeutics and Roche/Telavant transactions.

Still, the $10.8bn buyout by Merck & Co. of Prometheus in April is the only deal other than Pfizer/Seagen in the double-digit billions – 2023 to date has seen a continuance of the biopharma sector's preference for bolt-on deal-making.

With 18 biopharma M&A transactions with upfront values of $1bn or more as of early November, 2023 tops the 16 recorded in 2020 and 17 seen in 2022, and is on pace to surpass the 19 such deals seen in both 2021 and also 2019. That year just before the pandemic, however, saw two mega-mergers on a scale greater than any deals seen since: the $74bn BMS/Celgene takeout and the $63bn AbbVie/Allergan combination.

But that was a rarity: 2019 was the only the year in which two deals valued at $30bn or more were completed since 2009, when the sector produced three such transactions – Pfizer/Wyeth, Merck/Schering Plough and Roche acquiring the remainder of Genentech.

Deal size is trending upward, however. The five biggest deals of 2023 so far are mammoth in proportion to 2022's activity, in which there were two eight-digit expenditures (*see Exhibit 1*).

Cancer remains a perennial driver of deal-making for biopharma, while gastrointestinal disease is an area of high competition among numerous companies and mechanisms of action. Meanwhile, outside the five largest buyouts, 2023 has seen growing competition in another burgeoning space – obesity/weight-loss – Eli Lilly and Novo Nordisk engaged in deal-making as leverage against one another and to solidify their positions as the two major players in that arena.

1. Pfizer/Seagen ($43bn)

Facing a significant patent cliff, Pfizer acquired both revenue-generating products and new R&D capabilities with its proposed acquisition of Seagen – in a deal slated to close by the end of 2023. Seagen's four approved drugs – the ADCs Adcetris (brentuximab vedotin) for hematological malignancies, Tivdak (tisotumab vedotin) for cervical cancer and Padcev (enfortumab vedotin) for bladder cancer – along with the breast cancer drug Tukysa (tucatinib) are projected to bring Pfizer $10bn in revenue by 2030.

If those projections prove accurate, the proceeds will get Pfizer a significant part of the way to the $25bn in new product revenue it said it hoped to bring in to offset the impact of patent expirations of products like the breast cancer drug Ibrance (palbociclib) and a prostate cancer therapy partnered with Astellas, Xtandi (enzalutamide). During an investor briefing last December, Pfizer execs said they were attempting to add $25bn in new product revenue through business development by 2030.

Pfizer also said it decided to buy Seagen because it wanted to add ADCs to its portfolio both because biosimilar competition might be less likely to emerge and biologics have longer exemption from Medicare price negotiations under the 2022 Inflation Reduction Act. The merger's closure has been delayed by a review by the US Federal Trade Commission, but the recent settlement between the agency and Amgen has enabled that company's acquisition of Horizon to close, helping to ameliorate doubts about whether Pfizer/Seagen might face heightened FTC scrutiny.

2. Merck & Co./Prometheus ($10.8bn)

Merck made 2023's second-largest acquisition as of early November in a diversification play to acquire autoimmune disease-focused Prometheus for $10.8bn on 16 April. The New Jersey pharma agreed to pay $200 per share for Prometheus, an 80% premium to the San Diego-based firm's 10-day average trading price, and the transaction closed on 16 June.

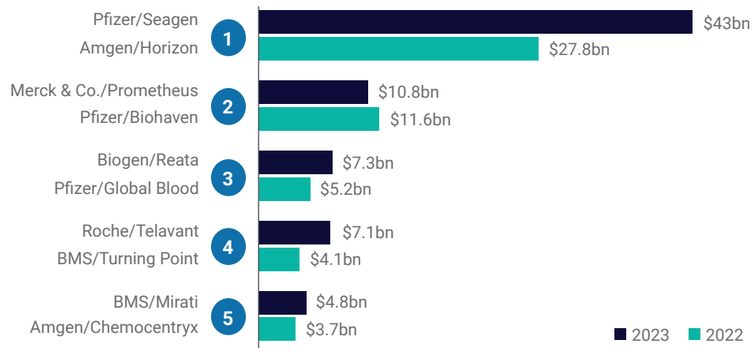
Merck sought to reduce its reliance on oncology and specifically its blockbuster anti-PD-1 agent Keytruda (pembrolizumab), which generated about 40% of the pharma's 2022 sales revenue, about five years ahead of expected biosimilar competition. The high price tag partly reflected the near-term earning potential of Prometheus's PRA023 (now MK-7240), an anti-TL1A agent nearing Phase III in multiple IBD indications.

Prometheus's R&D engine also was expected to enhance Merck's target discovery and precision medicine capabilities in autoimmune disease. Merck's buyout of Prometheus may have been driven in part by a failed attempt to acquire Seagen.

3. Biogen/Reata ($7.3bn)

On 28 July, Biogen agreed to pay $172.50 per share, a hefty 58% premium, to acquire Reata Pharmaceuticals and its recently approved Friedreich's ataxia (FA) drug Skyclarys (omaveloxelone), a predicted blockbuster. The transaction closed on 26 September.

Exhibit 1: Five Biggest M&A Deals Of 2023 & 2022



Source: Company filings

Dealing with generic competition to Tecfidera (dimethyl fumarate) and the failure of its Alzheimer's drug Aduhelm (aducanumab), Biogen picked up a product that would increase its position in rare diseases while adding a revenue-generator that might enable patience for the launch of its second Alzheimer's drug partnered with Eisai, Leqembi (lecanemab), and amyotrophic lateral sclerosis drug Qalsody (tofersen).

4. Roche/Telavant ($7.1bn)

Roche agreed on 23 October to pay $7.1bn up front for Roivant's subsidiary Telavant, due to that company's TL1A antibody therapeutic, RVT-3101 (formerly PF-06480605). Sanofi and Teva also have a TL1A inhibitor in development for IBD, creating a three-way competition by deep-pocketed commercial rivals.

Roivant had only acquired the candidate months before from Pfizer, in a deal that created the Telavant spinout and gave Pfizer a 25% ownership stake.

In a Phase IIb study, RVT-3101 has demonstrated better than the 30% remission and 50% response rates achieved by current treatments for ulcerative colitis.

5. Bristol Myers Squibb/Mirati ($4.8bn)

BMS agreed to pay $4.8bn up front on 8 October to acquire San Diego-based Mirati, reportedly prevailing in a competitive bidding process that also included Sanofi. Bristol's offer came in at $58 per share, a 52% premium to the biotech's 30-day average share price, and the deal also included a contingent value right worth up to $1bn tied to potential US Food and Drug Administration approval within seven years of deal closing for PRMT5 inhibitor MRTX1719.

But the deal's primary driver was Krazati (adagrasib), a KRAS inhibitor launched last December for previously treated KRAS G12C-mutated non-small cell lung cancer (NSCLC). BMS said the product inhibitor would diversify its cancer portfolio, including Opdivo (nivolumab) and Yervoy (ipilimumab), while Mirati's R&D pipeline would bring in additional anti-KRAS agents.

BUSINESS

Money Is Flowing Into Biopharma But Funders Are Investing Selectively

BY **MANDY JACKSON,**
MANAGING EDITOR

Fundraising has grown increasingly difficult since 2021, but while there are glimmers of hope, the rules for who can raise venture cash or launch an IPO have changed.

Sharply dropping stock prices and reduced investor interest in higher-risk sectors like the biopharmaceutical industry since 2021 have led to an increasingly difficult environment for drug developers looking to raise money, whether they are private, looking to go public or already trading publicly. Companies have adjusted by cutting costs to make cash on hand last longer and investors have shifted their focus to later-stage biopharma firms that they perceive as less risky opportunities.

While the world will always need new therapeutics to treat unmet medical needs, the industry still feels the impact of macroeconomic conditions, such as rising inflation and higher interest rates, and no one can predict when the US Federal Reserve will ease the rate hikes that have been implemented in hopes of slowing inflation. Until the cost of capital comes down, it is hard to know when financial conditions will improve for the biopharma sector – but the industry is adjusting to the new normal.

"There are two basic truths about the markets," said Tim Opler, managing director at Stifel Investing Banking. "The first is that the fundamentals matter. Interest rates are really important. If interest rates are high, it means you and I can take our money and put it into money market funds and get a very good return, so why would you go buy a biotech stock?" That biotech stock, Opler noted, is likely to take much longer to provide a return and with a greater risk of no return at all.

"The other factor that really matters is what I would call the interplay between greed and fear," he said. During the few years before late 2021, crossover investors could put money into a later-stage venture capital round before a biopharma company's initial public offering, the company would go public a few months later and the investors would make a 2x or 3x return on the initial public offering. "Basically, people are highly attracted to short-term financial returns, and so, the market got overheated."

Many investors are holding off on new investments while they conserve cash to keep their operations afloat and fuel existing commitments.

The Federal Reserve has indicated it may begin to ease interest rates in 2024 and when that happens drug developers should feel the impact right away. Even so, Opler said an improvement in the ease of biopharma fundraising will be slow. "It will be a process that takes years to get back to the kind of markets that we all wish we had right now," he said.

The Dropoff Is Steep

While venture capital investment in biopharmaceutical companies remains near historically high levels, this offers little consolation for startups that were not able to raise funding in 2023, when the amount of VC investment in the industry dropped sharply from 2022, which was down significantly from the record levels of funding seen in 2021.

Venture capital investment in biopharma peaked in 2021 at $38.7bn, according to Pitchbook and the National Venture Capital Association (NVCA), dropping by 22% to $30.2bn in 2022, which still was the second-highest year on record. The industry raised $16.3bn in VC funding in the first three quarters of 2023, down by 30.9% from the first three quarters of 2022.

If the 2023 pace of venture investment maintains its average of $5.4bn per quarter in the fourth quarter, the year's total of about $21.7bn would give 2023 the fourth-highest annual total for biopharma VC funding, despite the sharp year-over-year drop, because of the massive uptick in investment from $18.9bn in 2019 to $28.5bn in 2020 before reaching the record $38.7bn total in 2021.

"Now that we've been in a rising interest rate environment since March 2021 or so, it's actually not a surprise to see [limited partners (LPs)] plus generalist investors, retail investors, crossover investors kind of pull away," said Kouki Harasaki, founding and managing partner at Bioluminescence Ventures (BLV). "But we are very hopeful and we're seeing plenty of signs or glimmers of hope that we're kind of hopefully seeing the bottom and we're on our way back up."

BLV recently came out of stealth mode with $477m in assets under management, including $350m in its inaugural venture capital fund. Harasaki said the financial environment made it difficult for newer venture funds to raise capital, but noted that established VC firms have been able to raise some very large new funds despite the tough market as LPs see the value in the biopharma sector.

"Whether you're a venture firm or you're a biotech company, the best, most established biotech companies and venture firms will be able to raise large rounds or large funds even in downturns," Harasaki said.

The venture firm Abingworth closed its $356m Clinical Co-Development Co-Investment Fund (CCD-CIF) in October 2023, providing funding to help companies complete pivotal trial programs. Abingworth provides funding and potentially clinical trial support through its company Launch Therapeutics and in return the VC firm earns a return on its investment via fixed payments following a drug's approval.

The co-development/co-investment strategy gives Abingworth another investment vehicle and biopharma companies an alternative financing option during a difficult period for fundraising, Abingworth managing partner and chief investment officer Bali Muralidhar said.

Muralidhar noted the financial market challenges have been most acute in the public company arena, where valuations have fallen and the number of new IPOs has declined sharply as a result, but stock market turmoil has caught up to private companies.

IPOs Could See Upswing In 2024

Ayman AlAbdallah, a partner at Mubadala Capital in San Francisco, said conditions for venture capital exits, both in terms of M&A and IPOs, were likely to be mixed in 2024. "IPOs may slow down due to increased volatility in the public markets, but M&A could potentially pick up as large biopharma companies with strong balance sheets look to acquire smaller companies with promising pipelines."

"This dynamic creates a number of opportunities and challenges for biopharma companies seeking capital," he added. "On the one hand, companies that are contemplating an IPO may need to be more patient and wait for the right market conditions. On the other hand, companies that are able to attract interest from large biopharma companies could potentially find themselves in a strong negotiating position."

There were 21 biopharma IPOs in the US in 2023 as of 9 November, when CARGO Therapeutics Inc. grossed $281.3m in an offering of 18.75 million shares at $15 each, making it the fifth-largest first-time offering of the year – or the fourth-largest excluding the $3.8bn IPO launched in May by Kenvue Inc., the consumer health company spun out of Johnson & Johnson.

The year could end on par with 2022, when 22 companies went public in the US. By mid-November in 2022, only 20 drug developers had launched first-time offerings, so there may be hope for 2023 to produce a few more IPOs.

The IPO-tracking firm Renaissance Capital noted in its third quarter US IPO market review that while companies considering a public launch still were showing reluctance to enter the market, consumer brands and health care companies – largely VC-backed biotech firms – were the most likely candidates for fourth quarter IPOs. Market conditions have improved marginally for IPOs in general and some large offerings have provided satisfactory returns for IPO investors, so Renaissance Capital said it was "cautiously optimistic about IPO activity gradually accelerating through the rest of 2023 and into 2024."

BLV's Harasaki noted that the IPO market was opening for biopharma companies, but like venture capital investors considering funding for a private company, IPO investors were highly selective.

"IPOs are really only possible for proof-of-concept or near proof-of-concept, best-in-class/first-in-class, differentiated programs that are going after large indications or have the potential to move up in lines to a larger indication, and these assets have to have very robust IP portfolios," he said. "And it's also becoming more common for investors to want to see at least one big pharma [business development] deal as another level of technical validation."

Platform companies without a strong clinical-stage lead drug candidate still may be able to go public, but they need "strong proof points around the platform being a discovery engine," Harasaki said. Also, biopharma companies considering an IPO also need to make sure they will have strong insider participation in the offering from investors that already have put money into the company. In addition, drug developers may need to more realistically consider their post-IPO valuation.

Investors are keeping an eye on larger 2023 IPOs launched by companies such as Neumora Therapeutics Inc. and RayzeBio Inc., which raised $250m and $358m, respectively, in September, and Structure Therapeutics, which raised $161.1m in February, with mixed results for investors. Neumora's stock price was trading 35.8% below its IPO value at the end of the third quarter, while Structure was up by 395.3% and RayzeBio was trading 7.8% higher.

The performance of these larger offerings could be "canaries in the coal mines that everyone's going to be looking at to see if the IPO market is truly on like an upward swing," Harasaki said.

He said a lot of biopharma firms were filing confidential paperwork with the US Securities and Exchange Commission that allows them to begin meeting with potential IPO investors and determine whether there is enough interest in their company and when they might be able to pursue and IPO.

AlAbdallah of Mubadala Capital noted that despite the tough financial market, investors still were interested in biopharma opportunities because of the compelling scientific advances made by the industry and the need for new medicines, but funders want reassurances that companies are prepared to manage their operations through rough conditions.

"We evaluate several factors, including the strength of the management team, the differentiation of the therapeutics approach or technology with a clear clinical development path, the robustness of the pipeline of drug candidates, especially those focused on chronic diseases, and the soundness of the roadmap," AlAbdallah said. "Given the current market, we are also placing greater emphasis on the need for contingency plans that provide companies with flexibility."

The State Of TechBio Going Into 2024

The long-term success of TechBio is dependent upon the flow of investment and alliances with mature life sciences companies. This collaborative model has proven many times over to be an ideal framework for developing new treatments for patients.

BY **LUCA PARISI,** DIRECTOR OF CLINICAL ANALYTICS AND DATA SCIENCE

DANIEL CHANCELLOR, DIRECTOR OF THOUGHT LEADERSHIP AND CONSULTING

LUCIE ELLIS-TAITT, EXECUTIVE EDITOR

These are exciting times for the TechBio community, from the pioneering startups and academics to their industry partners and investors. Generative artificial intelligence has now become part of everyday conversation through the success of ChatGPT and other programs, raising awareness of some of the tools that underpin the technology aspect of TechBio companies.

Meanwhile, biotech drug pipelines are as deep as ever with the validation of new modalities and patient data being generated at pace. For those companies operating at this interface, the use cases are maturing rapidly with real-world examples. The evolution of the TechBio community will impact the broader life sciences industry in a critical way. It will need to be integrated into the whole continuum of R&D.

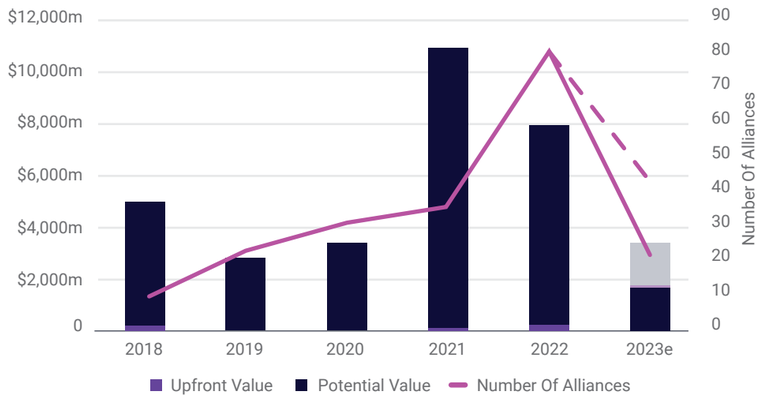
This includes AI-driven drug discovery, whereby algorithms are enabling the design and optimization of novel small molecules and proteins with accuracy and scale that conventional drug discovery cannot match. Furthermore, existing treatments can be repurposed using AI-derived biological insights, with multi-factorial matching of patients to clinical trials that are designed to maximize the likelihood of success. Such processes will expedite the overall R&D process and drug development pipeline, lowering the degree of attrition during late-stage clinical trials, thus addressing key industry productivity challenges.

Furthermore, expansion and integration of patient data into early R&D decision making will be transformational for the future of health care. The broad adoption of multiomics tools is generating new insights into fundamental human biology and precision medicine. Diseases are increasingly viewed as a function of such biomarkers, which ultimately guide diagnosis, treatment and connected care in the real-world setting.

The cost and complexity of drug development requires experienced and committed partners. Therefore, the long-term success of TechBio is dependent upon the flow of investment and alliances with mature life sciences companies. This collaborative model, long established between big pharma and emerging biotechs, has proven many times over an ideal framework to develop new treatment options for patients. The broader state of TechBio can therefore be gauged through such deal-making activity.

It is difficult to capture the totality and nuance of TechBio – which sits at the intersection of many different disciplines – within any standard industry. Citeline tracks global deal-making activity in life sciences and assigns an AI classification to companies and deals where relevant, which can be used as a proxy for the TechBio universe. Exhibit 1 summarizes partnership activities involving AI.

Exhibit 1: Partnership Deals In TechBio



Source: Biomedtracker, July 2023

Life sciences companies raised a record £9.4bn investment in 2022 to further advance their AI platforms and assets, with this total having doubled every year since 2018. The number of alliances with biopharma partners is also following a similar trajectory, although their value is more volatile and heavily swayed by milestone components. Nevertheless, £263m in upfront payments was a record for 2022, spread across 81 separate partnerships.

The first half of 2023 has not been able to sustain the incredible amount of global activity within 2022. Speaking to *In Vivo*, Ivan Griffith of BenevolentAI explained: "Investment and growth have slowed down and people are waiting to see critical readouts and data that validate the thesis that AI can significantly benefit drug discovery and reduce attrition."

Deal values and volumes are down sharply as TechBio has not been immune to broader market uncertainties, although the UK has been an outlier. Here, TechBio companies are on track to exceed last year's £161m in fundraising across 10 deals, with seven financings bringing in a total of £87m. This resilience is enabling the UK TechBio ecosystem to secure a prominent position in the global rankings. Across both financings and alliances, the UK is second only to the US for TechBio deal-making over the last 18 months (*see Exhibit 2*).

UK Companies Driving The AI Revolution

The UK TechBio ecosystem contains a range of different technologies and business models. Companies such as Exscientia and BenevolentAI are at the vanguard, becoming fully fledged biotechs with a blend of strategic alliances, such as multi-year strategic partnerships between BenevolentAI and AstraZeneca, out-licensed assets and internal drug pipelines. Several others are bidding to make the transition from discovery science to clinical-stage candidate. Earlier in the lifecycle, there are a range of venture capital-backed service providers with specific capabilities in a particular R&D step, therapy area or diagnostic tool.

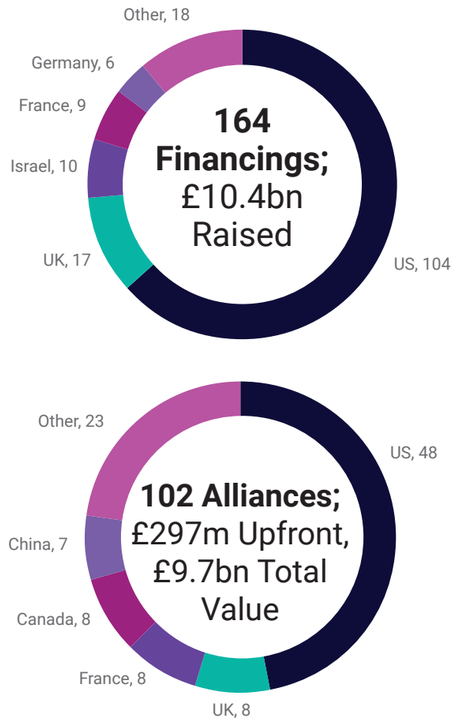
Having raised close to $500m from investors during its 2021 initial public offering and private placement, Exscientia has now progressed six assets into clinical trials, either through strategic alliances or as internal R&D programs. Three of these are under development by Sumitomo Pharma for CNS disorders, while the remaining programs target cancer and inflammatory diseases. Of note, the ELUCIDATE basket trial of a CDK7 inhibitor is underway, with broad potential application in a range of prevalent solid tumors. Exscientia also regained control of assets discovered in collaboration with Bristol Myers Squibb against the complex cancer targets LSD1 and MALT1.

Prior to founding Exscientia, CEO Andrew Hopkins spent 14 years at Pfizer Inc. and in academia, pioneering projects using data mining and machine learning. He expects the biggest gains for AI in biopharma to come from precision medicine.

He told *In Vivo*: "The area, I believe, where we will see the greatest impact is truly making personalized medicine a reality." In 2022, the company published results from the EXALT-1 trial – EXALT-1 was the first prospective interventional study of its kind. "Predictions made by the platform proposed which therapy would be most effective for hematological cancer patients based on testing drug responses *ex vivo* in their own tissue samples," Hopkins explained. "When we looked at results, about 25% of the patients four years later were progression free."

London-based Charm Therapeutics is one of the few TechBios to secure financing in 2023. New investment from Nvidia raises total fundraising to date to $70m and adds to an already impressive syndicate of venture capital firms. This investment will further fuel the development of Charm's DragonFold platform that can identify novel molecules through protein-ligand co-folding.

Exhibit 2: Financing And Partnering Activity By Geography



Data for 2022 and 1H 2023

Source: Biomedtracker, July 2023

In addition, Charm secured its first industry partner in BMS, leveraging DragonFold to discover novel molecules against targets of interest. BMS is able to exercise options to license and develop any compounds that arise from this collaboration. "Protein structure prediction using deep learning has the opportunity to greatly impact biopharma, not just due to having the 3D structure of any protein, but also the related algorithms people will develop inspired by it," Laksh Aithani, CEO of CHARM Therapeutics, told *In Vivo* at the start of 2023.

Also bucking the broader biotech downturn in 2023, BIOS Health received new funding from a range of investors, including the TechBio fund Selvedge Venture. BIOS is a trailblazer in combining AI technologies and precision neurology, and is providing its capabilities to the US National Institutes of Health as part of the REVEAL study. The ambition is to sequence neural biomarkers to elucidate the link to various disease states, much as genetic sequencing has resulted in significant breakthroughs for drug discovery in cancer and rare diseases.

About Catenion

Catenion is a management consulting firm devoted to helping **pharmaceutical** and **biotech companies** implement more innovative and effective strategies.

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01 We focus on **science-driven strategy**: we answer key questions through comprehensive multidimensional assessments conducted by our team of life science PhDs.

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03 We integrate **Data Science** in our analyses with a team of bioinformaticians, computational biologists and data engineers.

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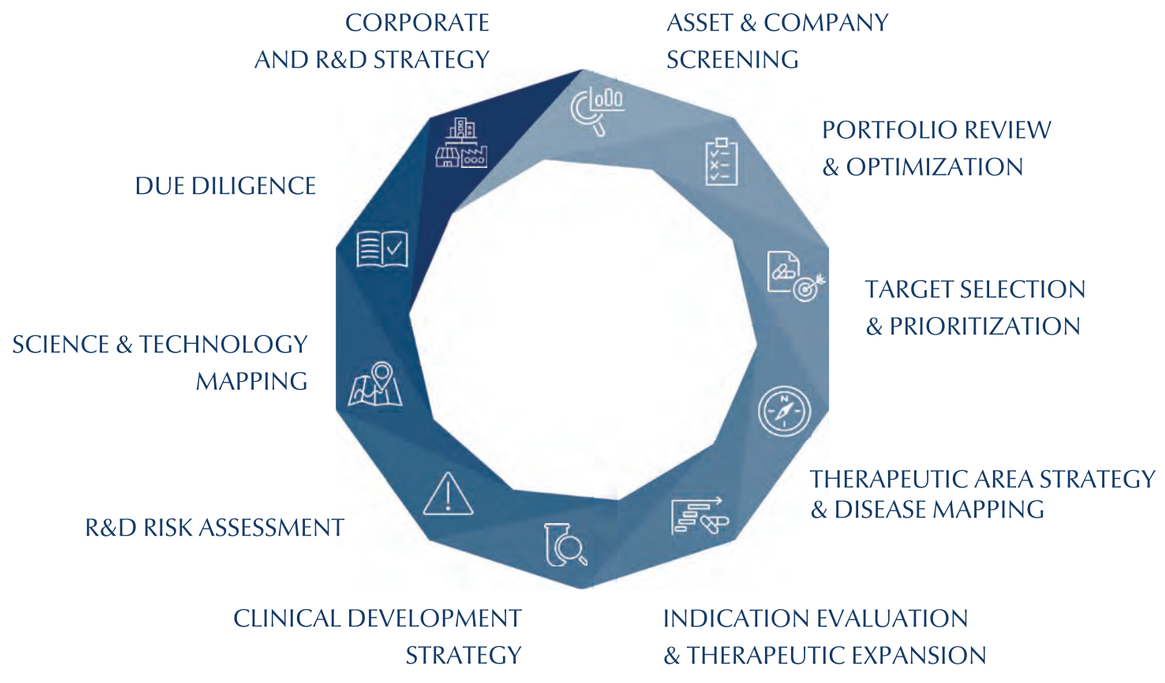

Building A More Sustainable Future For Pharma

Across industries and regions, companies are under significant pressure to make their operations more environmentally sustainable. Change is required to avoid crisis, with society already facing the alarming repercussions of increased global warming.

"Global climate change is appropriately in the news every day, and the pharmaceutical industry has certainly played its role in creating negative environmental impacts," states David Maier, Vice President and General Manager, Global Generics Market Unit at West Pharmaceutical Services, a leading supplier of packaging and services for injectable medicines. Studies have reaffirmed this stance, highlighting pharmaceuticals as a significant contributor to global warming.[1]

As pharma companies look to adopt greener, more sustainable processes, old ways of working need to be changed. This reality also presents opportunities to innovate and optimize existing practices in ways that will have lasting impact.

Balance Needed To Achieve Sustainable Generics

There are many environmental, economic, and social factors that must be considered for generics companies and their suppliers to make their operations more sustainable. "Generics are known for their cost-effectiveness. Balancing sustainability initiatives with financial constraints can be difficult, as changing practices often require upfront investments that may not yield immediate returns," notes Maier. Regulatory compliance is also key, and further spending is often needed to ensure that eco-friendly processes and technologies adhere to these requirements.

Additionally, it is not enough to change just one part of the generics manufacturing process. The industry relies heavily on a global supply chain for raw materials and active pharmaceutical ingredients (APIs). If one part of this fails to meet sustainability criteria – for example, the responsible sourcing of materials and ethical labor practices – it can mitigate the positive steps taken in other areas.

These challenges require industry to come together. Maier asserts that collaboration between vendors and customers is critical to improve sustainability and address emissions, energy and water usage, and waste reduction.

"To that end, West takes a concerted, cooperative approach with our customers and other stakeholders, working together to help each of us efficiently achieve our environmental, social, and corporate governance (ESG) targets for mutual benefits," he states. Means of doing this include investigating shared power purchase agreements, researching more sustainable materials, exploring shipping methods and studying beneficial reuses of products.

Performance Meets Sustainability In Packaging

One area of challenge for meeting ESG goals is packaging. In particular, the glass vials utilized for single-use, sterile, injectable medicines have historically resulted in significant waste. "It's been estimated that pharma and generics companies use around 150,000 tons of Type 1 glass annually to make vials. Due to complex regulations, most of this glass is then discarded as medical waste, ending up in landfills across the world," says Maier.

While there is a clear need to make sustainable decisions about product design, eliminating single-use glass vials is not viable, due to sterility and patient safety requirements for generic products. However, industry is continually innovating to create greener alternatives. In order to provide their customers with optimal design solutions, West Pharmaceutical Services has partnered with Corning Incorporated® to become the exclusive distributor of Viridian™ Vials. "Corning® Viridian™ Vials are fundamentally a Type 1 borosilicate vial, but they're better. These vials provide both operational and environmental improvements over existing products on the market," notes Maier.

The sustainable design of Corning® Viridian™ Vials reduces glass waste-to-landfill by 20%, and manufacturing CO_2e emissions by up to 30%.[2] However, their benefits are not limited to being environmentally friendly. The low coefficient of friction drives higher fill-finish speeds and throughput, which can increase manufacturing efficiency by up to 50% for improved output and value.[3] Additionally, their coating reduces the likelihood of cracks and damage, preserving product integrity during transportation and delivery, which is key for patient safety. Their conformity to ISO standard external dimensions also means they can be dropped into existing operations, without the need for significant changes or reporting to regulatory authorities.

Creating operational efficiency and safeguarding product quality is critical to the longevity of sustainable practices. If changes result in increased expenditure and reduced results, pharma companies will not embed them into their operations. This is particularly the case for generics firms that are already stretching the feasibility of their operations.

"We must explore new processes and methods without diminishing the quality and efficacy of the products we make, and that our customers and their patients rely on," states Maier. Thankfully, expenses can be decreased by reducing energy and water usage, providing incentives that, in turn, meet ESG targets. Furthermore, reduction of operational waste and secondary packaging, and finding beneficial reuse for products, can also be cost-positive and create efficiencies.

Focusing On A Responsible Future

In order to keep on track, most companies now have clear sustainability plans or policies which govern their operations, and West is no different. "As we celebrate our 100-year anniversary, we realize that we must continue to evolve our ESG strategy and be ambitious, innovative leaders in this area. Our sustainability program has been designed to target reductions in the areas where we can have the greatest impact," says Maier. "Our 2030 targets are expected to include achieving 50% renewable electricity; continuously improving energy-efficiency by 3% year-on-year; reducing absolute emissions by 40%; achieving a 15% water-intensity reduction; and eliminating up to 100% of operational waste to landfill."

West also recognizes its responsibility to collaborate with customers and lead them towards more sustainable product and process choices. "Beyond what West is doing for our own operations, we are working closely with our customers to help them achieve their environmental goals. For example, we partner with them to reduce, reuse, and recycle secondary packaging, and work together to explore sustainability improvements throughout the product life cycle and supply chain," notes Maier.

"Corning® Viridian™ Vials are fundamentally a Type 1 borosilicate vial, but they're better. These vials provide both operational and environmental improvements over existing products on the market."

David Maier, West Pharmaceutical Services

True sustainability goes beyond just environmental considerations, which West has acknowledged in its wider ESG priorities. These include:

- Climate
- Reductions in Operational Waste
- R&D for the Environment
- Responsible Supply Chains
- Talent Attraction and Retention/Engagement

The latter are critical in bringing expertise to customers and ensuring all decisions are made with sustainability in mind.

By taking such a comprehensive approach, Maier believes West will make a real impact. However, their work is by no means done in this area. "We will continue to monitor ever-developing global sustainability standards and regulations to ensure we are aligned with leading organizations and following best practices in setting science-based targets. This will enable West to provide a better world for further generations and look forward to our next 100 years in business."

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GENERICS AND BIOSIMILARS

Indian Leaders Climb Into Generics And Biosimilars Top 10

BY **DAVID WALLACE,**
EXECUTIVE EDITOR

Companies Lower Down In The Top 50 See Movement Amid Mixed Fortunes

In a year that has seen significant changes throughout the generics and biosimilars industry ranking, the top 10 has welcomed two Indian off-patent leaders. Meanwhile, companies lower down our ranking have enjoyed mixed fortunes, leading to a number of significant movements in this year's *Generics Bulletin* Top 50.

Change is a constant theme for our annual *Generics Bulletin* Top 50 ranking of the world's leading generics and biosimilars companies, and this year's rundown of off-patent industry titans is no different.

The top 10 players in 2023's roster are a different group to last year's leadership table, with two firms that were present in 2022's top 10 dropping out to make room for fresh faces to enter.

Meanwhile, even those familiar firms that regularly appear towards the top of the table have seen significant evolution over the past year, reshaping this year's top three yet again.

And further down the *Generics Bulletin* Top 50 ranking – which, as ever, compares by turnover the top players in generics and biosimilars, based on our lead category of Generics/Biosimilars/APIs/OTC sales – we have seen plenty of movement as companies jostle for position in a competitive sector.

Sandoz Maintains Lead

Our 2023 ranking is once again topped by Sandoz, which maintains its leading position of recent years despite last year seeing a slight dip in sales of 4% – albeit translating to a 4% constant-currency rise – to $9.2bn.

The firm has seen major changes in 2023, culminating in a long-planned spinoff from parent company Novartis that took effect in early October.

Next in line is Teva, which – like Sandoz – reported a slightly smaller total this year amid similar industry pressures. Unlike Sandoz, however, Teva is increasingly focusing on its more innovation-oriented business segments under the leadership of new CEO Richard Francis, although this does still include a major role for biosimilars as well as higher-value complex generics.

Moving down to the third position brings the first major change to our ranking this year, as Pfizer is absent despite appearing in third place in 2022. This is because the firm – which brings in biosimilars sales alone of around $2bn – no longer splits out its biosimilars or largely generic sterile injectables businesses as distinct reporting segments due to a recent change in company organization.

As such, Pfizer is no longer eligible for inclusion in the *Generics Bulletin* Top 50 as per our longstanding methodology, with the firm's absence from the table allowing Viatris to reassert its place in the off-patent industry top three.

Over the past year, Viatris – which boasts the largest turnover total of all of the companies in our ranking – has been experiencing changes in organization of its own. Not only has the firm undergone a change in leadership – with brand industry veteran Scott Smith taking the reins as CEO from the start of April – but it has also shed a major chunk of its business by selling its biosimilars interests to former partner Biocon in a deal worth around $3bn.

Dr Reddy's And Cipla Ascend Into Top 10

Moving further down the table, following on from the appearances of Sun Pharma and Shanghai Fosun – retaining their relative placings from last year but rising up a position due to the removal of Pfizer – we come to the second notable absence from this year's top 10.

Perrigo, which last year dropped out of the top five, has now dropped out of the top 10 entirely, in the wake of the divestment of its prescription generics unit.

This means that firms previously ranking beneath Perrigo in our top 10 – Stada, Fresenius Kabi and Aurobindo – all jump up another place this year, making room for Dr Reddy's and Cipla to join the leading group.

Dr Reddy's is increasingly pushing forward with a range of future initiatives falling outside of its core off-patent business, with CEO Erez Israeli explaining to *Generics Bulletin* earlier this year that the firm's longtime interests in active pharmaceutical ingredients, generics, branded generics and biosimilars were helping to generate proceeds to invest in future innovations.

And Cipla continues to make progress in generics and complex generics, despite recently facing down facility compliance issues.

Mid-Table Firms Also Move Up The Ranking

As a result of Dr Reddy's and Cipla ascending out of the middle table covering positions 11-30 in our ranking, and into the top 10, this has left room for further firms to climb up the charts in the second section of the *Generics Bulletin* Top 50.

Intas – parent company of Accord – now tops the second table, providing financial details directly to *Generics Bulletin*. The firm is followed closely behind by Hikma, both jumping up two places and filling the gaps vacated by Cipla and Dr Reddy's.

After this pair comes Perrigo – a firm that previously occupied a top 10 spot – which finds its new place at 13, with its figures calculated based on the split between branded and store-brand products in the consumer healthcare business that remains after the firm divested its prescription generics unit in mid-2021.

Lupin follows, with sales staying relatively steady in its latest financial year, ahead of a major launch that took place later in calendar 2023 with its generic version of Boehringer Ingelheim's Spiriva HandiHaler (tiotropium bromide inhalation powder) in the US.

Then underneath Lupin, two firms – Zydus and Krka – leapfrog Aspen this year to push the South African player down to 17th place.

Slightly further down the table, Amneal climbs from position 26 to 23 – after pushing up sales by 6% in 2022, driven by an increasing focus on complex generics and biosimilars – while India's Macleods enters the ranking at 27 after providing *Generics Bulletin* with detailed financial data for the first time.

Another noteworthy appearance in this ranking is Biocon, which climbs from position 31 on our bottom table last year to position 26 in our middle table this year, as a result of significant growth after absorbing the biosimilars business of former partner Viatris.

However, some companies that were seen in 2022's Top 50 are absent from this year's ranking altogether. Japan's Nichi-Iko – last year listed in 22nd place – was recently acquired by a private equity fund after a difficult couple of years, and has not published data for its most recent financial year.

And Sanofi – which last year rounded out the middle table at position 30 – has been removed from this year's ranking in line with our longstanding methodology as it no longer splits out the results of its generics business.

Lower-Placed Firms See Significant Movement

The third and final section of our annual off-patent industry Top 50 reflects positive and negative changes among lower-placed firms that have led to some meaningful movements at the bottom of the table in 2023.

Leading off our third table is Endo, which jumps up from position 34 last year to 31st place this year, amid growth for the company in our lead category of Generics/Biosimilars/APIs/OTC sales – and after the aforementioned firms in the upper tables were removed from this year's ranking altogether.

Following Endo is a very close pack of competing companies, with Jubilant Pharmova, Ipca Labs and Alembic Pharma separated by differences in sales of just a handful of millions of dollars.

Meanwhile, Latin American giant Hypera – which was last year ranked at 37 – has this year been removed from the Top 50 as it no longer splits out the relevant segments of its business, similar to earlier sections of the ranking that saw the likes of Pfizer and Sanofi eliminated from the comparison for the same reason.

Towards the bottom of our chart, we see several firms climbing the rankings or entering the Top 50 for the first time.

Amphastar has climbed from position 44 to 41 after a successful year, while Bangladesh's Beximco has advanced from position 47 last year to 43 in the current ranking – although this is based on results from its financial year to 30 June 2022, meaning more recent developments are not reflected.

This year has also seen China's Shanghai Henlius Biotech enter the Top 50 at position 45 on the back of a successful biosimilars business that now has multiple products in the market.

Meanwhile a couple of places lower, ANI Pharmaceuticals climbs into the table for the first time at position 47, after its business exceeded expectations in 2022.

Some firms have been less fortunate over the past year, however. This year's ranking has seen Lannett fall from position 42 to 46, after tough conditions for the firm ultimately sent it heading towards bankruptcy. The firm is unlikely to appear in next year's Top 50 after recently becoming a privately-held company in the wake of its reorganization.

And Coherus BioSciences rounds out our table, dropping from position 48 to 50 after a continuing decline in sales of its Udenyca (pegfilgrastim-cbqv) biosimilar – although the firm is hoping to capture increased market share via an autoinjector version of Udenyca that was approved earlier this year, as well as to benefit from its launch of a biosimilar rival to Humira (adalimumab) in a crowded field.

As the off-patent sector continues to face competitive and economic pressures, changing regulatory environments, and uncertainty over crucial aspects of how it does business, more change is doubtless on the horizon for leading generics and biosimilars players over the next 12 months.

The Generics Bulletin Top 50 Data

The *Generics Bulletin* Top 50 ranking compiles sales data for 2022 – 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.

GB50 Ranking	Company	Generics/ APIs/OTC ($m)	Prescription Brands ($m)	Other ($m)	Total Turnover ($m)	Change %	Notes
1	Sandoz	9,249	n/a	n/a	9,249	-4	
2	Teva	8,601	2,621	3,703	14,925	-6	
3	Viatris	6,329	9,889	n/a	16,218	-9	
4	Sun Pharma	4,598	871	27	5,496	13	Financial year ended 31 March 2023; Prescription brands is Specialty sales; INR: 0.0127 dollars
5	Shanghai Fosun	4,555	n/a	1,947	6,502	13	Generics/Biosimilars/OTC/APIs figure is pharmaceutical manufacturing segment and includes Comirnaty COVID-19 vaccine; Chinese yuan: 0.1484 dollars
6	Stada	4,009	445	n/a	4,454	11	Segmentation based on estimated 90:10 split for generics and brands; Euro: 1.173 US dollars
7	Fresenius Kabi	3,598	n/a	5,610	9,208	9	Generics/Biosimilars/OTC/APIs figure is Intravenous Drugs and Biopharmaceuticals units; Euro: 1.173 US dollars
8	Aurobindo	3,157	n/a	n/a	3,157	6	Financial year ended 31 March 2023; INR: 0.0127 dollars
9	Dr Reddy's	2,955	n/a	37	2,992	15	Financial year ended 31 March 2023,
10	Cipla	2,863	n/a	27	2,890	5	Financial year ended 31 March 2023; INR: 0.0127 dollars
11	Intas	2,506	n/a	n/a	2,506	1	Financial year ended 31 March 2023
12	Hikma	2,254	250	13	2,517	-1	Segmentation based on estimated 90:10 split for generics and brands
13	Perrigo	2,226	n/a	2,226	4,452	8	Segmentation based on estimated 50:50 split between branded and store-brand products
14	Lupin	2,066	n/a	47	2,113	1	Financial year ended 31 March 2023; INR: 0.0127 dollars
15	Zydus Lifesciences	1,905	n/a	284	2,189	14	Other = Consumer Wellness segment; Financial year ended 31 March 2023; INR: 0.0127 dollars
16	Krka	1,845	n/a	159	2,004	10	Other = Animal health products & Health resorts and tourist services; Euros: 1.173 US dollars
17	Aspen	1,732	627	n/a	2,359	2	Generics/Biosimilars/OTC/APIs comprises Regional Brands and Manufacturing segments; financial year ended 30 June 2022; South African rand: 0.0611 dollars
18	Glenmark	1,650	n/a	n/a	1,650	n/a	Financial year ended 31 March 2023; INR: 0.0127 dollars
19	Sawai	1,525	n/a	n/a	1,525	3	Financial year ended 31 March 2023; Yen: 0.00761 dollars
20	Gedeon Richter	1,496	435	461	2,392	16	Prescription Brands is Vraylar/Reagila (cariprazine); Euros: 1.173 US dollars
21	Alkem	1,473	n/a	n/a	1,473	9	Financial year ended 31 March 2023; INR: 0.0127 dollars
22	Towa	1,461	n/a	n/a	1,461	16	Financial year ended 31 March 2023; Yen: 0.00761 dollars
23	Amneal	1,432	374	406	2,212	6	Other = AvKare unit
24	Servier Generics	1,386	n/a	n/a	1,386	2	Financial year ended 30 September 2022; Euros: 1.173 US dollars

GB50 Ranking	Company	Generics/ APIs/OTC ($m)	Prescription Brands ($m)	Other ($m)	Total Turnover ($m)	Change %	Notes
25	Torrent Pharma	1,222	n/a	n/a	1,222	13	Financial year ended 31 March 2023; INR: 0.0127 dollars
26	Biocon	1,044	2	421	1,467	38	Financial year ended 31 March 2023; INR: 0.0127 dollars
27	Macleods	1,028	n/a	n/a	1,028	0	Financial year ended 31 March 2023; INR: 0.0127 dollars
28	Celltrion	1,008	n/a	760	1,768	21	Generics/Biosimilars/OTC/APIs figure is biosimilar segment, KRW: 0.000774 dollars
29	Ache	964	n/a	n/a	964	24	Brazilian real: 0.1936 dollars
30	Sopharma	896	n/a	n/a	896	4	Bulgarian lev: 0.5387 dollars
31	Endo	795	1,524	n/a	2,319	-23	
32	Jubilant Pharmova	732	n/a	66	798	2	Other = drug discovery services; Financial year ended 31 March 2023; INR: 0.0127 dollars
33	Ipca Labs	724	64	21	809	8	Financial year ended 31 March 2023; INR: 0.0127 dollars
34	Alembic Pharma	718	n/a	n/a	718	7	Financial year ended 31 March 2023; INR: 0.0127 dollars
35	Kalbe Farma	693	n/a	1,256	1,949	10	Indonesian rupiah; 0.00006735 dollars
36	Orion	654	713	206	1,573	29	Euros: 1.173 US dollars
37	Mallinckrodt	645	1,269	n/a	1,914	-13	
38	Adcock Ingram	532	n/a	n/a	532	12	Financial year ended 30 June 2022; South African rand: 0.0611 dollars
39	Genomma	488	n/a	352	840	9	Mexican peso: 0.0498 US dollars
40	Strides Pharma Science	480	n/a	n/a	480	18	Financial year ended 31 March 2023; INR: 0.0127 dollars
41	Amphastar	415	84	n/a	499	14	Branded segment is Primatene Mist
42	Wockhardt	410	n/a	n/a	410	17	Financial year ended 31 March 2023; INR: 0.0127 dollars
43	Beximco	371	n/a	n/a	371	18	Financial Year Ended June 30, 2022, BDT: 0.0107 dollars
44	Natco Pharma	352	n/a	5	357	38	Financial year ended 31 March 2023; INR: 0.0127 dollars
45	Henlius	347	50	80	477	91	Yuan: 0.1484 dollars
46	Lannett	341	n/a	n/a	341	-29	Financial year ended 30 June 2022
47	ANI Pharmaceuticals	252	39	25	316	46	Generics/Biosimilars/APIs/OTC = Generics & Rare Diseases segments
48	Nippon Chemiphar	240	n/a	n/a	240	-3	Financial year ended 31 March 2023; Yen: 0.00761 dollars
49	Mayne Pharma	224	7	63	294	6	Financial year ended 30 June 2022; AUD: 0.693 dollars
50	Coherus Biosciences	211	n/a	n/a	211	-35	

Source: Company Reports

The top 50 ranking compiles sales data for 2022 – or the closest reported year – for those firms for which generics and/or biosimilars is a major part of their business. For more information contact David.Wallace@citeline.com.

More Than Just Humira: US Biosimilars Enjoy An Eventful 2023

Adalimumab Competition Hits, Firms Settle On Stelara And New Biosimilars Approved

The launch of competition to Humira was the main event for US biosimilars in 2023 – but a number of other key developments also took place, including settlements on Stelara that set up a series of launches in 2025, as well as first approvals for natalizumab and tocilizumab biosimilars.

BY **DAVID WALLACE,**
EXECUTIVE EDITOR

In 2023, one story dominated the headlines for the US biosimilars sector: the debut of biosimilar competition to AbbVie's top-selling Humira (adalimumab) immunology brand.

A series of patent settlements between biosimilar sponsors and the originator had paved the way for multiple launches throughout the year, with competition eventually materializing in the form of an initial launch by Amgen of its Amjevita (adalimumab-atto) version at the end of January 2023, followed by a second wave of several Humira rivals that launched simultaneously at the start of July.

Amgen's initial launch was met with a reasonably muted response, with Amjevita bringing in $51m in its first two months on the market.

However, the effect on AbbVie's Humira sales was immediate, with the originator reporting first-quarter brand revenues in the US that were down by just over 26% – roughly in line with AbbVie's expectations – at just under $2.95bn.

Amgen had the biosimilar adalimumab market to itself for several months – but when the second wave of launches arrived in July, competition intensified considerably.

In the space of just a few days, launches were confirmed for Biocon's Hulio (adalimumab-fkjp); Boehringer Ingelheim's Cyltezo (adalimumab-adbm); Celltrion's Yuflyma (adalimumab-aaty); Coherus's Yusimry (adalimumab-aqvh); Fresenius Kabi's Idacio (adalimumab-aacf); Samsung Bioepis and Organon's Hadlima (adalimumab-bwwd); and Sandoz's Hyrimoz (adalimumab-adaz), with all of these biosimilars battling for a share of the market.

Differentiation efforts revolved around multiple factors, but one of the most important aspects was price. Amgen had launched its initial biosimilar with a dual pricing strategy – offering two versions at wholesale acquisition cost list prices that were set at 5% and 55% below the Humira list price respectively, albeit with the higher-priced version accompanied by a significant undisclosed rebate.

This approach, Amgen explained, was designed to "address the complexity of the US market," notably the preferences of pharmacy benefit managers. "PBMs have a business model that requires that they negotiate rebates with manufacturers," Amgen's management acknowledged, "and so they would prefer a high list price and negotiate rebates to net the price down and then pass those rebates through to their upstream employer clients."

Other biosimilar sponsors followed suit once they hit the market, with several adopting dual pricing strategies of their own. Meanwhile, others preferred to simply set a deep discount at the list price level, with Coherus announcing that it would be selling Yusimry at a massive 85% discount to Humira, as well as partnering with Mark Cuban's Cost Plus Drugs company to sell the biosimilar at an even steeper discount.

Eventually, it became apparent that many of the biosimilars in the market were going to have to compete at that kind of discount level to stay in the game. For example, Samsung Bioepis and Organon also offered their biosimilar at a 85% discount, while Sandoz and Biocon announced discounts of 81% and 85% respectively for their unbranded adalimumab products.

Price Not The Only Deciding Element

While price was a key factor, it was not the only element of differentiation between the various biosimilars on the market.

One aspect of interest was interchangeability, with Boehringer's Cyltezo the only biosimilar on the market in July with an interchangeability designation, which allows pharmacy-level substitution subject to US state law. Perhaps reflecting anticipation of gaining a key advantage from interchangeability, Boehringer offered a discount of just 5%-7% off Humira's price for its biosimilar.

Meanwhile, other suppliers hoped to gain an edge by offering a high-concentration 100mg/ml version of adalimumab – in line with the latest version of Humira – rather than the 50mg/ml lower concentration offered by many of the other biosimilars. Samsung Bioepis's Hadlima, Sandoz's Hyrimoz and Celltrion's Yuflyma were the only three biosimilars to have a 100mg/ml version approved at launch.

One biosimilar sponsor that had hoped to be able to offer both interchangeability and a high-concentration formulation was Alvotech, which had partnered with Teva for a planned US launch of its AVT02 adalimumab candidate as part of the July group. However, a series of US Food and Drug Administration complete response letters linked to its Reykjavik manufacturing facility prevented Alvotech from obtaining approval in time.

Nevertheless, Alvotech has pledged to compete in the market once the compliance issues are resolved, with management insisting that the story of Humira biosimilars in the US is "still being written."

Even for those firms that were able to enter the market, however, it was not necessarily a smooth ride. PBMs were selective about which biosimilars would be included on formularies – often only selecting two or three biosimilars for inclusion – and it appeared that Boehringer and Sandoz were frequently favored, with Sandoz recently claiming that it had "more lives covered than any other competitor" on adalimumab.

The market was reshaped further when Pfizer secured an interchangeability designation for its own biosimilar, Abrilada (adalimumab-afzb), making it only the second interchangeable adalimumab available, after Boehringer's Cyltezo.

As Pfizer revealed an October launch and a dual pricing strategy for Abrilada by the end of the year, Boehringer disclosed that it was bringing forward the launch of an unbranded version of Cyltezo from 2024 to 2023, with the product priced at a much steeper 81% discount than Cyltezo's initial 5%-7%.

In late 2023, AbbVie revealed the impact that biosimilars were having on its branded Humira revenues since the onslaught of multi-source competition began in July. The originator reported US Humira sales that dropped by almost two-fifths in the third quarter, again in line with previously stated expectations.

However, for many industry stakeholders, the anticipation is that 2024 will be when the true dynamics of the biosimilar adalimumab market begin to reveal themselves, as contracting cycles refresh and formularies prepare for the first full calendar year of competition to Humira.

Stelara Settlements Set Stage For 2025

Adalimumab was far from the only game in town for US biosimilars in 2023, however. Another major immunology brand – J&J's Stelara (ustekinumab) – was also the focus of plenty of attention.

While Stelara biosimilar launches had been expected to launch in the US as early as the end of 2023, a series of patent settlements with J&J struck by biosimilar sponsors this year has recalibrated expectations for the brand, giving four biosimilars confirmed launch dates in early 2025, assuming they receive FDA approval.

Amgen, which was first to settle with J&J, has gained a launch date of 1 January 2025 for its version. The firm is the first and so far the only sponsor to have garnered an approval for a Stelara rival, with the FDA authorizing its Wezlana (ustekinumab-auub) version as an interchangeable biosimilar at the end of October.

The Amgen settlement was followed by a J&J deal with Alvotech and US marketing partner Teva that offered a date no later than 25 February 2025 for their partnered AVT04 ustekinumab candidate.

Celltrion's settlement with J&J has given the Korean firm a 7 March 2025 launch date for its CT-P43 version. And partners Fresenius Kabi and Formycon can enter the market on 15 April 2025 with their FYB202 biosimilar.

It remains to be seen whether other biosimilar sponsors will settle with J&J and gain similar launch dates, but at this point Stelara feels like it could be the next Humira in terms of fierce biosimilar competition with multiple rivals launching at around the same time.

First Natalizumab And Tocilizumab Biosimilars Approved

The back half of 2023 also saw two other first-time registrations for biosimilar molecules in the US, with Biogen's Tysabri (natalizumab) and Roche's Actemra (tocilizumab) both seeing their first rivals approved by the FDA.

In August, Sandoz received approval for the Tyruko (natalizumab-sztn) biosimilar rival to Tysabri that it will commercialize in conjunction with development partner Polpharma Biologics.

Although litigation with originator Biogen is still ongoing, Sandoz has set out plans to launch the biosimilar in the first half of 2024.

Then in September, Biogen itself received approval from the FDA for the Tofidence (tocilizumab-bavi) version of Actemra that was developed by its partner Bio-Thera Solutions.

Big Pharma Shouts, Generics And Biosimilars Whisper: M&A In 2023

"A lot of companies are hurting because of the higher interest rates," one major CEO observed recently, summing up a year which saw little headline-grabbing news on the M&A front for generic and biosimilar sponsors.

BY **DEAN RUDGE,**
DEPUTY EDITOR

At the midway point of 2023, dealmaking for big pharma had roared back to life following relative austerity in the previous two years, as credit became harder to come by, interest rates spiked, and lenders tightened up in a challenging and volatile market.

Huge deals penned by COVID-rich Pfizer (Seagen: $43bn) and Merck & Co (Prometheus Biosciences: $10.8bn) showed that the world's biggest companies still had an appetite for dealmaking, and would put up the cash – dipping into their reserves, if not going directly to a lender – in order to placate investors spooked by patent cliffs.

"I know a lot of companies are hurting because of the higher interest rates," acknowledged Hikma's recently instated CEO, Riad Mishlawi, speaking in November 2023.

On the side of the aisle where Hikma mainly operates, perhaps for this very reason, headline-grabbing deals for generic and biosimilars have dipped in 2023, following a fairly fruitful 2022.

A colorful prior year included Biocon Biologics splashing out more than $3bn for longtime partner Viatris' biosimilars business; Fresenius Kabi's €495m purchase of an initial 55% stake in Insud Pharma's biopharma unit, mAbxience; and Hikma acquiring US sterile injectables specialist Custopharm for up to $425m.

Meanwhile, a landmark special purpose acquisition company (SPAC) merger delivered a much-desired public listing for Alvotech; and Novartis – looking to tighten its focus on innovative assets – announced that it was separating its Sandoz generics and biosimilars unit into a publicly traded, standalone company.

The partners have recently struck a settlement deal with Roche to end patent litigation over tocilizumab, with details of the launch date still unclear – although the originator indicated that it continued to expect competition to Actemra in the US "in 2024."

IRA Price Negotiation Casts Shadow Over Sector

Elsewhere in the US biosimilars sector, 2023 also saw rivals to Lucentis (ranibizumab) start to capture market share in a more meaningful way than in 2022, with both Samsung Bioepis and Biogen's Byooviz (ranibizumab-nuna) and Coherus' Cimerli (ranibizumab-eqrn) making gains as the year went on.

While the two biosimilars each held just a 4% market share as of Q1 2023, the second quarter saw Cimerli shoot up to 17% while Byooviz boasts 8% of the market.

This year has also seen relatively new players in the biosimilars space begin to make their mark, such as Amneal making inroads with its initial trio of Alymsys (bevacizumab-maly), Releuko (filgrastim-ayow) and Fylnetra (pegfilgrastim-pbbk).

Amneal has also struck a deal with mAbxience to gain US rights to two denosumab biosimilars referencing the Prolia and Xgeva brands that have annual US sales in excess of $4bn. Meanwhile, Meitheal recently announced a deal to bring in insulin aspart, insulin lispro, and insulin glargine candidates from Tonghua Dongbao Pharmaceutical.

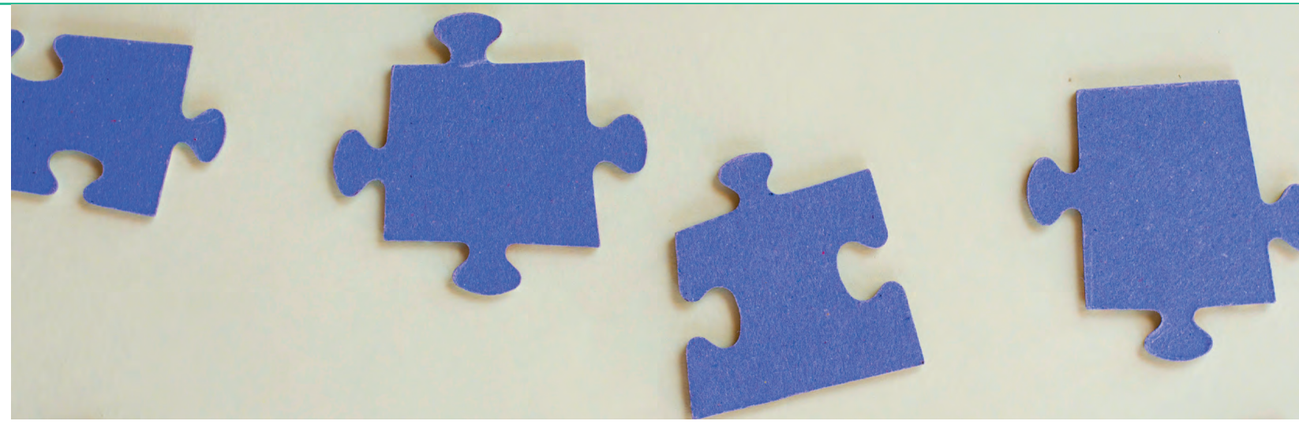
On the regulatory front, the FDA's approach to biosimilars continues to evolve, with the agency recently publishing guidance on labelling that suggests that the US interchangeability designation for biosimilars may become less prominent in future. The FDA has now recommended omitting details of interchangeability from biosimilar labels altogether, in favor of a statement of biosimilarity – although interchangeability information will still be contained within its online Purple Book database.

However, 2023 also brought a development that may cast something of a shadow over the future of the biosimilars sector, with both Stelara and Novo Nordisk's NovoLog (insulin aspart) being included in the initial Medicare price negotiation list under the Inflation Reduction Act.

The move surprised some observers – with many assuming that biosimilar competition on the near-term horizon may disqualify these products from price negotiation – and could lead to a chilling effect on biosimilar development, with the US off-patent industry having long been opposed to the IRA and its price negotiation mechanism.

Another potential barrier for biosimilars is the continuing distortions caused by PBMs, with opaque rebates and contracting practices often making it difficult for new biosimilars to get traction in the market.

The current state of the market was perhaps best summed up in 2023 by Craig Burton, executive director of industry body the Biosimilars Council: "In a word, complicated."



Viatris Offloads

In a similar vein to Novartis/Sandoz, Viatris' clearly-mapped-out desire to turn its attention to a select group of mostly novel assets provided for one of the year's most significant deals.

Viatris in October moved to offload four businesses that it has deemed unfit for the next phase of its strategic roadmap, including its six-facility-strong active pharmaceutical ingredients operations in India, in the process bringing in what it said was the company's original total target in value terms.

The for-sale API business is set to become a part of privately held Indian player IQuest Enterprises, encompassing three manufacturing sites and a R&D lab in Hyderabad, three manufacturing sites in Vizag, and third-party API sales.

IQuest is controlled by Nimmagadda Prasad, the Indian industrialist who previously founded Matrix Laboratories. In 2006/07, the former Mylan company closed deals for a majority stake in Matrix, swallowing up the remainder two years later.

In the wake of closing the Biocon-biosimilars-deal, Viatris also confirmed definitive agreements for its Women's Healthcare business and commercialization rights in certain non-core markets that were acquired as part of Mylan's merger with Upjohn.

Meanwhile, Viatris received an offer to divest substantially all of its OTC business, under which it will hang on to two of its powerhouse brands, Viagra (sildenafil) and Dymista (azelastine/fluticasone).

Including the previous biosimilars sale, Viatris believes it is in line to bag up to $6.94bn in gross proceeds.

Bolt-On Deals

In a year marked by a paucity of big deals, a small amount of companies have in some cases found the strategic rationale to throw their respective lots in together.

Meanwhile, other generic and biosimilar players – hamstrung by a challenging business environment – favoured bolt-on and tuck-in type deals, looking to augment already built-up areas or geographies of their businesses.

One of the largest players in the sector, Dr Reddy's Laboratories, did just this, acquiring the US prescription generics portfolio of Australia's Mayne Pharma in a deal worth at least $90m.

Generating sales of $111m in Mayne's 2021/21 financial year, the portfolio included approximately 45 commercial products, four pipeline products and 40 approved non-marketed products, most notably a hormonal vaginal ring and a birth control pill, as well as a cardiovascular product.

Meanwhile, Hikma acquired a selection of assets from bankrupt Akorn in July for as similar purchase price, $98m, including manufacturing equipment and portfolio and pipeline products that will support the company's businesses in the US.

One major story to keep an eye on is the fate of German giant Stada.

The Future For Stada

As 2023 ticks over into 2024, one major deal to keep eyes on is the fate of German generics and biosimilars giant Stada.

Earlier this year, the company's owners, Bain Capital and Cinven, were revealed to be mulling the possibility of selling Stada, the company's CEO Peter Goldschmidt said.

Acknowledgment of a potentially major deal came almost exactly six years to the day since the private equity duo took control of the Germany-based, European generics and biosimilars giant.

Goldschmidt's comments, made to the German Press Agency, followed reports in *Bloomberg* that Bain and Cinven were considering a potential sale valuing Stada at around €10bn. Reports included the potential to conduct an initial public offering for the German firm.

Goldschmidt, who recently celebrated five years in his current role, said he did not expect a decision to be made before 2024 and insisted that Stada's "financial investors have no pressure to sell."

However, he added, "What speaks in favour of a sale process is that it is common for financial investors to exit after five to six years," he reasoned.

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The New Challenge For The Architect Of Wegovy

Mads Krogsgaard Thomsen, CEO of the Novo Nordisk Foundation and the man who supervised the development of semaglutide, describes the unprecedented growth of the obesity market and what might come next for Novo.

BY **KEVIN GROGAN,** MANAGING EDITOR

Few people are better placed to comment on the phenomenon that is Novo Nordisk A/S's stunning growth in the past couple years with Ozempic and Wegovy than Mads Krogsgaard Thomsen, the man who supervised the development of the diabetes and obesity blockbusters and is now the CEO of the foundation that controls the Danish drugmaker.

Thomsen, who served over 20 years as chief scientific officer at the Copenhagen-based group, was appointed as CEO of the Novo Nordisk Foundation in March 2021. Speaking at a recent international press event held at the foundation's headquarters in the Danish capital, he said that in particular "nobody would have expected" such a successful launch for the obesity drug Wegovy (semaglutide injection 2.4mg), noting that a change to traditional marketing model had not been necessary because the GLP-1 agonist "is just being pulled off the shelf."

He added that the company could be forgiven for not predicting such an impact as Wegovy was the first entrant into "a market that didn't exist," given that previously the only clinical option for obese patients was bariatric surgery. "It's been a big surprise that certain people are talking about a $100bn market and it has happened almost overnight," he added.

"It's been a big surprise that certain people are talking about a $100bn market and it has happened almost overnight."

Mads Krogsgaard Thomsen, Novo Nordisk

Whether that $100bn forecast proves to be fanciful remains to be seen but what is certain is that the fortunes of the Novo Nordisk Foundation are going to be transformed by the spectacular commercial success of the weight loss blockbuster, notwithstanding the manufacturing issues Novo Nordisk is addressing for the drug.

Thomsen noted that the windfall coming from Ozempic and Wegovy has given Novo Nordisk "much more ability to do more transformative things" in the M&A area, noting the recent EU approval of Rivfloza (nedosiran), the lead product from its late 2021 acquisition of Dicerna Pharmaceuticals, for primary hyperoxaluria. He said that by using its considerable funds on innovative deals, the company "has many more horses to bet on." In the last couple of months, Novo Nordisk has been expanding its presence in the obesity field with the acquisitions of Inversago Pharma and Embark Biotech.

These types of deals will help Novo Nordisk prepare for a time when semaglutide will not be such a cash cow, Thomsen noted, giving the example of AbbVie's ability to replenish its pipeline while skilfully managing the life cycle of the $20bn mega-blockbuster Humira (adalimumab). He is also excited about the prospects of label expansions for semaglutide, highlighting the recent full set of stellar data from the SELECT cardiovascular outcomes trial (a study he helped initiate in 2018) and has particularly high hopes for the drug's potential in obese patients with heart failure with preserved ejection fraction.

He pointed out that Novo Nordisk and fellow metabolic disease giant Eli Lilly and Co., which has just received US approval for its GIP/GLP-1 drug Zepbound (tirzepatide), "are investing as if there were no tomorrow" to meet demand for their products. His old employer is spending more than DKK42bn ($6bn) to expand its existing manufacturing facilities in Kalundborg, Denmark, and Thomsen said that being able to produce high yields at lower cost will mean that access will be improved in the major markets and elsewhere; once the next generation of obesity drugs have been developed, the capacity will then be in place for Novo Nordisk to offer its older GLP-1 analogues to the world's poorest countries "at dirt cheap prices."

"There is actually indirectly an affordability benefit for low-income countries in us pursuing innovation."

Mads Krogsgaard Thomsen, Novo Nordisk

Novo's Philanthropic Mission

The company will not have any significant earnings from those poorer countries "and it can make profits from the new generation of products in Europe, the US and countries that can afford it. This shows that there is actually indirectly an affordability benefit for low-income countries in us pursuing innovation," Thomsen said.

While Novo Nordisk has tried to demonstrate that societal responsibility and profit can go together, the foundation that Thomsen now heads also has a three-pronged philanthropic mission. He has been instrumental in setting the direction for how the foundation wishes to contribute to society towards 2030 and has helped identify the three areas for its grant-awarding activities, namely sustainability, the life sciences ecosystem and health with, unsurprisingly, a focus on the prevention and treatment of cardiometabolic and infectious diseases.

Denmark is a focal point for most of the foundation's grants but one partnership that Thomsen is especially enthusiastic about is the Novo Nordisk Foundation Center for Genomic Mechanisms of Disease, an initiative with the Broad Institute in Cambridge, MA, and supported by a grant of up to $47.5m. A key activity of the center is to facilitate close collaborations between the Broad and researchers at Danish universities, with an initial focus on understanding type 2 diabetes and obesity and mapping human gene regulation.

Thomsen said that at the foundation's Center for Basic Metabolic Research at the University of Copenhagen, "we have really got to grips with a lot of things for more than a decade but we didn't quite understand how it all relates to the genes in our body." Citing Broad's pioneering role in the Human Genome Project, he said that "the idea was to team up with the best in the world and get the best out of them. They had the same feeling about us, that we were strong on the biochemistry front and what was happening inside cells, so it is a happy marriage."

He quipped that when he asked minister of finance Nicolai Wammen "what was his feeling about us taking DKK300m out of Denmark and giving it to Boston, he just smiled and said, 'That's absolutely fine because it will also strengthen the Danish ecosystem'."

Taking A Wider View

In addition to cardiometabolic diseases, the foundation is also focusing on epidemic preparedness and the board is expected to sign off shortly on the €200m Initiative for Vaccines and Immunity which hopes to generate knowledge on a variety of technologies and translate it into vaccines that provide broad immunity against respiratory pathogens. Its mission also involves fighting inequality in health care and Thomsen noted that the Wegovy windfall means more funds for the food programs the foundation runs in Rwanda and Uganda among other places, "providing healthy school meals and supporting the local farmers that produce them, creating a whole ecosystem."

Although there are certain elements about his time as Novo Nordisk R&D chief that he misses (Thomsen got wistful talking about the excitement of being among the first people to hear positive results from major pivotal trials), the broader goals of the foundation and moving beyond human into planetary health holds great appeal for the 62-year-old Dane. He is equally enthusiastic talking about the foundation's efforts to fight the impact of climate change and its quantum computing programs in collaboration with the Niels Bohr Institute as he is outlining initiatives to promote healthy weight in teenagers.

Thomsen is also enjoying his blooming friendship with Bill Gates. "The first thing he said when he met me was 'All I know about your foundation is that your company makes Wegovy' and I had to educate him a bit that we are much more than Wegovy," he recalled, and now there are a number of projects up and running with the Bill & Melinda Gates Foundation.

The foundations recently joined forces to set up a two-year $29m R&D project aimed at creating a sustainable source of protein for human food derived from CO2. The Gates Foundation has also awarded a grant to launch an initiative focused on women's health care to the Danish foundation's BioInnovation Institute and the two are also working together with Open Philanthropy on the Pandemic Antiviral Drug Discovery initiative.

"We meet quite a lot and there are so many smart people in his foundation. With the sheer amount of brains he's been able to put together, as we also have done in our foundation, it produces a lot of creativity when you're sitting for two or three days together, breaking out into workshop sessions and discussing what could be done," Thomsen concluded.

Industry CEOs Talk Drug Pricing, Value And The IRA

Value-based pricing for drugs remains largely a pipe dream in the US, industry leaders say, even as drug pricing pressure mounts.

BY **JESSICA MERRILL,** SENIOR EDITOR

With US drug pricing under pressure from a new Medicare drug price negotiation program being implemented within the Inflation Reduction Act (IRA), some of industry's top leaders said they were doubtful the US would ever move toward true value-based pricing.

Pfizer CEO Albert Bourla, Eli Lilly and Co. CEO David Ricks and Seagen CEO David Epstein discussed some of the pressing issues facing the pharmaceutical industry, including US drug pricing pressure and potential consequences from the IRA legislation, during the Galien Forum in New York City in late-October 2023.

Pfizer's Bourla was particularly pessimistic about the future of value-based drug pricing in the US. The best opportunity, he said, remained in working with integrated health care systems like hospitals, where the costs of drugs are offset by savings in other parts of the system that can be easily quantified. When it came to working with the three largest payers in the US and their pharmacy benefit managers, however, interest in value-based pricing was underwhelming, he said.

"The problem is the PBMs are so lucrative," Bourla said. "What they want is not value … It is very high list prices and very big discounts."

"They don't care how high is the list price. It might be twice the value that you bring," he added.

The issue, in which drug companies pay high rebates to payers to secure formulary placement for drugs, resulting in a wide list-to-net price differential, is one drug manufacturers have been trying to shine a brighter spotlight on for several years. Lobbying efforts have not made much headway in Congress, however, though some PBM reform is currently under review.

Pfizer has many value-based pricing agreements with payers, Bourla confirmed, but they still only account for roughly 2% to 3% of fluctuations in overall costs for payers. The cost of measuring an outcome and calculating potential savings was higher than what was at stake in savings, he said.

"That's why we have problems in the US. It's not because we don't have the right way to measure it. It's not because there's no competition," he explained. "It is that the system doesn't care about cheaper. [It] cares about the higher price and the higher discount."

Epstein, the CEO of Seagen, a company that Pfizer is acquiring for $43bn, agreed with Bourla's sentiment on value-based pricing.

"Every time I go to a panel, they ask us about value," he said. "I feel like I'm playing off someone's script where they just made up something because we don't really have value discussions and you can't, in this system, have value discussions."

He urged drug makers to put their effort into making better medicines, where the value of the medicines is clear.

"And eventually, whether because of patent law or the IRA, those drugs, which often cost hundreds of millions of dollars, if not billions of dollars to develop, will be readily available as cheap generics," Epstein said.

Lilly's Ricks advocated for improved value-based pricing metrics that are more aligned with drug companies. Some of the existing value-based pricing models that are established in single-payer countries in Europe, for example, exclude important measures of value, he said.

"The ones we have now are built to do one thing, which is push the value down, not properly assess it," Ricks said. In Europe, value-based pricing models tend to measure the direct costs that are being offset in health care, but not indirect costs that impact society.

"That's actually the bigger cost. It is lost work days and caregiver time and so many other societal drags of people who aren't fully well and functioning at their best," he said.

Ricks argued that price discussions and negotiations came at a time when the least was known about a new product, after it had completed Phase III testing. "Usually later, we learn a lot more things that … [are] more valuable in the end than when you started, so you're underpricing from the beginning," he explained.

ALBERT BOURLA, CEO, PFIZER

DAVID RICKS, CEO, ELI LILLY

DAVID EPSTEIN, CEO, SEAGEN

IRA Brings New Worries To The C-Suite

The three CEOs also used the Galien stage as an opportunity to underscore some of the potential serious and unintended consequences of new US drug pricing policy stemming from the IRA that will pave the way for the Centers for Medicare & Medicaid Services (CMS) to negotiate drug prices for certain big selling drugs beginning in 2026.

Much of the focus was on one of industry's standard talking points since the legislation was first passed in 2022: the shorter nine-year life cycle granted to small molecule drugs before facing negotiation versus the 13-year life cycles granted to biologics.

Ricks speculated the result of the negotiation policies will mean there will be less investment in small molecules, less investment in medium-sized indications and less investment in drugs for older patients.

"The way the law works is they negotiate top sellers. What you don't want to do is be caught being negotiated but never really get a return on your capital, so I think we'll try to guess niche markets which may still go forward versus big markets," he said. "Big markets and small molecules will still go forward, but perhaps in a different way … But I think a number of diseases which end up being sort of medium size will be under served."

Lilly, Ricks said, has already changed more than half a dozen research programs to adapt to the law. In some cases that could mean accelerating new indications to run programs in parallel as the time clock for a drug starts when it first reaches the market.

"I think that's probably good for big companies because we have the capital to do it. It's bad for small companies, but maybe also bad for the industry because inherently those programs will have more risk because you're doing things in parallel," he said.

Another consequence of the shortened window of time could be that drug makers choose to launch a drug outside the US first before launching in the US – something that does not often happen today. A company may choose to hold off on a US launch to debut with multiple indications at once.

"I've heard a couple of CEOs talking about this, which could happen, is that if you can't parallel process and you're convinced you have to go serially, we may now enter an age where the US doesn't launch first," Ricks said. "That may shift, where smaller indications launch in Europe first, where we don't have this clock-starting effect, and then later in the US."

Esptein said a company the size of Seagen would face serious challenges running clinical trials in parallel. "As a small or medium company, how would it be possible that we could do three or four Phase III pivotal trials in parallel? Where is that capital going to come from? And, if we get it wrong, the company is gone," he said.

R&D Decisions Already Being Impacted

Epstein also highlighted a provision for orphan drugs that exempts them from negotiations as long as they are only approved for only one indication. The exemption would be removed if a second indication is approved, which is something that is common with drugs for rare diseases. That is the case with Seagen's Adcetris, for example, which is approved for seven orphan indications.

"There will never be a drug like that again," Epstein said, unless lobbying efforts underway to change the language in the bill are successful. "It will be one indication. You will stop, and then if you thought the other indications had some value, you might bring another molecule with all the inherent costs and risk associated with it," he added.

Another implication that has been discussed frequently by industry is less investment late in a drug's life cycle, where a company's investment might not be recouped. Epstein said the issue is already coming up with Seagen's own antibody drug conjugate Padcev (enfortumab vedotin), which was a breakout star at the European Society for Medical Oncology meeting on the strength of positive Phase III data, including in combination with Merck & Co.'s Keytruda in first-line urothelial carcinoma.

Seagen and its partner Astellas Pharma are also studying Padcev in earlier-stage muscle invasive disease, where an indication could be approved in 2025 or 2026. But another program in non-muscle invasive disease, which had also shown promise, was under review, he said.

Pfizer's Bourla said the negotiation program was more about politics than drug pricing. "When they voted for this bill, they didn't want to do any of these things, but they were so furious to vote something that would be against pharma because they're thinking this is their main political win."

LEADERSHIP

Cell And Gene Therapies Are Altering Patient Expectations, Says CGT Catapult CEO

BY **CHLOE KENT,**
SENIOR REPORTER

Patients Will Expect Their Condition To Be Taken Away, Rather Than Treated

The Cell and Gene Therapy Catapult was established in 2012 and exists to advance the growth of the UK's CGT industry, supporting companies in this space throughout product development and beyond. *In Vivo* caught up with CEO Matthew Durdy, who took over the role from Keith Thompson in 2020, to learn what the first three years of his tenure have taught him and how he sees the future of advanced therapies progressing.

Matthew Durdy, CEO of the Cell and Gene Therapy Catapult, told *In Vivo* "two obvious things" have changed in the advanced therapies space since he took over the role in spring 2020.

"I walked straight in to the COVID-19 crisis," he said, "so the first year was all about maintaining an organization through COVID-19. The pandemic was both disruptive and positive. It injected a huge amount of capital into the system, but some of the investment environment has been difficult. In addition to COVID-19, you've got the political uncertainties which have knocked things around, alongside the changes in interest rates and investment profiles. During the pandemic we participated in the Vaccine Task Force efforts, preparing manufacturing capability should it be needed. In the end, it wasn't called on."

He continued: "The second thing is that the underlying science of the industry has continued to progress rapidly, as has the excitement. The first few years [in the gene therapy space] were marked by establishing proof of concept. If you go back 10 years, we didn't know if it was ever going to work, how you'd be able to manufacture it; we didn't know if regulators would ever let us put it into people and we didn't know if anyone was ever going to buy it. Now we're past all that and we've got established gene therapies that are in regular use."

Durdy was part of the UK Catapult's 2012 founding team, working as chief business officer until he became CEO in 2020, taking over from founding CEO Keith Thompson. "At the time that Keith retired, we were 250 people," he said. "We are now just over 400 people and have three new sites. We've had a massive expansion to try and keep up with the demands of the industry. As the industry grows, people expect more from us and we have to try and serve that."

Over the past five years, and intensifying over the past three years, investment in gene therapy has expanded into "all sorts of different areas," said Durdy. The field has moved from focusing on areas of very high unmet medical need – early gene therapy approvals included medications such as UniQure's Glybera (alipogene tiparvovec), designed to reverse lipoprotein lipase deficiency – to more prevalent chronic conditions, such as hemophilia, sickle cell disease and even dementia.

While gene therapies for rarer diseases with high unmet medical need typically come with a very high price to make them economically viable, gene therapies for higher-prevalence diseases with lower unmet medical needs are "facing a lower willingness to pay from an economic perspective," Durdy said.

"That means we're entering into what I would describe as a classic technology cycle of a new class of therapeutics," he explained. "Going forward, we need a flow of good new therapeutics coming down through the scientific process. We need the cost of goods to come down dramatically. We need the industry to have the capacity to deliver in the kinds of volumes that patients are demanding, and we need to make sure that the health care system has the capacity to deliver it all."

Durdy maintained that the successful delivery of cell and gene therapies would be of substantial benefit not just to the patients receiving the treatment, but to health care systems at large.

"If you take somebody that has just been diagnosed with hemophilia, they hopefully have at least another 60 or 70 years of life left with conventional treatments today," said Durdy. "Those conventional treatments might cost £100,000 ($121,470) to £150,000 per patient per year, which over a lifetime adds up to several million. They also require a health care infrastructure to deliver regular checkups and regular administration of therapeutics to the patient, going in and out of hospital with a relatively okay quality of life, but not as good as it would be if the disease was taken away."

A therapy which could overwrite the faulty genetic mutation that led to hemophilia – effectively 'curing' the disease – would allow health care systems to redeploy resources used to treat patients with the disease. This same logic applies to numerous other conditions caused by genetic abnormalities that require lifelong, intensive treatment.

"There's a massive opportunity for a restructuring of the way we think about health care," Durdy said. "In 20- or 30-years' time, people will be expecting their condition to be taken away altogether as opposed to treating it. It's a different mindset. The concept of modifying the disease as opposed to treating the symptoms will become an expectation in the future as our industry matures."

Strategic Priorities

The Catapult is focused on six strategic priorities. First, it aims to help emerging technologies acquire the financing and support they need to grow and thrive. Once these emerging technologies acquire funding, the Catapult can then support their clinical development and validation. It also aims to support manufacturers, making sure they have the capabilities to produce at scale.

The organization also works to ensure that the supply chain is in place to serve the growing manufacturing capacity of the industry. Mapping onto these endpoints, it also seeks to make sure that the UK's health care system is prepared for gene therapy, working on convergence and standardization of processes so that when new therapies enter the hospital system clinicians are prepared to deploy them.

"The last of these six is all driven by people," Durdy said. "There's a skill shortage, so we have a program of developing skills as and when they're needed." This involves identifying areas where up-skilling will be needed, such as understanding new regulatory or quality control techniques, as well as democratizing the opportunities in the space and bringing in apprentices.

The Catapult launched the world's largest and first apprenticeship scheme leading young people into the CGT space, Durdy said. The Advanced Therapy Medicinal Products program provides young people in the UK with an alternative to university which will direct them toward a career in the sector, helping to address the UK's demand for specialized, skilled industry personnel.

"The use of machine learning and artificial intelligence, the use of databasing, is a big opportunity and blocker for developers in the industry, and we need to get up to speed on it."

Matthew Durdy, Gene Therapy Catapult

In collaboration with immersive technology company FourPlus, the Catapult has also been working on developing a mixed reality training platform for the pharmaceutical and health care industries, which will provide training for a wide range of manufacturing roles within the CGT, biopharmaceutical and life science sectors. Once developed, the platform will be tested with apprentices from the Catapult's Advanced Therapies Apprenticeship Community, with a first release anticipated for demonstration by the end of the year.

"If we can train people outside of the laboratory space, then we can train more people at a time," said Durdy. "There's also the ability to, in the future, reach out into further places. As long as somebody can access the headset equipment you can train people anywhere, so we can reach into communities we haven't previously had access to."

Unifying Industry Standards

Convergence in industry standards, particularly across manufacturing, will be a fundamental driver of scale and costs across the gene therapy space, Durdy believes.

"An analogy that I often use is the mobile phone industry," he said. "Around 30 years ago, mobile phones were an extraordinarily expensive, niche tool for people who had very

high cash flow and got very high benefit from them. When the Global Standards Memorandum was signed it took the floor out of the cost of mobile phones; it dropped something like 90%. I think there is an analogous event that is likely to take place in the cell and gene therapy space, where companies realize the basis of their competition is clinical efficacy, not in their manufacturing capability, and can then start to assess where they can collectively reduce manufacturing cost."

Another area the Catapult has identified where the industry would benefit from a standardized platform is adeno-associated virus vector manufacturing. Durdy said the organization has been "working very intensively" to create a platform that can be used by all drug developers for numerous different therapeutics.

The Catapult has also identified data synchronization as being potentially beneficial. Durdy said that simply handling basic CGT data would require much more efficient systems than are available today. "The use of machine learning and artificial intelligence, the use of databasing, is a big opportunity and blocker for developers in the industry, and we need to get up to speed on it," he emphasized. "We need to do it in a coordinated fashion together to develop those platforms."

Automation of manufacturing processes is another critical area. Making as many aspects of the manufacturing process non-human as possible is a priority, from robotic arms to well-designed bioreactors. "Taking the human out and enabling more to happen in a smaller space is going to be a big driver of our ability to deliver these therapeutics in the future at a sensible cost," Durdy said.

Commercialization Strategy

A final factor Durdy raised that will be crucial for cell and gene therapy developers aiming for future success is a robust commercialization strategy.

"If you are developing a new science that you think has huge potential for patients, you need to also develop your commercialization strategy to understand how that product will be used in the clinical environment, to understand how you can bring down the cost of goods to a level that it can fit within the willingness to pay of the health care system," he explained. "You need to prepare all that information from the very beginning."

Whether a CGT product is single-dose or repeated-dose, for instance, will have a significant implication for the commercialization prospects of the therapeutic.

To gain the confidence of the investment community, scientific innovators must be able to demonstrate a commercial strategy. Investors need to be assured about the potential of a technology and that it has the capacity to get all the way to market, from a logistical view.

"As an industry," Durdy said, "we need to do a better job of helping wider society understand the massive, massive potential of cell and gene therapies to improve patient outcomes, bring patients and their caretakers back into economic activity and reduce the cost of health care. Gaining the attention and support of the public and of politicians will drive further change and acceleration within the industry."

"The use of machine learning and artificial intelligence, the use of databasing, is a big opportunity and blocker for developers in the industry, and we need to get up to speed on it."

Matthew Durdy, Gene Therapy Catapult

Manufacturing Devices In The Rollercoaster UK Market

BY **ASHLEY YEO,** EXECUTIVE EDITOR

A scale-up strategy is the missing link in the UK devices industry, claims business research organization CPI. Pennine Healthcare and Renfrew Group give their take on the environment for manufacturers and the opportunities for strengthening the industry base.

A new report issued in fall 2023 by research organization CPI is the latest initiative to highlight the need for better long-term support for medtech industry manufacturing. It proposes a strategy for scale-up.

Its focus is the UK, and its recommendations are designed to galvanize the national system into supportive decision-making. But the principles can be applied to the established medical devices industry, which is dominated by small- and medium-sized enterprises (SMEs), in any geography.

The report, *Challenges and Opportunities for UK HealthTech Manufacturing Scale-Up*, is a follow up to an Innovate UK-commissioned survey, published in winter 2022-23 under the Health Technology Regulatory and Innovation Programme.

Medtech regulation was a major theme of that first report, which, like the follow up, had input from the Association of British HealthTech Industries (ABHI). It engaged with 350 stakeholders, representing around 8% of the 4,353 UK medtech businesses. It found that SMEs need a simple regulatory roadmap.

The later report focused on the challenges of scale-up, and sampled the experiences of around 100 manufacturers and other stakeholders over a two-month period.

The devices manufacturing ecosystem, including CMMOs and CMOs, has welcomed the report while observing that its focus could be widened.

Pennine Healthcare is a Derby, UK-based own brand and major commercial contract medical manufacturer and packaging company that exports to some 50 countries. It is a market authorization holder for a range of devices.

The company's CEO is Graeme Cameron, formerly a director at B Braun Medical Ltd. He said: "The report identifies the challenges we talk about all the time. There's a workforce and skills gap for all manufacturers, and we see resilience as a significant issue."

In addition, costs have risen to stressful levels. "Within health care we have seen a 40%+ inflationary rise at product input level in the past 24 months, including compounds, cardboard boxes and packaging," Cameron continued.

"We must add to that the rise in energy costs, the cost to ensure environmental sustainability and the plastic tax cost," he said. Companies will also assume a further rise in costs when the UK living wage is increased in 2024. These cost increases are hard to pass on in a taxpayer-funded health system. "There have been some ups and downs in the UK – it's been a real rollercoaster market," Cameron said.

CPI's report on the UK manufacturing ecosystem represents an effort to understand, document and highlight the key barriers faced by medical device SMEs in particular, which account for 85% of the industry base.

The study, overseen by CPI director of market strategy Alex Cole, is a sober analysis of the potential for and weaknesses surrounding medtech manufacturing scale-up in the UK.

The research pointed to a missing connection between initial device concept and manufacturing, which, the report said, was stifling innovators from successfully upscaling novel healthtech ideas into high-value businesses and applications.

It further highlighted poor regulatory knowledge among SMEs, low access to proof-of-concept or translational funding, a lack of mid-volume manufacturing capabilities, a risk-aversiveness and/or short termism in the private sector towards innovation, low awareness of national innovation system support and a lack of incentives within academia to commercialize research.

Mike Phillips, design development director at innovation and design consultancy and CDMO Renfrew Group International, agreed that many of the report's findings were true, and hoped that useful conclusions would be drawn. But a big question for him is: How funding can be directed towards the private sector to enable it to improve what is needed?

"The industry loses a lot in translation before we get to higher-volume production and commercial products," he said. "Britain has great strengths at the innovation end, but more support for the private sector is needed – and perhaps a better tax regime to help it compete with overseas competitors."

Phillips suggested more funding should be put towards the discovery of market opportunities and meeting unmet needs at the "problem end." He observed that the AHSNs, now 10 years old, were conceived to fund and prompt innovation, but their focus tends to major on adoption. Meanwhile, the UK's Catapult Centers do not have much crossover with industrial strategy.

A Long-Term HealthTech Strategy

The main recommendation of the report is that the UK government develops a future "long-term healthtech strategy" which includes reference to manufacturing scale-up. The issue was debated at the 2023 annual conference of the ABHI, where it was suggested that a future strategy could for example be an augmentation of the current Life Sciences Vision or the Medical Technology Strategy, being developed by Medtech Directorate.

Respondents to the CPI survey initiative observed that the ecosystem of manufacturers in the UK is fragmented and disjointed. Technology developers (TDs) find it difficult to identify suitable companies to engage with, and often tend to look internationally. Support for companies navigating the ecosystem does exist, but this too is criticized for being too fragmented and/or regionalized.

"The UK manufacturing scale-up ecosystem together with support structures needs to be mobilized and linked through unifying interventions, to enable TDs to find the stakeholders they need to progress efficiently and at pace," the report stated.

It further said:

- TDs need strong and specific support with funding and investment as they move closer to market;
- Grant and finance options, such as VC and PE, do not support TDs throughout the whole product development lifecycle;
- The ecosystem must maximize public: private financing partnerships to reduce risk. The industry faces unusual cashflow constraints and time-delays in the scale-up phase pre-market due to regulatory requirements;
- Skill shortages in engineering, software and other technical aspects are impacting manufacturing scale-up. Industry and training providers should engage to help develop the required skills and courses; and
- Upskilling in scale-up manufacturing requirements is needed.

CPI's research also identified significant infrastructure capability and capacity gaps, particularly for clean rooms, wet and dry lab space, and high-quality industrial units. Existing facilities are commonly oversubscribed and not always available under the terms required (e.g., short term lets) for scale-up use, it said.

However, Pennine's Cameron observed – in view of "resilience" having become such a significant issue post-COVID – that a number of manufacturers have cleanroom space that could be better utilized. "We are building more opportunities within that space," he said, adding that the government could do more to support UK manufacturing in ways that are needed.

Pennine, an employee-owned trust, has its own cleanrooms on a 150,000sq foot manufacturing site in Derby. The company, marking 60 years as a medical device company in 2023, distributes to some 50 countries.

Cameron sees as vital more central funding support for the UK manufacturing sector to investment in machinery. He said: "For us, there is very clear business case to invest in automation that would allow us to compete better with the Far East." But finding channels to get the support and investment needed was a challenge, he admitted.

Nevertheless, Pennine has strong roots in the UK and remains supportive of the National Health Service and its needs, even if that position comes with an economic cost. "The company will often support NHS needs even to the detriment of ourselves, and we find we can't simply cancel NHS orders or pull products if they're not economically viable as patients' lives would be placed a risk."

Complying with the stricter regulatory requirements of the EU Medical Device Regulation is a different matter. Here, Pennine spent half a million pounds to move its entire portfolio from the former EU directive to the new more stringent regulation in a timely manner. But the steep rise in the cost of compliance meant it had to drop six product portfolios. Many other organizations have had to do likewise, Cameron noted.

He believes tax credits would be a good option in an ecosystem that could feed off such opportunities. Mechanisms like grants to enable investment in the equipment and automation would help to overcome some of the current workforce challenges.

In the global market, UK manufacturers are coming up against competitors whose cost and tax bases are often much lower in their own geographies.

Renfrew's Phillips voices a similar position about the need for more support for UK device innovators. One section of the CPI report notes that SMEs want more support for scale-up and manufacturing for their UK operations. There are few options to do this, but support for reshoring/onshoring would be one avenue of approach.

Syngene Eyes Sweet Spot As New Modalities Hog Limelight

BY **ANJU GHANGURDE,** EXECUTIVE EDITOR

Syngene's CEO discusses its work in ADC development and trends in the CRDMO space as US biotechs navigate a funding squeeze and manufacturing opportunities loom in areas like GLP- 1 receptor agonists.

"Think of us as a technology platform company, with capabilities that cover the full range of what the market and our clients want to access. You don't bet everything on just one technology," said Jonathan Hunt, managing director and CEO of Syngene International Ltd.

In a wide-ranging interview with *In Vivo*, Hunt outlined how the Indian contract research, development and manufacturing organization's scientists and labs were advancing capabilities in modalities like chimeric antigen receptor T-Cells (CAR-Ts), messenger RNA (mRNA) and antibody-drug conjugates (ADCs) at the discovery services end.

"In the ADCs space, we're sort of further through, both in discovery and into development. We have each of the components – if you disaggregate ADCs, we can do the antibody discovery, development and manufacturing," the former AstraZeneca executive said.

Syngene has enabled next-generation ADCs for clients by effecting modifications to classical ADCs including designing dual binding sites on the antibody to enhance the precision of targeting the cancer cells and improving the delivery of cytotoxic drugs to cells via internalization. The addition of non-cytotoxic immunologic payloads, designed to stimulate the innate immune system, then allows the immune cells to kill cancer cells.

"The small molecule discovery, development and manufacturing capabilities are there for the payload and we have development conjugation capabilities. You put the three together, you have an ability to add value in all three elements of the discovery, development and ultimately manufacture of an ADC," Hunt explained.

While the first antibody-drug conjugate, Mylotarg (gemtuzumab ozogamicin), arrived on the market over two decades ago and there were some setbacks along the road, the class has seen a resurgence in development with recent headline-grabbing large deals including the $22bn Merck-Daiichi Sankyo alliance, which is estimated to entail the largest ever biopharma licensing upfront fee.

Proteolysis targeting antibodies chimeras (PROTACs) is another area that Syngene has "invested a lot of time" potentially emerging with one of the largest discovery groups in the industry, with over 400 scientists engaged in the area. The CRDMO provides end-to-end expertise in PROTACs from target identification to clinical and commercial manufacturing and had earlier partnered a clinical stage biotech to develop a PROTAC molecule for cancer.

More recently, Syngene gained access to ERS Genomics' foundational CRISPR/Cas9 patent portfolio via a licensing deal, opening up a new era of gene editing capabilities for its global partners.

Finding That Sweet Spot

The advancement of new modalities is creating a multitude of opportunities for small and large biopharma firms to develop new treatments – CRDMOs that have been able to match and evolve their suite of offerings alongside also have much to gain.

Earlier this year Boston Consulting Group noted that after decades of development, new modalities are reaching an inflection point - in 2021 alone, around 100,000 journal articles were published on these new therapies.

"Some 4,000 clinical trials of new modalities (92% at the early stage) are underway. And approximately 1,500 new companies have been formed in the past 20 years to develop new treatment modalities and technologies, of which approximately 150 went public," executives from the consulting group said in an article.

Hunt, however, underscored that it was pivotal for the company from a "capability development, balance sheet and investment point of view" to work closely with partners and "really see where the market's going."

"You don't want to be too far in front of your clients on the leading edge. You don't want to be a laggard – can you get into that sweet spot? I think we're managing to do that on the monoclonal antibody side and we're looking quite closely at the CAR-T, mRNA, ADCs space."

In 2022, Syngene sealed a 10-year manufacturing agreement with animal health company Zoetis, under which the CRDMO is to manufacture the drug substance for Librela (bedinvetmab), a first-in-class monoclonal antibody used for treating osteoarthritis in dogs. The duo has a long-running alliance initiated way back in 2011, under which the Indian firm had undertaken work on several animal health mAbs, including developing and manufacturing clinical supplies of a treatment for allergic or atopic dermatitis, now widely used, and Librela.

> **"You don't want to be too far in front of your clients on the leading edge."**
>
> Jonathan Hunt, Syngene

Earlier, Syngene's chief operating officer Mahesh Bhalgat had similarly indicated that the company's facilities for biologics are also set up for manufacturing mRNA, providing a cost advantage by not having to build new sites, while alongside being geared to address aspects of thermostability, as well as other components of cost on the raw materials front.

Bhalgat, had, at the time, emphasized that having that vertical integration of raw materials and mRNA manufacturing all set up within a site is where the firm believes it is "better prepared" to serve clients with advanced therapies, which are more biologics-based.

Space for Extra Capacity In Biosimilars, Antibodies

While the advancement of new and emerging technologies means biopharma has "more approaches scientifically to throw at solving scientific problems" as is reflected in industry's pipeline, in turn both the services sector and pharma are also changing their capital deployment, building new capabilities/plants.

"But we're not there yet. I still think that there is an under capacity in a number of sort of biotech-type areas – on the biosimilars and the antibody side of manufacturing there's space just for extra capacity to come online," Hunt said.

While Syngene is a relatively new entrant in the segment – an area where leading Korean firms have carved a niche for themselves – the Indian company is forward integrating and appears confident that it can hold its own.

"Where we are the same and where we can compete is we operate to the same level of innovation, the same level of cost of goods, and the same regulatory standard," CEO Hunt asserted.

The executive referred to two bellwether events over the recent past where in small molecules, the firm received regulatory approval from the US Food and Drug Administration for its commercial manufacturing facility in Mangalore, while also sailing through an FDA pre-approval inspection of its biologics site in Bangalore in November last year.

The company is also adding capacities and in July went on to acquire a biologics manufacturing facility in Bangalore from Stelis Biopharma Limited. The site, initially set up to manufacture COVID-19 vaccines, is being repurposed to make monoclonal antibodies.

The Stelis site brings with it an additional 20,000 litres of installed biologics drug substance manufacturing capacity for Syngene. It has the potential for future expansion of up to a further 20,000 litres of biologics drug substance manufacturing capacity and also includes a commercial scale, high speed, fill-finish unit – a key capability for drug product manufacturing.

Syngene expects to make additional investments to repurpose and revalidate the site, which bolsters capacity and capability years ahead of the firm's internal capex program.

Once done, it will bring on more capacity in a market that has "capacity shortages at a very competitive price point" and with the endorsement of the very highest levels of regulatory standards, the CEO maintained.

"So that really becomes the value proposition – new capacity, proven FDA track record already manufacturing and supplying into markets and we're competitive. And there is an element around the firm – we just try harder. We're very aware that we're a new entrant and that appeals to an awful lot of customers."

Biologics manufacturing is capital intensive, and the current tight funding environment may well nudge more US emerging biotechs to look to CRDMOs; for large biopharma firms, bulking up on investments in capacity for new products can be tricky given limited certainty around demand dynamics.

"Relying on CRDMOs offers flexibility while delivering speed to market and capex avoidance," COO Bhalgat said in an article.

Bhalgat referred to the Annual Report and Survey of 'Biopharmaceutical Manufacturing Capacity and Production,' published in 2022 by BioPlan Associates, which indicated that 86.9% of respondents outsourced some biopharmaceutical

manufacturing in 2022, up from 82.6% in 2021. The most frequently outsourced activities were analytical testing/bioassays at 31.7%, followed by toxicity testing at 31.6%, fill/finish operations and testing of cell line stability at 26.7%.

At the time of the Stelis deal, Hunt said he anticipates healthy demand for high quality biologics manufacturing capacity from sectors ranging from large pharma to emerging biopharma (EBP) companies.

Syngene's overall roster currently includes 400-plus active clients, including 13 of the top 15 pharma companies with areas like development services seeing an uptick in collaborations with EBP companies in 2022-23.

The company's model provides for a combination of dedicated research sites for large biopharma like Amgen, Inc., Baxter, and Bristol Myers Squibb Company, while Syngene's smallest client, Hunt indicated, is a one-woman, virtual biotech, where the executive is lead scientist, and CEO, but pretty much handles "everything in there," with business essentially entailing working through collaborations and partnerships.

The EBP segment is estimated to represent over 60% of biopharma's total drug development pipeline; smaller biopharma is also reported to be debuting 69% of their own discoveries in the US, suggesting growing lower dependence in the commercialization journey.

New Normal For US Biotech Funding

But with the US biotech segment adjusting to a new normal when it comes to the funding environment and some EBP firms becoming "increasingly sensitive" about how they slow their burn rate or get best value, do CRDMOs like Syngene need to temper their outlook, at least for now?

Hunt acknowledged that there is an element of "price sensitivity and price negotiation being a bit more heightened", but asserted that it isn't "a bad environment" for firms like Syngene.

"We have a largely Asian-Indian operating base that does give us an awful lot of operating cost advantage, particularly in the bits of our industry that are very labour intensive, like discovery science where you need talented scientists, Master's and PhD scientists in the labs doing the work," said Hunt.

In fact, well-funded biopharma firms value that operating cost advantage evermore. One of the propositions the Indian CRDMO has for its clients – particularly in the US – is make your funding go further.

"Working with a company like Syngene, compared to doing that activity in-house, can potentially make your money go two- three times as far," Hunt maintained.

Like other CRDMOs, Syngene also offers multiple and more flexible engagement models and ways of working from dedicated teams and full-time equivalent (FTE) contracts through to fee-for-service, among others, with Hunt indicating that on occasions the company may even consider putting in "some sort of equity into the models."

"At the same time, you've got to remember what you strategically are trying to achieve and what your role in the value chain is. CROs are there to take science forward and deliver service, we're not necessarily a surrogate for venture capital investment," he underscored.

'China Plus One Is Real'

At the other end of the spectrum, there are several large and medium-sized biotech and pharma companies that don't rely on venture capital for their investments, making them "pretty immune" to the current funding dynamic in the US.

Those firms, Hunt said, are spending money and looking to rebalance parts of operations. There the trend is largely around supply chain/partnership resilience, assessing where they can access "great science in the world" and these companies not bound by particular countries or regions.

"So, this China plus one is real. It's a more glacial trend, it's solid and going in one direction. That reflects some of the underlying dynamics in the biopharma industry – we're highly regulated and very conservative in the pace at which we drive change," he explained.

Nevertheless, Hunt emphasized that there are some very good companies in China and it's not as if clients are necessarily shifting out because they don't like the support and service they get. "They're just rebalancing to some very good companies in other parts of the world".

On whether Syngene is looking for a play in contract manufacturing of glucagon-like peptide-1 (GLP-1) receptor agonists, an area where large Chinese peers like Wuxi appear to have made gains, Hunt sought to distinguish between the manufacturing and discovery services bit.

There has been a time gap of almost a decade between the discovery, first beginnings of a research project on GLP-1s and products coming through to the market and the clinical data, he explained, indicating that the excitement in the analyst community is about the "next stage of revenue generation."

"From a discovery research point of Syngene's business that's scientific archaeology, rather than what's going on in the marketplace. On the CMO piece everybody's looking at… can they find a position/partnership, because it looks to be a growing, very large volume potential part of the industry," he stated.

Analysts estimate that the market for GLP-1 peptides targeting diabetes and obesity can be as large as $45bn by 2028. "Using the thumb rule of 7-10% of sales as revenues for CDMO this represents a substantially large $4bn market for CDMOs," Berstein analysts said in a report in October.

Morgan Stanley noted that WuXi is a key manufacturing supplier of tirzepatide from Eli Lilly, a blockbuster drug in diabetes and obesity. "We model $534m revenue in 2030e from the Mounjaro manufacturing contract," analysts from the investment bank and financial services company said in a report in October 2023.

CRDMOs like Syngene will clearly be watching that space closely, while also banking on biopharma continuing to increasingly recognize the real benefits of having a very broad connect to the "scientific waterfront," as Hunt put it, to be able to access pockets of innovation, science and capabilities the world over, rather than just trying to do everything in-house.

CGT Development Is Booming, But Manufacturing Workforce Must Keep Up

Due to the unprecedented growth in the development of cell and gene therapies over the past decade, there is now high demand for certain workforce roles, especially in highly specialized areas and entry-level manufacturing positions.

BY **SHARDHA MILLINGTON,** CONSULTANT, CONSULTING & ANALYTICS

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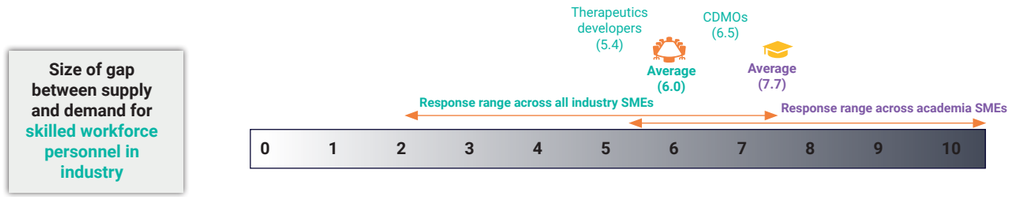
Research into workforce demands in cell and gene therapy, conducted by Citeline in collaboration with the Alliance for Regenerative Medicine (ARM) and performed with industry and academic subject matter experts (SMEs), was prompted by an executive order issued by the Biden administration in September 2022 to launch the National Biotechnology and Biomanufacturing Initiative. The order aims to coordinate the US government's approach to advance biotechnology and biomanufacturing toward innovative solutions in multiple sectors. ARM shared the results of the qualitative and quantitative research publicly in their workforce gap analysis report, published in March 2023.

The cell and gene therapy sector has expanded tremendously, with the number of drugs in development growing nearly six-fold from 511 development-stage candidates in 2013 to just over 3,000 in 2023, according to Citeline's Pharmaprojects. Attempting to meet the high demand for specialized skill sets to produce these advanced therapies has been challenging, with the workforce traditionally struggling to keep up and fill certain roles. In recent years, though, the supply of skilled workers has somewhat improved, albeit for negative reasons: Increasing layoffs and workforce reductions in the overall biotech industry has caused a boost in the number of people looking for new jobs.

Even so, industry and academic stakeholders representing the cell and gene therapy sector who participated in the research believed that this increase in supply was only temporary, and that demand will pick up again for skilled workers, especially across several key areas including manufacturing. As opposed to traditional small molecules or biologics, manufacturing in advanced cell therapies requires highly specialized and unique skill sets and considerations, including novel approaches to upstream processing, downstream processing, analytical development, and logistics.

Specifically, one of the biggest gaps is in entry-level manufacturing, where there is a need for training facilities in good manufacturing practices (GMP). Experts believe an effective way to solve this would be to establish GMP training facilities to widen the applicant pool in entry-level manufacturing roles. To boost the workforce further, wider availability of training could increase the number of qualified candidates in other functions, too, including quality and development.

Exhibit 1: Quantifying The Worforce Gap In The Cell And Gene Therapy Market



Source for all exhibits: Citeline; Alliance for Regenerative Medicine primary research

Ultimately, the research showed the gap between demand and supply still very much exists and is substantial (*see Exhibit 1*). To quantify the gap, industry and academic subject matter experts in cell and gene therapy were asked to rate the size of the gap in the workforce on a scale of 0 to 10, where 0 meant no gap and 10 meant an extremely big gap. According to academic stakeholders, the extent of that gap is large, with academic participants scoring an average 7.7 out of 10. Industry participants were slightly more optimistic, but still weighted toward a large gap in supply and demand with an average score of 6.0 out of 10. Among the industry representatives, therapeutics developers were even more positive, likely because of the current widened pool of potential applicants due to industry downsizing, giving an average score of just 5.4 out of 10.

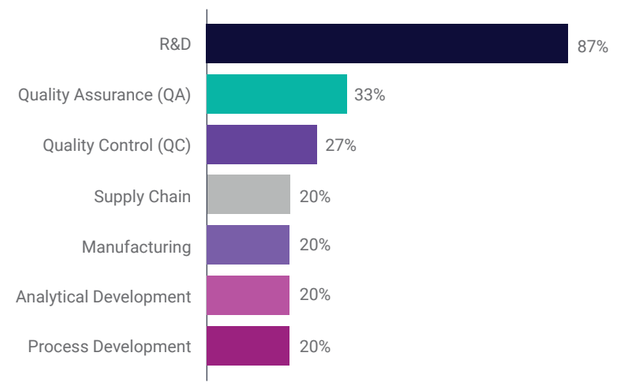
Collaboration Between Academia And Industry

Academic and industry stakeholders have identified that in-person training is generally preferred due to the hands-on nature of the education and the benefit of being able to tailor training to the institution or company in question, such as training on very specific manufacturing processes and GMP requirements. While methods such as virtual reality (VR) have been explored, usage is still limited with only 33% of interviewed industry stakeholders mentioning they had experience with VR training. Of those industry stakeholders who have used external training resources, the ones reported to be most useful are National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), and Master of Science (MSc) programs such as those provided by Case Western Reserve University, Johns Hopkins University, University of Southern California, and Wake Forest University.

Although internal company training is seen as highly important and beneficial, alignment and collaboration between academia and industry is where the greatest success can often be found for skill development: 60% of academic respondents have partnerships with industry for workforce training and report a success rate of 78%. The advantages are numerous; the greatest benefit is the job opportunities for students who can use the industry partner as a doorway into employment. Other advantages to partnerships include the guidance and funding that industry can provide for workforce training development based on real industry needs.

Importantly, in addition to an understanding of the current training landscape, feedback from the academic and industry stakeholders in this research has provided good direction for where further development on education and training can be focused to close the gap between supply and demand for skilled industry workforces. An examples includes the need for further training on more specific niches within regenerative medicine subjects and workstream areas. Training is currently heavily focused on the general topic of "research and development," with the more niche elements such as supply chain, analytical development, and process development receiving less coverage (*see Exhibit 2*). Similarly, the coverage of regenerative medicine areas in academic programs focus highly on genetically modified cell therapies, gene therapies, and non-genetically modified cell therapies, yet often neglects topics such as gene editing and tissue engineering. In response to this deficit in the curriculum, academic institutions are looking to both expand their offerings to cover a broader range of subject material, but also offer courses that are more specific and focus-in on an

Exhibit 2: Workforce Functions Covered In Academic Training Programs (% Of Responses)



individual workforce function, e.g. offering courses that focus solely on supply chain.

Although improvement opportunities have been identified and offerings are looking to be expanded, there are long-standing barriers to the access and availability of training that need addressing. Among the more commonly mentioned challenges is a lack of awareness and interest. Besides the contribution of the "Bad Pharma" image, the low visibility of training programs is associated predominantly with the difficulty that disadvantaged and under-represented individuals have in envisaging themselves in industry roles as a result of poor exposure to opportunities. Cost barriers also exist, not just in terms of training cost, but also additional personal expenses such as childcare while a parent is in education, accommodation, and travel. These access issues for certain sub-populations and minorities are reflected both in the figures seen for difficulty of enrollment in workforce training, where only 13% of respondents felt enrollment was "Not at all difficult," but also in the demographics of training programs and the applicant pool for workforces (*see Exhibits 3 and 4*).

Exhibit 5: Most Challenging Workforce Functions To Recruit (Number Of Mentions By Industry SMEs)

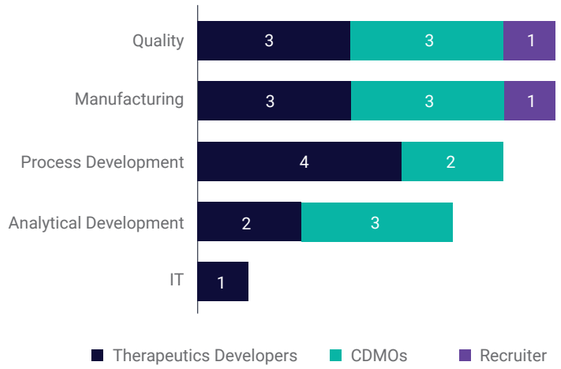


Exhibit 3: Races Or Ethnicities That Are Under-Represented In Enrollment In Workforce Training (% Of Responses)

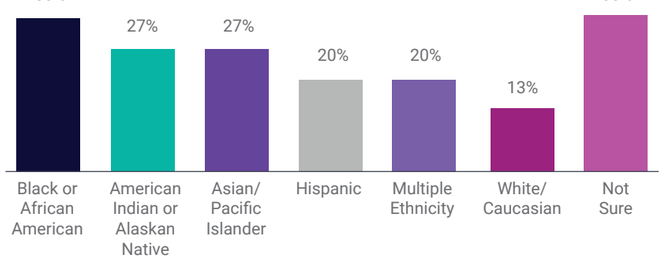
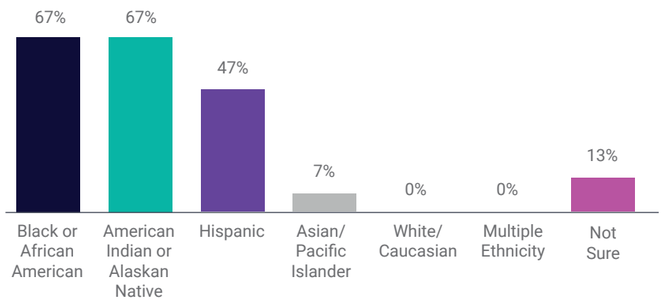


Exhibit 4: Races Or Ethnicities That Are Under-Represented In Applicant Pool For Workforce (% Of Responses)



To combat these barriers, some solutions have been proposed including the sponsorship of workforce training by companies, leveraging networks such as NIIMBL for partnerships with community colleges, and training schoolteachers to better position them to educate the new generations on the workforce opportunities that are available.

Emerging Biotech Hot-Spots Offer Untouched Resource Pool

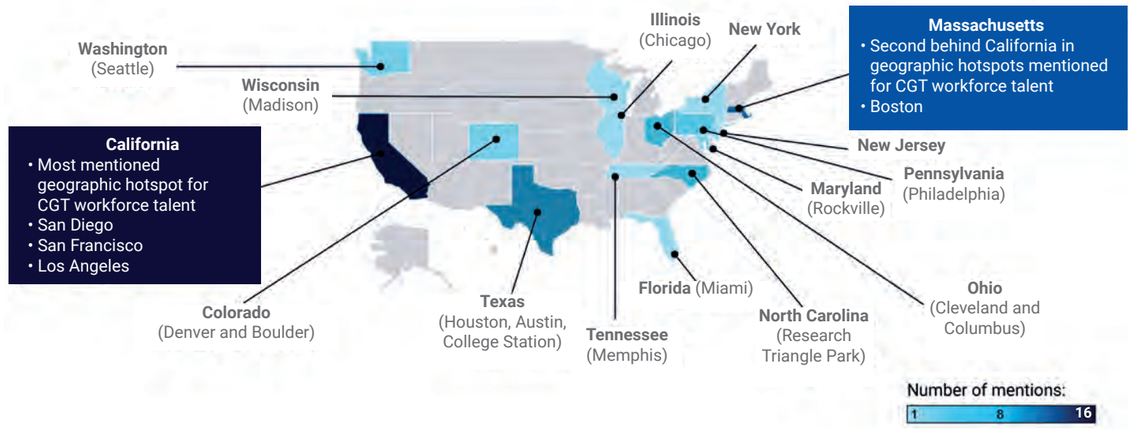
The demand for a skilled workforce stretches across the development and production chain for cell and gene therapies and will continue to heighten and apply pressure on CDMOs and therapeutics developers as the number of programs progressing through the pipeline increases. This is particularly the case for CDMOs who intensify recruiting in response to client activities, i.e. in line with approvals and need for manufacturing scale-up. The biggest threats that employers face to recruiting efforts to meet their demand are a lack of established training programs, compensation competition, and job-hopping. The inability for therapeutics developers to compete with the high compensation and salary competition from CDMOs is also a big challenge when it comes to retention of current employees, according to interviewed industry stakeholders. This is something felt by academic employers, too, who in turn struggle to compete with the salaries that industry as a whole can afford to offer. Academic experts also highlight that industry needs to branch out beyond traditional forms of recruitment to have greater recognition of, for example, the value of shorter (2-year) degrees and qualifications. Workers graduating from these shorter-term programs could expand the eligible workforce in the cell and gene therapy sector, especially in manufacturing.

Although the aforementioned recruitment challenges apply across the board, the workforce functions in regenerative medicine that see the greatest challenges are quality, manufacturing, and process development (*see Exhibit 5*). These functions experience the longest recruitment times due to a combination of the need for highly technical skills and the lack of supply of skilled workforce that can fill those roles. The consequences of the difficulty faced in finding sufficient talent is only considered to have negatively impacted clinical development timelines by a minority of 40% of respondents, however, when timelines have been altered, the impact is usually moderate-to-high.

An interesting idea to remedy the lack of skilled workforce available to hire is to recruit outside of the regenerative medicine, or even the scientific, sector and employ individuals from alternative backgrounds such as ex-military leadership roles, UPS or FedEx workers in shipping/supply chain positions, and lab technicians with experience with blood samples. These individuals will all possess transferable skills in communications, logistics, structure, safety, and project management which can readily be applied in a cell and gene therapy context.

Looking to specific geographic areas can help with recruitment, based on how concentrated the regenerative medicine workforce is across the US. Hotspots of talent have formed around the sites of cell and gene therapy developers, CDMOs, and universities/academic centers (*see Exhibit 6*).

Exhibit 6: Geographic Hotspots Identified By Industry SMEs For Cell And Gene Therapy Workforce Talent



Note: Darkness of colors on map represent number of mentions by industry SMEs; the darker the color, the more mentions

Taking advantage of these geographic areas can help employers easily identify local talent; however, it also exacerbates the issue of job-hopping due to the high numbers of competitors within the same vicinity. Although these pockets exist, we are now seeing new areas emerging as biotech clusters, which can offer an untouched pool of talent, including: Denver and Boulder (Colorado); Cleveland (Ohio), where the state is providing tax incentives or lump sums to encourage relocation; Rockville (Maryland), where secondary education is focused on biotech; Philadelphia (Pennsylvania), which has a low cost of living relative to other hotspots; and Houston (Texas), which is building large lab, office, manufacturing, and training spaces.

Conclusions

Industry and academic stakeholders in the cell and gene therapy sector have noted many challenges in the supply and demand of hiring personnel in manufacturing and other functional areas, and have identified training gaps and recruitment issues. Despite these challenges, industry and academic SMEs are optimistic about the future, proposing solutions such as building more training suites and facilities, especially for entry- or low-level manufacturing; subsidizing expenses of training consumables; and focusing training on specific functional areas where there is a high unmet need, such as process and analytical development. Additionally, to ensure there is a strong future generation in the workforce made up of a diverse pool of candidates, key stakeholders can come together to provide educational initiatives, starting even at the elementary level, to increase awareness of regenerative medicine career paths. There are many opportunities for cell and gene therapy leaders to build a strong base as the industry prepares for more advanced therapies to enter the market.

Global Medtech Recovers Core Growth After A Year Like No Other

Analyzing The Latest Medtech 100 League Tables

With many medtechs restructuring for core growth in the post-pandemic era, Abbott relied on organic growth in 2022 to move to the top of the global medtech ranking. The strength of the US dollar was not kind to companies reporting in local currencies.

BY **ASHLEY YEO,** EXECUTIVE EDITOR

It has been several years since Medtronic has not topped the annual Medtech 100 ranking of global medical device, diagnostic and digital health companies by revenues. But that was the outcome after the latest fiscal year-end reports were filed.

Both Medtronic and Abbott exceeded $31.2bn in revenues, with Abbott shading the contest by $40m after Medtronic reported a 1.4% decrease in 2022-2023 revenues. Strict comparisons are hard to draw for an industry comprised of so many segments.

Abbot's *in vitro* diagnostics portfolio, which grew exponentially in 2020 and 2021, hit $16.6bn in 2022 revenues – with COVID-19 associated revenues making up a significant portion. Its COVID-19 revenues have been significant. Medtronic earned ventilator revenues during the pandemic, but during that time its large elective care portfolio suffered.

Abbott's recent spree of major device acquisitions served to propel its overall growth; as recently as 2019, the company was below the $20bn revenues threshold, and in 2020, it trailed both Medtronic and Johnson & Johnson when it was third in the rankings.

Diabetes

Abbott's diabetes care division grew 10% to $4.8bn in 2022, driven by continuous glucose monitoring system FreeStyle Libre's $4.3bn revenues. Abbott's overall medtech revenues reached $14.7bn in 2022, up 2% from 2021.

Abbott's *in vitro* diagnostics portfolio hit $16.6bn in FY 2022 revenues.

Medtronic's diabetes group revenues in fiscal year 2023 were down 3% at $2.3bn. After a long wait, US Food and Drug Administration approval of the MiniMed 780G insulin pump system was duly granted. This was a group highlight for Medtronic in 2022-23.

The largest pureplay diabetes technology company, Dexcom, reported $2.9bn in 2022 revenues. The aforementioned companies plus Roche Diagnostics' diabetes care division, privately held LifeScan and Ascensia Diabetes Care account for the majority of worldwide sales of glucose testing systems.

Medtronic said early in 2023 that it was executing with urgency on a new growth strategy that will see it, among other things, spin off patient monitoring and respiratory interventions, a $2bn combined business. This, in the words of CEO Geoff Martha, was aimed to deliver "durable growth."

The company also formed a joint venture called Mozarc Medical with DaVita to host its renal care business. Medtronic's Intersect ENT acquisition provided $98m in revenues. Looking to the future, it signed a strategic collaboration with NVIDIA to accelerate AI innovation for health care.

Revenues at Johnson & Johnson rose by a modest 1.4%, due to flat sales in its two larger divisions, surgery and orthopedics. This was counterbalanced by mid- and single-digit growth in interventional solutions and vision, respectively. Interventional solutions is the cardiology franchise that will integrate Abiomed's business fully in 2023.

J&J combined its consumer and surgical ophthalmic segments into a single $4.5bn Vision business within its Medtech segment. Away from medtech, the company separated its consumer business as a new publicly traded company called Kenvue as of 8 August 2023.

In general, increased procedure volumes boosted the performances of the industry's top companies in 2022. COVID-19 revenues will be markedly less significant across the industry in 2023, and this will further alter the balance of individual company performances and the Medtech Top 100 rankings.

Top 100 Rationale

In Vivo's Medtech Top 100 ranking provides a snapshot of the leading global players in the medical devices, diagnostics, digital health care/healthtech segments, based on data reported by the companies in public disclosures or personal communication.

Over many years, the Medtech 100 ranking has reflected the consolidating industry and highlighted the breadth of new technology innovators that drive the industry's growth. Recently, Chinese companies have been more evident higher in the tables, owing to local share listings/IPOs or simply rapid growth.

The rankings exclude private players/private equity, which are not required to disclose financial information. Where possible, the tables exclude consumer products, service revenues and inter-group sales. Prior year restatements are reflected only if they affect the definition of the current year's revenues.

Currency Translation Factor

Foreign currency fluctuations have a dramatic effect on local revenues converted to US dollars. In 2022, the strength of the dollar dampened the often strong growth recorded by many European and Japan-based companies in the Medtech Top 100.

Endoscopy device innovator Olympus Medical commented on the weaker yen against the dollar in 2022. The Japanese currency dropped by more than 30% from around JPY115 at the beginning of 2022 to low of JPY152 in October 2022, "a level not seen since 1990," it said. Against the Euro, the value of the dollar appreciated by almost 11% in 2022.

Average exchange rates for the calendar year are used in the MT100 for comparative purposes.

Japanese Top 30 Players

Olympus, long a Medtech 100 top 30 player, has voiced ambitions to become a truly global medtech by allocating management resources to endoscopic and therapeutic solutions.

In April 2023, the company transferred its scientific solutions business to new subsidiary Evident Corp, based in Japan. The re-organization was designed to provide agility, flexibility and a platform to develop Olympus' health care business.

Among Japanese-headquartered medtech businesses in the global market, Olympus is second to Fujifilm, which in December 2022 acquired the digital pathology software business of Inspirata.

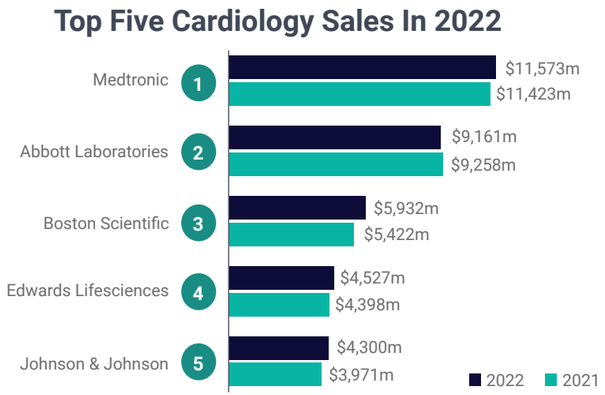
Canon Medical Systems, which acquired the Toshiba brands in March 2016, reported the highest ever sales of its medical system business unit in 2022-23, in spite of the Japanese government ending its capital spending initiative in 2021. European and US demand for the company's computed tomography and magnetic resonance imaging systems picked up once COVID-19 fears waned. It reported strong sales of diagnostic ultrasound systems.

Terumo has responded to the major paradigm shifts in health care with a new strategy: 'From devices to solutions.' The strategy takes account of the rapidly increasing incidence of chronic diseases and the aging population. It is a bid to

TOP 10 MEDTECH COMPANIES BY SALES

Abbott Laboratories	1	$31,271
Medtronic	2	$31,227
Johnson & Johnson	3	$27,427
Siemens Healthineers	4	$22,846
Becton Dickinson	5	$19,372
Roche Diagnostics	6	$18,581
Stryker	7	$18,449
GE HealthCare	8	$18,341
Royal Philips	9	$17,786
Cardinal Health	10	$15,014

All sales in $M.



Source: Company Annual Reports

capitalize on the traction gained by personalized medicine as genomic medicine matures and the application of artificial intelligence becomes more common.

Despite a delayed recovery in medical demand due to the COVID-19 pandemic, new products in the vascular graft division and an overall recovery in medical demand prompted a 16% revenue growth at Terumo, Japan's third largest publicly owned medtech player in the global market.

Asahi Kasai is a Medtech 100 company on the strength of its Zoll Medical (critical care) and health care divisions. The latter includes some pharma business. The group's sales increased by JPY81bn to JPY496.9bn.

Teijin restructured its orthopedic implantable devices business, which comprises Teijin Nakashima Medical Co. Ltd. and Teijin Medical Technologies Co. Ltd. Moving them from 'Health Care' to 'Others' is intended to position them as a new business. The company's home health care business benefited from a trend among medical institutions towards encouraging home oxygen therapy. Its CPAP device rental revenues rose by some 5% in 2022.

Diagnostics

The global market for in vitro diagnostics companies in 2022 was impeded by inflationary pressures, economic slowdown, rising interest rates and foreign exchange rate volatility. Companies faced shortages or delayed delivery of certain raw materials and other components.

Newly merged company QuidelOrtho said in its 2022 10-K filing that it expected results of operations to be impacted for some period of time by supply chain, production, logistics and distribution challenges, labor availability constraints and rising labor costs.

Sysmex, Japan's largest diagnostics company, scored a 13% rise in revenues in Yen, which turned into a 5% decrease when reported in US dollars. The company signed a global OEM hemostatis agreement with Siemens Healthineers in March 2023. In December 2022, away from diagnostics, Japanese national insurance coverage for gastroenterology and gynecology indications was granted to the company's hinotori surgical robot system.

The 15 largest stakeholders in the market for in vitro diagnostics currently account for 65% of the worldwide market (including diabetes tests).

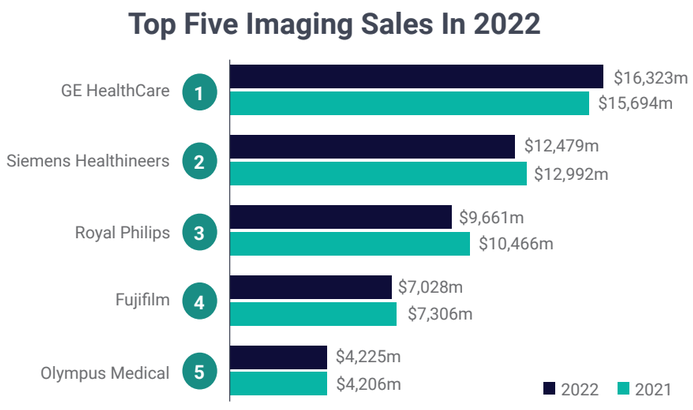
Global market leader Roche Holding's annual sales for 2022 were flat on a reported basis at CHF17,730m, and up by 3% on a constant currency basis. The Swiss company reported a 10% decrease in sales of COVID-19-related products.

On 8 November 2023, Siemens Healthineers reported fiscal 2022-23 figures that revealed a topline of €21.7bn. This was on a par with the previous year, despite markedly lower revenues from COVID antigen tests (€121m in 2022-23, compared with €1.5bn in the prior year).

A day later Becton, Dickinson and Company reported the same trend in its 2022-23 annual results. A 2.7% rise in overall revenues on a reported basis included COVID-19-only diagnostic testing revenues of just $73m, compared with $511m in the previous year. New BD acquisitions included Parata and Medkeeper (medical segment); Cytognos (life sciences); and Venclose and Tissuemed (interventional). BD sold its surgical instrumentation platform (interventional segment) to Steris.

Away from the pandemic, bioMérieux scored 9% growth in clinical applications revenues in its euro reporting currency, which is reflected as a 3% reverse when converted to US dollars. The company does not compete in either diabetes testing or clinical chemistry testing.

Exact Sciences has more than doubled its revenues since 2019. In May 2022, the company added biomarker discovery company OmicEra to its revenue base.



Source: Company Annual Reports

The acquisition, which also brought Exact a proteomics lab in Germany, will advance future blood-based colorectal cancer and multi-cancer early detection (MCED) tests, among others.

The merger of Quidel and Ortho Clinical Diagnostics was completed in May 2022 for total consideration of approximately $4.3bn. Ortho's revenues are included in QuidelOrtho's labs and transfusion medicine business. The company's transfer of its BNP business to Beckman Coulter (Danaher) held back its 2022 revenues. The transaction settled litigation that began shortly after Quidel purchased the BNP business from Alere in October 2017.

Seeking to enter the molecular disease testing market with a differentiated platform, Bio-Rad Labs acquired Curiosity Diagnostics, a late-stage, pre-commercial platform company developing a sample-to-answer, rapid diagnostics PCR system for the molecular diagnostics market.

Focusing On Core Growth

Having completed the sell-off of its applied science, food and enterprise services businesses, PerkinElmer rebranded itself as Revvity in 2023, aiming to chart a new path in discovery and analytical solutions (life sciences) and clinical diagnostics divisions.

Including service revenues in its 2022 reporting, the company's clinical diagnostic revenues totaled $2.02bn, compared with $2.93bn in 2021 (and $1.97bn in 2021, excluding service revenues).

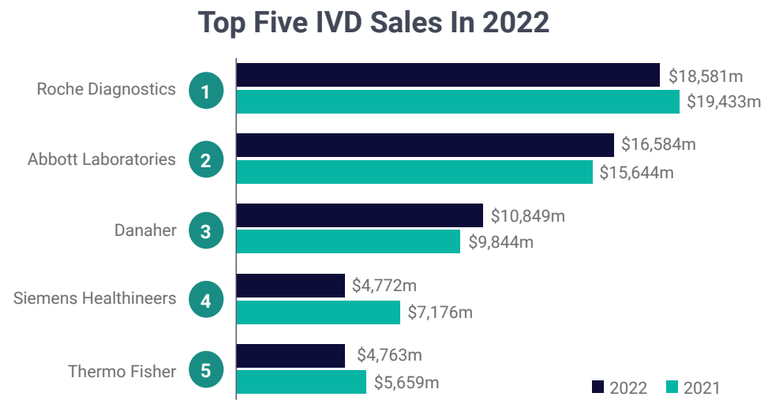
Other notable restructuring initiatives were seen at:

- Chicago-based GE HealthCare Technologies, which in January 2023 completed its spin-off from General Electric with a remit to grow adoption of precision care as a tool to improve individual outcomes, contain costs, customize care and improve provider efficiency;
- DJO brand-owner Enovis (formerly Colfax), which in April 2022 completed the separation of its fabrication technology business and set up two new operating segments: prevention & recovery; and reconstructive.

PerkinElmer rebranded itself as Revvity in 2023.

During 2022, the company completed six acquisitions, including that of Australian company KICo Knee Innovation Company trading as 360 Med Care, and Insight Medical Systems, which owns the Arvis surgical navigation system;

- ICU Medical, which acquired Smiths Medical 2020 Ltd, the holding company of Smiths Group plc's global medical device business. The acquisition added syringe and ambulatory infusion devices, vascular access and vital care products to ICU's portfolio, and a 75% increase in revenues in the P&L account;
- 3M, which in July 2022 announced its intention to spin off its health care business as a separate public company, called Solventum. 3M expects to initially retain 19.9% of the spun-off company. The company expects to complete the tax-free transaction by the first half of 2024;
- In March 2022, Zimmer Biomet completed the spin-off of its spine and dental businesses into a new public company, ZimVie, which is large enough to feature among the Medtech 100 top orthopedic companies;
- BD completed the spin-off of its diabetes care business as a separate publicly traded company (named Embecta) on 1 April 2022;
- Baxter International included a full year of revenues in 2022 from is late 2021 purchase of Hill-Rom, which helped the company's medtech sales climb by 29% to $11.4bn. In January 2023, it proposed to spin off its renal care and acute therapies product categories into an independent publicly traded company (transaction expected to be completed in H1 2024) – a $4.5bn business combined. It also proposed to simplify its operations, inject more agility into its business and pursue strategic alternatives (including a potential sale) for its biopharma solutions business; and
    - Medtronic's planned separation of its respiratory interventions and patient monitoring businesses into a combined unit, expected to be completed in the second half of its fiscal 2024.



Source: Company Annual Reports

MEDTECH

Medtech 100 Ranking 2022 (2021)	Company	Fiscal 2022 Sales ($m)	Fiscal 2021 Sales ($m)	Industry Activity
1 (2)	Abbott Laboratories	31,271	30,011	IVDs, rhythm management, EP, HF, cardiovascular, neuromod, diabetes
2 (1)	Medtronic	31,227	31,686	Cardiovascular, medical surgery, neuroscience, diabetes
3 (3)	Johnson & Johnson	27,427	27,060	EP, neurovascular, orthopedics, surgery, vision
4 (4)	Siemens Healthineers	22,846	25,692	Imaging, IVDs, radiotherapy, advanced therapies
5 (7)	Becton Dickinson	19,372	18,870	Medication delivery, syringes, needles, infusion therapy, delivery systems, IVDs, critical care, urology, peripheral intervention
6 (5)	Roche Diagnostics	18,581	19,433	IVDs, tissue diagnostics, POC, patient self-testing, next-gen sequencing, lab automation, IT, decision support
7 (9)	Stryker	18,449	17,108	Orthopedics, medsurg, neurotech, spine
8 (8)	GE HealthCare	18,341	17,725	Imaging, ultrasound, acute care systems, contrast and molecular imaging agents
9 (6)	Royal Philips	17,786	20,299	Diagnosis & treatment, connected care, personal care
10 (10)	Cardinal Health	15,014	15,887	Sharps, incontinence, nutritional delivery, wound care, fluid suction, urology, OR supplies, electrode products
11 (11)	Boston Scientific	12,682	11,888	Endoscopy, urology, CRM, EP, neuromod, cardio & peripheral vascular
12 (14)	Baxter International	11,412	8,860	Dialysis, IV solutions, infusion systems, parenteral nutrition therapies; inhaled anesthetics; generic injectables; surgical hemostat and sealant products; patient support systems; frontline care (diagnostic technologies, respiratory health devices, patient monitoring)
13 (12)	Danaher	10,849	9,844	IVDs/lab diagnostics, critical care, molecular & analytical pathology
14 (13)	B Braun	8,957	9,300	Infusion, nutrition and pain therapy, infusion pumps & systems, surgical, suture materials, hip and knee implants, dialysis equipment, ostomy, disinfection, wound care
15 (15)	3M	8,177	8,090	Healthcare procedure coding/reimbursement software; skin, wound care, and infection prevention; dentistry and orthodontia; filtration and purification systems
16 (17)	Fujifilm	7,209	7,306	X-ray, ultrasound, cell culture media, pharma, life sciences
17 (16)	Zimmer Biomet	6,940	7,836	Orthopedic recon, sports medicine, biologics, extremities & trauma products; spine, craniomaxillofacial and thoracic; dental implants
18 (18)	Olympus	6,662	6,717	Endoscopy & therapeutic solutions
19 (20)	Grifols	6,390	5,837	Blood plasma-based products, devices, clinical lab reagents
20 (19)	Terumo	6,280	6,402	Cardiac and vascular grafts, hospital care solutions, blood bags
21 (21)	Intuitive Surgical	6,222	5,710	Robotic-assisted surgery products
22 (23)	Edwards Lifesciences	5,382	5,233	TAVR, TMTT, structural heart, critical care
23 (24)	Smith & Nephew	5,215	5,212	Advanced wound management, sports medicine, ENT, orthopedics
24 (26)	Alcon Laboratories	5,045	4,703	Ophthalmic surgery
25 (22)	Thermo Fisher	4,763	5,659	IVDs, reagents, culture media, instruments
26 (31)	Mindray	4,507	3,922	IVD systems and reagents, ultrasound, critical care & patient monitoring
27 (33)	ResMed	4,223	3,578	Respiratory & sleep products, software as a service
28 (27)	Fresenius Medical Care	4,194	4,429	Dialysis, disposable renal products
29 (-)	Illumina	3,975	3,973	Sequencing- and array-based solutions for genetic and genomic analysis
30 (28)	Canon Medical Systems	3,931	4,378	CT, MR, X-ray, ultrasound, healthcare informatics, ophthalmic equipment
31 (29)	Dentsply Sirona	3,922	4,251	Dental equipment, implants & consumables
32 (32)	Asahi Kasai (Zoll Medical)	3,805	3,790	Pharma & diagnostic reagents, artificial kidneys, therapeutic apheresis, virus removal filters, AEDs, wearable defibrillators
33 (30)	Align Technology	3,735	3,953	Dental scanners, alignment technology
34 (25)	Hologic	3,280	4,191	IVDs, breast, gyne, skeletal health, products for women
35 (51)	QuidelOrtho	3,266	1,699	Rapid diagnostic testing solutions
36 (35)	bioMérieux	3,204	3,299	IVDs
37 (38)	Coloplast	3,198	3,090	Ostomy, urology, continence, wound & skin care, laryngectomy
38 (34)	Sysmex	3,143	3,315	Hematology, hemostasis, urinalysis, immunochemistry, medical robotics
39 (37)	Shimadzu	2,991	3,139	X-ray, fluorescence imaging
40 (41)	Dexcom	2,910	2,449	Diabetic care continuous glucose monitoring
41 (36)	Getinge Group	2,806	3,154	Acute care (critical care, cardio/vascular surgery, cardiopulmonary), disinfection products
42 (39)	Teleflex Medical	2,791	2,810	Vascular access, anesthesia, interventional, surgical, interventional urology, respiratory, urology
43 (-)	Envista	2,569	2,509	Dental implants, orthodontics, digital imaging, diagnostics
44 (44)	Straumann	2,432	2,212	Dental implants, scanners, orthodontics
45 (60)	ICU Medical	2,280	1,316	Infusion therapies and systems, critical care, vascular access
46 (-)	Sonova Holding	2,197	2,138	Audiology
47 (43)	Qiagen	2,142	2,252	IVD kits & instruments, bioinformatics
48 (50)	Exact Sciences	2,084	1,767	Cancer screening, IVDs
49 (45)	ConvaTec	2,073	2,038	Advanced wound care; ostomy, continence, critical & infusion care
50 (46)	PerkinElmer	2,020	1,971	Diagnostic tools for reproductive health & applied genomics
51 (47)	Carl Zeiss Meditec	2,005	1,948	Ophthalmic devices & microsurgery
52 (40)	HU Group	1,998	2,487	IVDs, sterilization (SRL, Fujirebio, Nihon Stery, Care'x companies)
53 (-)	Mölnlycke	1,968	1,995	Woundcare & OR solutions
54 (42)	Dräger	1,919	2,442	Critical & neonatal care, anesthesia, monitoring
55 (48)	Bausch Health	1,872	1,903	Intraocular lenses, ophthalmic surgical equipment, aesthetics devices
56 (52)	Elekta	1,673	1,696	Radiotherapy for cancer & neurological diseases
57 (49)	Nihon Kohden	1,582	1,869	EEG, ECG, AEDs, pacemakers, monitors
58 (76)	LePu Medical Technology	1,574	1,655	Lab consumables, cardiovascular, hemodialysis, surgical, IVDs, orthopedics
59 (58)	Enovis (formerly Colfax)	1,563	1,426	Orthopedics (prevention/recovery and reconstructive segments)
60 (54)	Integra LifeSciences	1,558	1,542	Specialty surgical (Codman) & tissue technologies
61 (55)	Bio-Rad Labs	1,451	1,516	IVDs
62 (57)	DiaSorin	1,434	1,464	IVDs, instruments
63 (53)	Teijin	1,400	1,673	Orthopedics, home healthcare devices, pharma
64 (56)	Shinva Medical Instrument	1,377	1,472	Sterilization equipment
65 (62)	Cochlear	1,359	1,233	Hearing implants, acoustics

Medtech 100 Ranking 2022 (2021)	Company	Fiscal 2022 Sales ($m)	Fiscal 2021 Sales ($m)	Industry Activity
66 (61)	Masimo	1,340	1,239	Pulse oximetry, monitoring & surveillance
67 (-)	United Imaging	1,339	n/a	Imaging, therapeutic devices, IT, services
68 (65)	Integer	1,330	1,183	Cardio, vascular, CRM, neuromod, surgical, orthopedics (outsource manufacturer); Greatbatch Medical & Lake Region brands
69 (-)	Insulet	1,305	1,099	Diabetes insulin delivery systems
70 (67)	NuVasive	1,202	1,139	Spinal solutions
71 (74)	Haemonetics	1,169	993	Blood & plasma collection, surgical suite, hospital transfusion services
72 (68)	Merit Medical Systems	1,151	1,075	Cardiology, embolotherapy, radiology, oncology, spine, critical care, endoscopy devices
73 (-)	Embecta	1,120	1,130	Diabetes care (pen needles, syringes, safety injection devices)
74 (63)	Omron	1,088	1,212	BP monitors, nebulisers, pain relief, smart thermometers
75 (81)	Cooper Companies	1,065	771	CooperSurgical: fertility, diagnostics & contraception (office and surgical)
76 (73)	Konica Minolta	1,055	1,002	Digital radiography, precision medicine
77 (69)	Jiangsu Yuyue Medical Equipment	1,054	1,070	Respiratory, cardiovascular & endocrine system devices
78 (72)	CONMED	1,046	1,011	Minimally invasive general and orthopedic surgery
79 (64)	Fukuda Denshi	1,031	1,204	Diagnostic & monitoring equipment, pacemakers, ventilators
80 (75)	Globus Medical	1,023	958	Orthopedics, robotics
81 (70)	LivaNova	1,022	1,035	Cardiovascular, neuromod
82 (-)	Fisher & Paykel Healthcare	1,005	1,189	Critical & at-home respiratory devices
83 (-)	Hoya Group	942	982	Endoscopes, ophthalmic equipment (Pentax Medical), artificial bone, orthopedic implants
84 (-)	ZimVie	909	1,009	Spine & dental
85 (-)	GN Store Nord	889	848	Hearing aid instruments
86 (-)	Penumbra	847	748	Thrombectomy and embolization devices; 3D rehab
87 (80)	MicroPort Scientific	841	779	Cardiovascular, CRM, heart valves, orthopedics, neurovascular, robotics
88 (-)	Tandem Diabetes Care	802	703	Insulin delivery systems
89 (78)	Guerbet	794	866	Contrast media
90 (79)	AGFA Healthcare	744	808	Radiology & healthcare IT
91 (77)	Invacare	742	872	Non-acute DME (respiratory, wheelchairs)
92 (82)	Myriad Genetics	678	667	Molecular diagnostic testing (oncology, women's and mental health)
93 (83)	Varex Imaging	675	644	X-ray imaging
94 (84)	Hamamatsu Photonics	632	602	Electron tubes
95 (-)	NovoCure	538	535	Tumour Treating Field electric field therapy
96 (85)	Ypsomed	522	508	Delivery systems & diabetes care
97 (-)	Shockwave Medical	490	237	Intravascular lithotripsy
98 (87)	Orthofix Medical	461	465	Biologics, spine & extremities
99 (98)	Organogenesis	451	467	Woundcare & sports medicine regen med
100 (88)	Accuray	448	430	Radiotherapy solutions

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MEDTECH

Macro Challenges Make Calls On Newly Resilient Medtechs

Global medtechs had a big enough challenge with COVID-19 and its aftermath before the full-scale regional conflict in Ukraine added more uncertainty to the question of when market normality would return.

BY **ASHLEY YEO,** EXECUTIVE EDITOR

For medtechs, 2022 will be remembered as one of the most challenging years the industry has seen in decades. The COVID-19 pandemic continued to impact operations for much of the year – especially in China – and disrupted supply chains. In addition, soaring inflation and rising interest rates combined to test the industry's resilience and drag a big shadow over the global economic outlook.

That was how the ostomy and wound care products company Coloplast described the events of 2021-2022. But these could have been the words been of any of the leading devices, diagnostics and digital health care innovators as they looked back.

The Medtech 100 listings for FY 2022 depict an industry emerging from the global pandemic, reshaping around core offerings, preparing for more place-based, remote health care delivered by digital means and getting into position quickly to maximize the benefits offered by artificial intelligence.

The listings show that the M&A activity of Abbott and the increased penetration of its diagnostics portfolio in recent years gave it the momentum to rise to first place in the global ranking for FY 2022. Based on organic growth alone, it pushed Medtronic off the top spot for the first time in several years.

Johnson & Johnson retained its top-three ranking, having integrated the revenues of coronary heart disease and heart failure technology innovator Abiomed, purchased in late 2022. Abiomed was a $1bn revenues earner in 2021. Philips lost ground commercially after its ventilator recall issues.

Baxter International reported the biggest revenue increase in the Medtech 100 ranking. It was able to include a full year of the Hill-Rom business in 2022 and was knocking on the door of the top 10. In January 2023, the company announced a major business restructuring involving the separation of its $4.5bn kidney care business into a publicly traded company by July 2024.

The trend of Chinese companies reinforcing their presence on the global medtech stage was again evident. Imaging company United Imaging completed its IPO in Shanghai in late summer 2022. Mindray experienced another year of strong growth in both its imaging and in vitro diagnostics franchises. It moved up the rankings.

Pandemic Outlook And Digital Surge

Microport, a leading Chinese and global player in both its cardio and orthopedic franchises, reported that the continued mutation of the COVID-19 Omicron strain impacted many regions in China in and stifled economic recovery. The country finally changed its pandemic prevention and control policy in late-2022, allowing domestic production to be restored.

Vascular access company Teleflex said COVID-related measures and staffing shortages at health care facilities led to reduced demand in certain segments and product lines due to lower elective procedure volumes compared to pre-pandemic levels.

Swedish acute therapies company Getinge Health Care echoed that view. In March 2023, it said health care had still not recovered to pre-pandemic levels regarding elective surgery.

The drive to raise health care productivity accelerated medtech R&D programs around smart products and services, and digital offerings.

Residual resistance to the deployment of digital health care has faded as users finally agree that the new capabilities allow for more patients to be diagnosed and treated safely. Enhanced provider satisfaction, positive impact on clinical workflow efficiencies and costs being kept under control are among the other dividends of implementing digitally enabled health care programs.

Aging Population

At the same time, demographic change – which for medtech businesses means greater demand through global population growth, an aging population and the related rising prevalence of chronic diseases – exacerbated already strained health care systems and strengthened the case for digital health care.

As FY 2022 unfolded, software applications using AI and machine learning technologies were increasingly accepted by clinicians as a way to help with diagnosis and treatment of patients.

The US Census Bureau projects that by 2030, more than 20% of the country's population will be aged over 65: a 50% increase compared to 2010. The US population will grow to an estimated 400 million by 2050.

Coping with this exploding demand of an aging population will require growth in national health care expenditure of 5% annually. By 2028, that trajectory would see US health care spending exceed GDP growth by 1%, according to the Center for Medicare & Medicaid Services (CMS).

With providers under pressure to deploy care in ways that deliver the best outcomes at lowest cost, one solution would be to deliver care in lower acuity settings, says GE HealthCare. Driven by lower operating costs and expanding access to more of the population, this, it reports, is one of the fastest growing trends in health care.

Macro Influences On Medtech's Business

As COVID's impacts subsided, medtechs were able to resume focus on their core business, conscious of the need to continue monitoring the macro-economic impacts of the pandemic.

The conflict in Ukraine contributed to material and services inflation and exchange rate volatility, as well as trade and tariff activity. These impacts will continue to affect businesses.

Global monetary tightening pointed to a risk of worsening business conditions for medtechs, the Tokyo-listed endoscopy company Olympus Medical warned. The 124-year-old company summed up the recent key business impacts as being:

- Increased COVID-19 infections in China;
- The war in Ukraine;
- Global inflation leading to rising raw material prices;
- Supply chain constraints; and
- Shortages of semiconductors and other components.

Germany's Council of Economic Experts (Sachverständigenrat Wirtschaft) noted how, in addition to the human catastrophe in Ukraine, medical technology companies were also impacted by the ongoing war.

Increased energy prices are also part of the mix, said Germany-based critical care devices manufacturer Dräger. Inflation impacted customers' ability to invest as well medtech innovators' abilities to operate efficiently, it said.

China Recap

The reform of China's health system continues, with sights fixed on achieving the goals prescribed in the "Healthy China" 2030 agenda.

Microport reported that the government was committed to expanding access to high-quality medical resources, improving basic public services and generally prioritizing the protection of the population's health.

China stepped up investments in medical infrastructure in recent years to improve the supply of medical resources. As a result, China's medical devices market has seen renewed growth.

The government issued a number of policies under the 14th Five-Year Plan, which, among other things, underlined the value of medtech innovation. It also set targets for local companies in terms of accessing high-end, high value medtech segments in the international business setting by 2025.

To promote volume (i.e. state)-based procurement (VBP) tenders for medtech, the National Healthcare Security Administration (NHSA) promised to roll out more tenders for high-value consumables on a case-by-case basis. Medtronic, in its fiscal year 2023 financial report, commented on the unfavorable business impact of provincial Chinese VBP tenders.

There were positive signals on Chinese reimbursement for innovative medical devices. In July 2022, the Beijing Municipal Medical Insurance Bureau proposed that innovative medical devices and drugs could be paid outside diagnosis related groups. The new system was called the CHS-DRG payment management measures for new drugs and new technology exclusions.

The E in ESG

Sustainability compliance is viewed as a necessary but complex subject that stretches deep into every corner of a company's commercial and manufacturing operations.

Compliance with greenhouse gas emission goals and other sustainability themes is not negotiable. The costs must be borne, but so far, the cost of compliance is difficult to quantify for medtechs. There are many variables to factor in. SpO2 device manufacturer Masimo explained that, with customers, distributors, and retail partners likely to include ESG provisions in procurement policies, the costs of compliance will rise. Managing procurement-for-compliance will be difficult, given the complexity of supply chains and outsourcing of component manufacture.

Non-compliance by medtechs and suppliers risks loss of business, fines, legal action and, possibly most costly of all, irrevocable reputational damage. Greenwashing would be an even worse avenue to take.

Coming directly after COVID, the pressure to ensure sustainability compliance to restrict the acceleration of global warming may be the next big exogenous challenge to the global medtech industry. Medtechs are once again called upon to co-operate closely with third parties and to a certain extent are being asked to look beyond their own P&L accounts.

POLICY & REGULATION

Medicare Price Setting And The Value Of Post-Approval R&D Spending

Will scrutiny by the Centers for Medicare and Medicaid Services eventually lead to shifts in investment away from improving older drugs toward developing new products?

BY **CATHY KELLY,** SENIOR EDITOR

One of the more prominent arguments against the Medicare drug price negotiation program is that by limiting the number of years that products can be marketed before price caps are imposed, the scheme discourages development of additional indications. New research on the 10 drugs selected for the initial round of negotiation both reinforces and complicates that narrative.

Research and development spending to date for most of the 10 drugs is well above the often-cited $2.5bn industry benchmark for R&D, according to an analysis conducted by health care research and advisory services firm ATI Advisory. But most of those studies were conducted well before the nine-year cutoff on market pricing that the new Medicare program would impose.

Spending estimates for six of the drugs were $3.5bn or above and ranged up to $7.8bn for Bayer/Johnson & Johnson's anticoagulant Xarelto.

For most of the drugs, the greatest share of R&D spending came after approval, averaging 61% across all products, according to the study. Boehringer Ingelheim/Eli Lilly's antidiabetic Jardiance and Novartis' heart failure drug Entresto were the only two products in the analysis with spending that was higher in the pre-approval space, but the difference was minimal.

R&D spending might look higher than is widely understood.

The estimates were derived from publicly available clinical trial information. The researchers did not estimate R&D spending for Novo Nordisk's Novolog insulin and Amgen's anti-inflammatory Enbrel because their development preceded modern clinical trial reporting standards.

The study is meant to shed light on the kind of information that manufacturers of the selected drugs were required to submit to the Centers for Medicare and Medicaid Services in October to facilitate the negotiation process. CMS will look at R&D spending to assess the degree to which developers have recouped their investment. The agency announced the list of 10 drugs in late August.

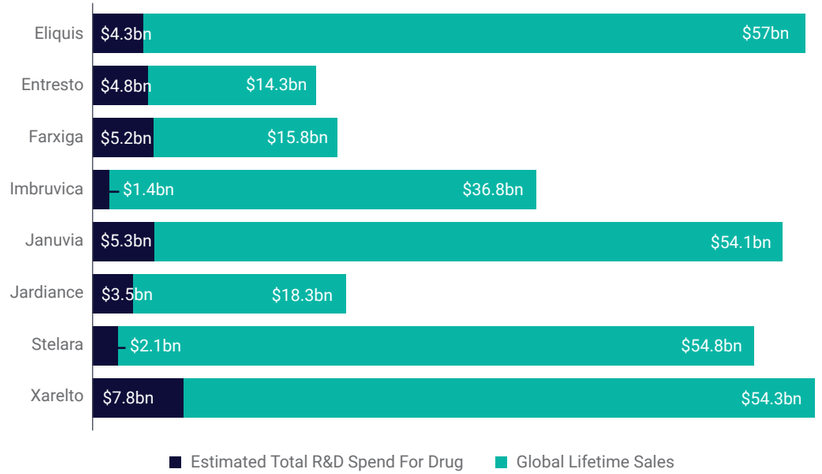
Anna Kaltenboeck, head of ATI's prescription drug reimbursement practice, discussed the findings and how the data might be received by CMS in an interview.

"We were struck by how high some of the spending was, it was pretty remarkable. And when we dug deeper we found that it is split in this way," she said. "Part of the reason we created this report is that the negotiations are going to be behind closed doors ... but we wanted to create some sort of benchmark to give people a feel for ... the magnitude of the numbers that CMS might be seeing once they get these submissions, and also to interpret them."

She also pointed out that although R&D spending might look higher than is widely understood, global sales for each of the products on the list are greater than the expenditures by orders of magnitude. Therefore, there would be no question in CMS' mind as to whether companies had recouped their investment, Kaltenboeck said.

Exhibit 1: A Strong Return On Investment

Gross sales figures do not include rebates



Source: ATI Advisory Analysis

All But One Drug On The List Added Indications Post-Approval

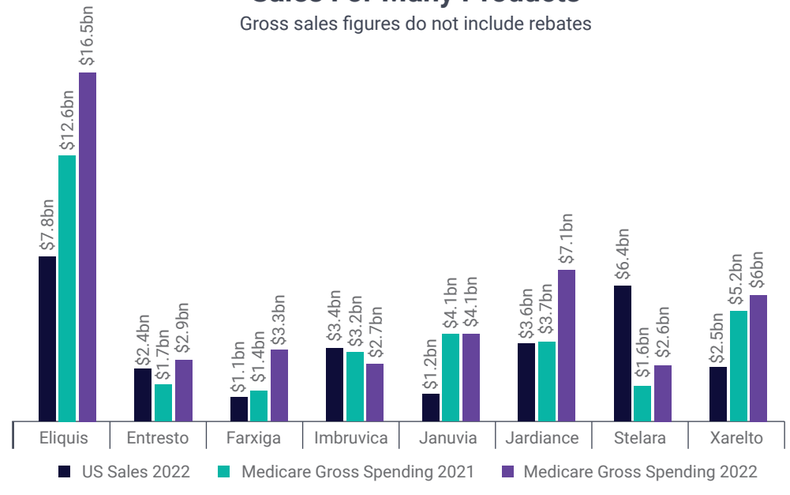
Kaltenboeck observed there are important differences in the nature of R&D spending pre- and post-approval. "When you're talking about the R&D work that you have to do before a drug comes to market, it's riskier because there's always the possibility that you end up with zero revenue," she noted. After approval, there is less risk because developers are already fairly familiar with the drug and its target audience.

Post-approval R&D work can satisfy postmarket commitments from the US Food and Drug Administration. It also includes market expansion efforts.

"Some of this is adding more indications and in a lot of instances, you'll see companies doing clinical studies not so much for the FDA's benefit but actually for the benefit of the payers, to ensure they can get coverage on formulary ... to demonstrate their value. And then you also have studies to support reformulation of the product at later stages of life,

Exhibit 2: Medicare Gross Spend Eclipses Sales For Many Products

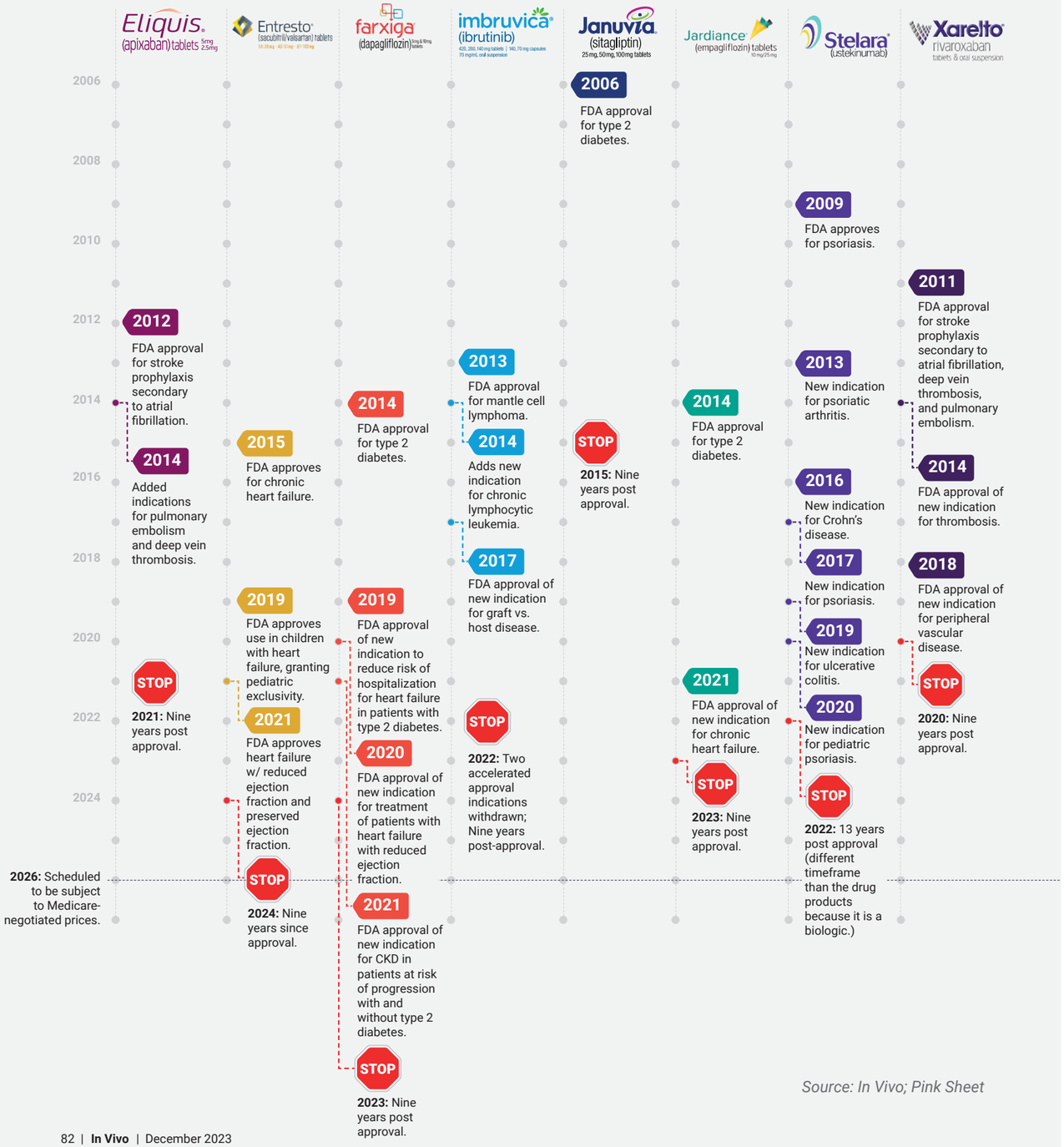
Gross sales figures do not include rebates



Source: ATI Advisory Analysis

Will The Medicare Price Negotiation Program STOP Post-Approval R&D?

A timeline of when drugs selected for Medicare price negotiation received supplemental indications. The stop signs indicate when they would have been eligible for negotiation had the program existed when they were initially approved.



Source: In Vivo; Pink Sheet

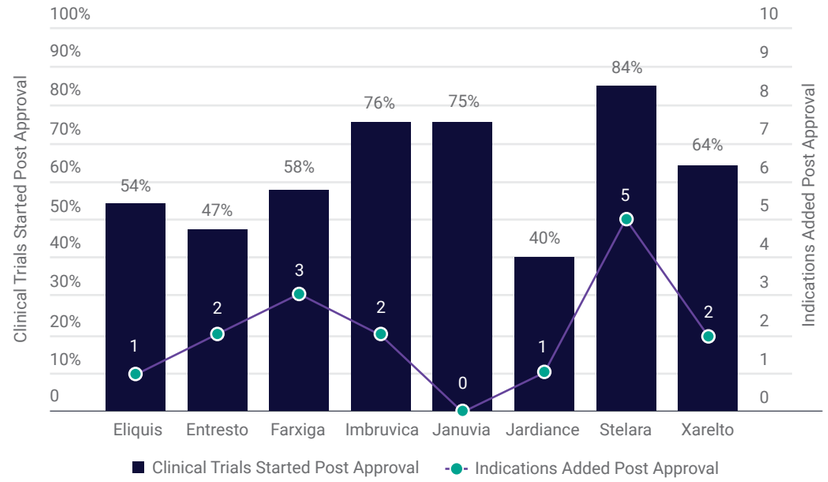
so you sell more of the drug," Kaltenboeck explained.

"These tend to be big studies, which is a major cost driver and that's a lot of where you see those essentially benchmark costs going up in the post-approval phase," she noted.

For example, Bristol Myers Squibb's antidiabetic Farxiga "has added some new indications recently that puts it into the heart failure" space. "It's a strategic decision they're making" to either expand their market share or ensure it stays where it is.

All but two of the drugs, Merck's antidiabetic Januvia and Novolog, added at least one indication after initial approval. Johnson & Johnson's anti-inflammatory Stelara added five indications. And other drugs have additional indications in the works. Boehringer Ingelheim and Lilly announced 22 September that the FDA had approved a major new indication in chronic kidney disease for Jardiance.

Exhibit 3: Big Post-Approval Spending Does Not Always Mean Many New Indications



Source: ATI Advisory Analysis

Spending More On Approved Drugs Than Developing New Ones?

Industry has maintained the prospect of facing negotiated prices nine years after approval will dampen future work on additional indications. But Kaltenboeck maintained the analysis suggests otherwise.

"When the industry points to how much they spend on R&D, they tend to couple it with this argument around, 'Well it takes this much money to create a new drug.' And I'd like to point to the fact that what this shows is that the industry is spending a lot of money not on the creation of new drugs but on the advancement of older products, which is fine, there's value in that too. But it's not the same thing. And I think we need to be very aware of the fact that those activities and the risk they're taking is not the same."

Another takeaway from the study is that "companies often do this [post-approval R&D] simply as the result of competitive pressure, which means that it's not necessarily on the payer to work that into the price, that's not part of the equation," she observed. "It's simply for [manufacturers] to maintain their part of the market. So I want CMS to understand that."

Thirdly, "there's obviously effort and resources expended in the post-marketing phase and the question now becomes not so much about the payer, it's actually more of a societal question, which is 'Where do we want companies to be putting their money?'" she continued.

"Is it reasonable for them to develop these really very large studies that are very expensive for progressively smaller

Industry is spending a lot of money ... on the advancement of older products.

increments of patient benefit? Where is that tipping point where we would like them to start to invest that money into the development of new therapies?"

Kaltenboeck suggested this kind of scrutiny is healthy. "I actually think this is going to stimulate demand for new pipeline candidates and R&D there," she said. "What might shift ... is perhaps they might prioritize bigger indications sooner or they might try to get more indications compressed and into the market more quickly so that they can get to peak revenues before the out years in terms of their projections. That's where I would expect some changes in behavior."

In the end, R&D investment "is not a simple story in the way that industry sometimes tries to portray it. It's really a very nuanced question of what kind of studies are being done and the kind of value that confers to patients," Kaltenboeck explained.

She said such questions may not ultimately matter for CMS as it considers a "fair" price for the negotiated drugs "because all of the money has been recouped here." But "I do think as we go forward with the evolution of this policy ... we're going to have to have that conversation at some point as to where we are spending money on R&D and what's the most efficient way of doing it."

Splits Over Data Protection Could Hamper EU Pharma Revision

The chances of reaching agreement on proposals to overhaul the EU pharma rules before the European Parliament elections in June 2024 are receding as disagreements emerge over key issues such as regulatory data protection and how to encourage antimicrobial R&D.

BY **IAN SCHOFIELD,**
EXECUTIVE EDITOR

Lawmakers are gearing up for what could be a long and arduous debate over the European Commission's proposals for revising the EU pharmaceutical legislation. The revision package, consisting of a draft regulation and a draft directive, is wide-ranging and covers a multitude of areas relating to pharmaceutical regulation. First published in April 2023, it was formally presented to the European Parliament in September.

The contentious nature of many of the proposals bodes ill for a smooth journey through the legislative machinery at the European Parliament and the Council of the EU.

A key obstacle will be the commission's plan to shave two years off the baseline period of regulatory data protection (RDP) for originator drugs. This has, unsurprisingly, caused uproar among R&D-based pharmaceutical companies. It has also sharply divided opinion among members of the parliament's environment and public health committee (ENVI), which is responsible for leading the parliamentary debate on the package and producing final texts to be voted on at a plenary session.

Less contentious but far from universally welcomed are proposals for a "sandbox" environment to test out new regulatory approaches, a "transferable exclusivity voucher (TEV)" to boost antimicrobial R&D, and a new definition of "unmet medical needs."

Other plans include a radical streamlining of the structure of the European Medicines Agency, reductions in new drug assessment times, additional measures to tackle drug shortages, new environmental risk assessment requirements, and more actions to address antimicrobial resistance.

RDP The Main Sticking Point

Such are the divergences on certain key points that the parliament will find it hard to reach a unified stance on the package as a whole before the parliament breaks for the elections in June 2024. This means the legislative process will have to be put on hold and only restart once the new assembly is in place.

By far the biggest headache for legislators is the RDP proposal. The commission is proposing to cut the baseline period of protection from eight years to six, a move designed to allow earlier generic and biosimilar competition.

Companies could earn back some added periods of RDP by meeting a number of conditions, such as launching a product in all EU member states, fulfilling an unmet medical need, or gaining a new indication. An additional year could also be secured if a company was awarded one of the proposed "transferable exclusivity vouchers" intended to incentivize the development of new antimicrobials. Products would continue to benefit from two years of market exclusivity at the end of the RDP period.

The proposed provisions on market exclusivity for orphan medicines are less complex but also based on a "modulation" approach. The standard 10-year ME period would be reduced to nine years, although an orphan drug meeting a "high unmet need" could still benefit from 10 years. A year of additional ME would be available for marketing in all member states and for a new therapeutic indication (the latter could be granted twice).

Needless to say, the R&D-based pharmaceutical industry body EFPIA is adamantly opposed to any dilution of existing protections – even with the array of extensions proposed – saying that reducing RDP will impair the economic case for investing in innovative new medicines.

For its part, the off-patent industry has suggested that the proposed additional RDP protections should be replaced with extensions of market exclusivity.

These divergences are broadly reflected in the positions taken by the ENVI rapporteurs in their respective draft reports on the package, which were published on 3 October. Tiemo Wölken is the rapporteur for the draft regulation and Pernille Weiss for the draft directive.

Wölken likes the commission's idea of a modulated approach to RDP. In his report, he welcomes the "stepping away from the model of 'one-size-fits-all' towards a stepwise approach of incentive models, where actual innovation is promoted and rewarded."

Weiss, on the other hand, has attacked the cut in the baseline RDP period and has even recommended raising it from eight years to nine – a proposal that will please the R&D-based industry.

This, of course, does not augur well for the chances of reaching an early agreement in parliament. "The draft reports demonstrate that the rapporteurs for the regulation and directive have adopted diverging positions regarding the commission's proposals in matters such as the proposed changes to the periods of regulatory protection for medicinal products," says Elizabeth Anne Wright of law firm Cooley.

"The Rapporteur for the regulation was also fairly critical of the pharmaceutical industry, with a number of proposed revisions intended to impose penalties on companies for failures to comply with regulatory obligations, particularly in relation to post-authorization activities," Wright said.

"Given the breadth and sensitivity of the proposed revisions," she added, "we would anticipate that the proposals will be subject to substantial debate both within the ENVI committee and subsequently within the European Parliament before a single text is adopted by the EP."

Complexities Will Hinder Talks

EFPIA insists the commission's proposals will "significantly reduce" the industry's protections while adding "complex incentives" for additional RDP periods that in practice would be "impossible to achieve."

It is not alone in this view. The RDP extensions are "subject to many conditions, and meeting all of them for a single drug seems like a purely theoretical possibility," according to the Polish law firm Wardyński & Partners.

"If these conditions are not clarified or modified in the course of further legislative work, they could become bottlenecks difficult to pass in practice, and create uncertainty about the effective duration of the data exclusivity period in a particular case," it says.

Gaining a two-year extension of RDP by showing a product was marketed in all EU member states is a particularly problematic issue.

"The condition that a drug has been marketed and is continuously supplied in quantities and presentations meeting the needs of patients in those markets where it is registered within two years of registration (three years in the case of SMEs) can be interpreted differently," Wardyński & Partners pointed out. "Furthermore, meeting this condition is largely beyond the control of the pharmaceutical company."

Lobbying

The R&D-based industry is likely to engage in strong lobbying over the RDP proposals as the package moves through the

Proposed Changes To Data & Market Exclusivity Periods

Current	Proposed
Non-Orphan Drugs:	
8 years RDP[1] + two years ME[2]	6 years RDP + 2 years ME
+ 1 year ME for a significant new indication	+ 2 years RDP for marketing in all EU member states (+ 3 years for smaller firms/non-profits)
	+ 1 year RDP for a new indication
	+ 6 months RDP for meeting unmet needs
	+ 6 months RDP for conducting comparative clinical trials with a New Active Substance
	+ 1 year RDP for use of TEV[3]
Orphan Drugs:	
10 years ME (for each indication)	9 years ME
+ 2 years ME if results of studies conducted in accordance with a Pediatric Investigation Plan are included in the product information	10 years ME for product meeting high unmet need
	5 years ME for orphan approved with bibliographic data
	+ 1 year ME for marketing in all EU member states
	+ 1 year ME for new therapeutic indication of orphan drug (can be granted twice)
Other Changes:	
A new four-year RPD period for repurposed medicinal products showing a significant clinical benefit	
One year of RDP for "significant non-clinical tests or clinical studies" that lead to a change of prescription status.	

[1]Regulatory Data Protection; [2]Market Exclusivity; [3]Transferable Exclusivity Voucher

legislative processes at the parliament and the Council of the EU, which represents member state governments.

"Given the importance of the innovative pharmaceutical industry in the EU, the Council, and possibly to a lesser extent the EP, may take these concerns into consideration when adopting their position," Wright said. "At the least, lobbying pressure may increase the time for the co-legislators to agree on the legislation."

She noted that the revisions proposed by Weiss in her draft report on the directive were "largely practical, uncontroversial proposals that would appear unlikely to cause much debate."

However, because Wölken has built on the commission's proposal and suggested strengthening the provisions on reducing RDP, "sometimes in contradiction to related proposals in the directive, the R&D industry may focus its lobbying activities on the draft regulation," she suggested.

Wright believes that industry lobbying may have more impact in the council than in parliament. "Suggestions by EFPIA that the proposals will have a negative impact on access to innovative treatments and research and development in the EU may resonate with the EU member state governments," she said.

Given that the council votes by qualified majority, "the support of EU member states that have substantial pharmaceutical R&D activities on their territory may gain in relative importance, resulting in an opposition that could potentially block the legislative process," she added.

Off-Patent Industry View

On the other side of the fence, the off-patent pharma industry body, Medicines for Europe, believes that the commission's plans will lead to uncertainty as to when generics and biosimilars firms could file for approval. It has also observed that originators could in theory obtain a maximum of 13 years of RDP plus ME protections, compared with 11 years at present.

It agrees with the reduction of baseline RDP to six years, which would allow generics firms to reference the originator product data two years earlier than at present.

But instead of offering various extensions of RDP, it suggests that an extra year of market exclusivity should be offered for pan-EU launch, and an extra year of ME for an additional indication. Catering to an unmet medical need or conducting comparative clinical trials would each earn a six-month market exclusivity bonus.

But Wright is not convinced. "Experience suggests that the proposal by the off-patent industry to replace the RDP extensions with market exclusivity extensions may be considered to go too far," she said.

The commission's proposal to reduce the current periods of data exclusivity "was based largely on the argument that the loss in data exclusivity, rather than the market exclusivity, can still be compensated through incentives intended to increase access to innovative medicinal products in the EU," she noted. "The RDP extensions are an important bargaining element that the Institutions rely on to advance negotiations on the new pharmaceutical package."

Wright also pointed out that RDP was "considered relatively more important than market exclusivity" in encouraging the development of new drugs, given the financial investment needed to develop products and conduct clinical trials, and their high failure rates. "Debates are, therefore, primarily centred around regulatory data protection."

Other Proposals

RDP is far from the only proposal that could hold up agreement on the package. The regulatory sandbox, the TEV, a new temporary emergency marketing authorization (TEMA) and the definition of unmet medical need all have the potential to throw a spanner in the works.

The commission describes the regulatory sandbox as a "controlled environment" in which new approaches could be used to test and assess novel kinds of medicines and other technologies that might not fit into the current regulatory framework.

The idea is backed by industry and the EMA's Emer Cooke. But Wölken is "dubious" about the idea and has proposed deleting this part of the draft regulation. He describes the proposal as "vague in nature" and says he has "not been satisfied with explanations or examples of which types of products could be eligible for such a regulatory sandbox."

Similarly, he sees the TEV scheme as an "indirect and non-transparent" mechanism that would impact national health budgets in an "unpredictable manner and delay the entry of generic medicines to the market." As for the proposed TEMA, he insists "robust transparency measures and standards" must be put in place for the EMA's related regulatory activities.

The definition of unmet medical need is another sticking point. The commission has proposed a provisional set of criteria to define "unmet medical need" (UMN) and "high unmet medical need" (HUMN).

However, EFPIA says while some of the criteria are "clear and comprehensible," others are "ambiguous" and increase uncertainty for medicine developers. It claims the proposal "could impede the EC's goal to direct innovation to areas in which UMNs exist from a patient and healthcare perspective."

Plenty of scope, then, for a lengthy legislative debate lasting until, and likely beyond, the June 2024 parliamentary elections. Things could also be held up by the change of the European Commission later that year.

Wright says that meetings and debates on the revision package in the ENVI committee are expected to take place throughout November and December 2023. "Given the breadth and contentious nature of the proposals and added lobbying pressure from both sides of the pharmaceutical industry, negotiations in the EP are likely to last well into 2024," she said.

She thinks it unlikely the parliament will reach a unified position on the proposals before the elections. "Conflicting views may also arise in the Council, which will examine the European Commission's proposals in parallel to the EP," she observed.

The elections, and the subsequent end to the current commission in October 2024, "could delay the legislative procedure for the pharmaceutical package even further by requiring the Council to realign its position with a different political constitution in the EP."

Navigating Innovation To Deliver For Patients

Christelle Huguet, Head of R&D at Ipsen, discusses how External Innovation is central to Ipsen's R&D strategy and provides a spotlight on Rare Disease, where the portfolio has seen strong movement in 2023.

Innovation is "really accelerating" in the pharmaceutical R&D space right now, according to Christelle Huguet, Head of R&D at Ipsen. There is greater connectivity and collaboration, enabling companies to bring together their expertise in different fields, as well as many exciting developments in biotech and academia that will certainly change the treatment landscape for patients in the future. However, we continue to see "changes and challenges" in the regulatory environment and so, if we want to really harness this innovation, then as an industry it is crucial that we connect the right incentives to scientific progress. Bridging that gap is far from easy but the team at Ipsen remains committed to working collaboratively to help move towards this collective goal. Ipsen's strategy is to exclusively source the best scientific innovation from biotech and academic institutions. Ipsen then helps to accelerate research and development by providing commercialization expertise across their key focus areas: Oncology, Rare Disease and Neuroscience.

"We are building a diverse and sustainable pipeline at every stage and through acquisitions, partnerships and collaborations, have expanded across early development, clinical programs, and also commercial assets," Huguet says. "Our expertise is used to complement the strengths of our partner. We add most value by using our internal know-how to translate early science into a clinical candidate molecule and take it through development all the way to patients."

New technologies are helping Ipsen continue to develop novel treatment solutions, she adds, including real-world evidence and digital technology and the use of artificial intelligence (AI) in clinical trial design to mine data more deeply. Ipsen has also used model-informed drug development (MIDD) to analyze data and work out how a new treatment could benefit more patients. Exploring the potential role for novel technologies remains a strong focus for Ipsen, while recognizing that it must add the right value, contributing to clinical development and the regulatory process to ultimately deliver innovations to patients.

Open Dialogue With Regulatory Agencies

"At Ipsen, we welcome the opportunity to work with global regulators as early as possible, including within our early development portfolio, to shape and prepare for clinical development with the aim of a submission following the completion of a rigorous development program," Huguet says. However, there are some circumstances where the regulatory environment could discourage innovation. "It could impact the types of indications that the industry might invest in. There are pressures on some geographies where the patient ultimately loses out, and that is concerning," Huguet says.

Open dialogue with authorities and regulators is paramount and must continue, she adds. More than that, "we need to continue to foster greater collaboration in the ecosystem between industry, regulators, and patient organizations, so we can encourage continued innovation and bring more options to patients." For Ipsen, the voice of the patient is particularly crucial, and it will continue to keep them at the center of its investment and focus.

To address the evolution of regulatory pressures, Ipsen has: invested in the requisite skills as well as in digital and AI; strengthened its regulatory group; kept in constant dialogue with regulators at all stages of medicine development. This helps Ipsen to understand the agencies' needs and where they can work more effectively with them.

"We have a dedicated team with cutting edge skill sets that complement our more traditional drug development capabilities, so that we can apply new technology where it's going to have the biggest impact," Huguet says. "We want to ensure our 'heritage' expertise remains equally advanced, so we train our people in all aspects of clinical development, trial design, and using predictive toxicology more in non-clinical drug safety."

Driving Progress In Rare Disease

Rare disease is one of Ipsen's three strategic therapeutic areas and the company has seen strong expansion in recent years through acquisitions and partnerships with both biotech and academic institutions. In particular, the rare disease clinical pipeline has more than doubled since 2020 with eight investigational programs in development, including in rare bone and rare liver diseases. The company defines rare diseases as those affecting up to six in every 10,000 people globally, but also in terms of whether patients can access treatments and how the treatment paradigm differs in different geographies.

A key consideration when developing treatments for rare and ultra-rare diseases is "to work carefully on endpoints and trial design" in Huguet's view. Endpoints that are well validated for larger indications are often not appropriate for rare diseases, where there is often no precedent in initiating clinical development programs. Ipsen works closely with regulators, patient associations, and healthcare professionals to refine endpoints that are both meaningful for patients and accepted by the regulators.

"Thinking about alternative trial design, we would like to see greater use of natural history and real-world evidence. For a rare disease where a child is born with a defect so severe that their life expectancy will be six to twelve months, there is no way we could use a traditional placebo-arm approach here," says Huguet.

Accelerated approval mechanisms have helped in such cases, enabling drug developers to quickly bring solutions to patients in need, sometimes defining the endpoint as development progresses. In the case of palovarotene "the first global Phase III trial crossed futility, largely due to the selection of an inappropriate statistical methodology. But the raw data clearly showed there was efficacy and so we worked with the FDA to look at the strength of the totality of the data, assess the risk-benefit profile, and listen to the voice of the fibrodysplasia ossificans progressiva (FOP) community. In the end, palovarotene was approved in the U.S. for people living with FOP.[1] That was trailblazing, and a true collaboration across all stakeholders from industry, regulators, clinical experts, and the patient community." Although this is not always possible, Huguet adds, it shows what can be achieved.

More generally, Huguet notes, there is more openness to using, as yet, unvalidated endpoints in rare disease research. There are also more opportunities for earlier discussions with regulators and modified trial designs in consultation with both regulators and patients. All this gives Ipsen the confidence to expand into new areas. The ultra-rare disease space, by contrast, is much harder to operate in. "It's going to need a different societal approach and a much longer conversation, but with commitment and drive across the ecosystem we can be successful."

CHRISTELLE HUGUET, HEAD OF R&D, IPSEN

Key Learnings

Distilling her experience of regulatory filing processes in rare diseases into advice for those developing programs today, Huguet says: "Talk early and often with the regulators. Work very, very closely with healthcare professionals on the endpoint itself. Really listen to the patients – what do they need?" The biggest impact may come from preventing disease progression, though this may be a long time coming because endpoints in slow-progressing diseases are very difficult to establish.

Other endpoints that should be considered, in her view, include quality of life – for the patient's family as well as the patient – because of the demands placed on them as caregivers. Drug developers should also think about the economic landscape and payers, so that insurers can understand what will make a big difference for the patient and what they should consider themselves.

Data are much less available in rare diseases than in other areas, such as oncology. Ipsen seeks to extract the most value by combining multiple data sets, including registry data, real-world evidence, and data collected by prospective studies sponsored by patient organizations. "All of these matter in terms of the rare disease environment and how we can best serve the patient," Huguet observes.

She believes that regulators are interested in 'new' forms of data but there is more dialogue to be had before they are used more widely. The field is evolving, and regulators may be taking it into account more in the oncology space, where accelerated approval is not always being followed by traditional confirmatory evidence. "It's piquing their interest, but we're not there yet in terms of truly using those datasets as a body of evidence on their own."

Future Potential

Looking forward, Huguet is resolute that the courage to pioneer science and trial design, alongside prioritizing listening to the patient, will be vital to drive drug development in the rare disease space. These foundations are not just limited to Ipsen's work in rare disease, but are at the core of the company's approach to their three therapeutic focus areas. "We believe that the best science is delivered by biotech and academic centers and are excited by the continued scientific progress we see across oncology, rare disease and the neuroscience landscape," explains Huguet. "We are confident that by uniting expertise through exclusively building our pipeline through external innovation, we can harness Ipsen's end-to-end excellence to convert today's molecule into tomorrow's medicine for patients around the world."

[1] Sohonos (palovarotene) is approved in the U.S. and Canada for the reduction in volume of new heterotopic ossification in adults and pediatric patients aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP)

Investment In New Products: Looking Beyond The R&D Line

Johnson & Johnson and Roche lead the most recent Scrip 100 ranking for R&D spend, but a look beyond investment in internal development highlights a big year for Pfizer and Bristol Myers Squibb.

BY **EDWIN ELMHIRST,** DATA JOURNALIST

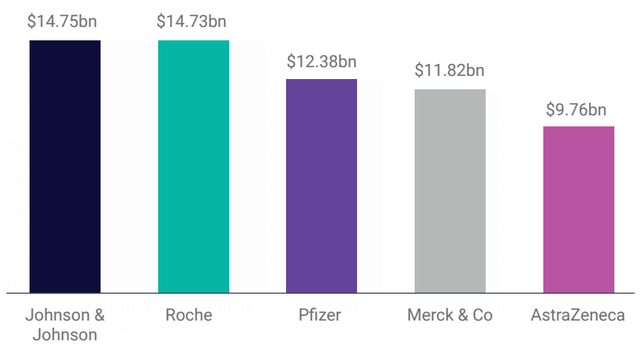
The Scrip 100 leading five companies, according to R&D spend for 2022, shows many of the usual suspects at the top of the rankings (*see Exhibit 1*). However, a deeper look at these numbers and taking into account "external" R&D spend such M&A and licensing reveals some upsets and surprise appearances.

Johnson & Johnson and Roche's top billing according to the research spend metric is, perhaps, unsurprising. Both companies, in addition to their large presence in biopharma, have portfolios in diagnostics and medtech – which also require R&D budgets. However, comparing R&D spent only on pharmaceutical projects shows Roche spent $12.7bn in 2022 pushing it ahead of the previous year's pharma only leader, Pfizer (*see Exhibit 2*). Whilst Roche continues to invest heavily in its oncology portfolio part of its increasing spend on research is due to the company's efforts in gene therapies. Roche has been putting more R&D funding into the assets acquired as part of the 2019 takeover of Spark Therapeutics including treatments for both hemophilia A and B.

Pfizer had a standout year for spending – driven largely by its M&A spree.

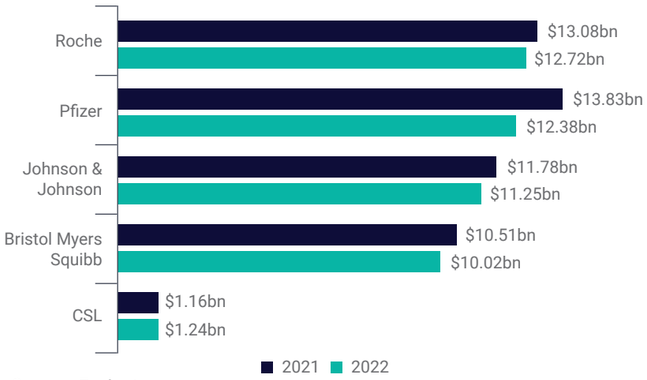
Pfizer has dialled back its research investment by roughly 10% compared to 2021 – now that COVID-19 spending is no longer a priority. However, that is not to say that the company has been resting on its pipeline. R&D spend is only one way to invest and restock.

Exhibit 1: Top Companies By 2022 R&D Spend



Source: Scrip 100

Exhibit 2: Top Companies By Pharma Only 2022 R&D Spend



Source: Evaluate

Exhibit 3 shows the top five spenders when company acquisitions as well as product deals are added to internal, organic, R&D spend.

Here we see that Pfizer has had a standout year for spending – driven largely by its M&A spree. Over the course of 2022 Pfizer spent just over $24bn on company takeouts including: an $11.6bn acquisition of migraine treatment developer Biohaven, the $6.7bn buy of Arena for its immuno-inflammatory portfolio, and the $5.4bn takeout of Global Blood Therapeutics to consolidate Pfizer's position in the sickle-cell anemia market. But Pfizer has not stopped there – the $43bn takeout of Seagen will almost certainly put them at the top of combined spenders in 2023. This surge in spending is not only fuelled by the revenue made by Comirnaty, Pfizer's COVID-19 vaccine, over the past couple of years but also by the hole that will be left in the company's sales line as the demand for the vaccine dwindles.

J&J also more than doubled its spend by following through with a plan to do more medtech M&A. This was in the form of the acquisition of heart-pump maker Abiomed for $16.6bn. The company's deal-making in pharma, however, remained far more restrained.

Whilst the addition of M&A and licensing upfront spend on top of R&D did little to change Roche's topline investment in new products it did alter the top five to include two new entries: Bristol Myers Squibb and CSL.

Although in raw R&D spend BMS came in narrowly behind AstraZeneca, its acquisition of Turning Point Therapeutics for $4.1bn pushed it into the top five overall. Turning Point was the latest in a string of bolt-on deals for BMS to bolster its oncology pipeline as the big pharma's marketed assets begin to age and Revlemid (lenalidomide) faces generic competition.

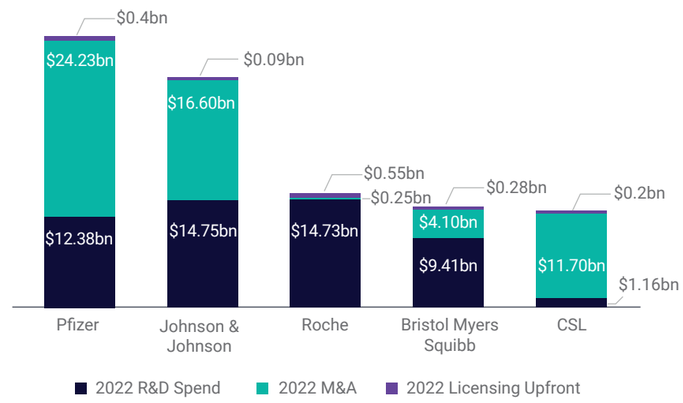
The only non-big pharma to feature in the analysis was CSL. The Australian company closed an $11.7bn deal for kidney disease specialist Vifor. This deal, an anomaly in its size for CSL, was seen as an attempt for the company – which is known for its blood products and vaccines business – to diversify its portfolio.

Exhibit 4 shows the recent product investment history for each of the top five companies by combined spend and reveals that 2022 was somewhat of an exceptional year for many of them.

Among the top five combined spenders Pfizer, Johnson & Johnson and particularly CSL had a year in which they exceeded usual spending habits. In each case this came from deal-making as R&D spend flatlined or fell across most of big pharma – with the exception of AstraZeneca and Sanofi – as the urgency of the pandemic fades. The historic chart also puts into perspective the size of Pfizer's 2022 haul as it is dwarfed by BMS's 2019 purchase of Celgene.

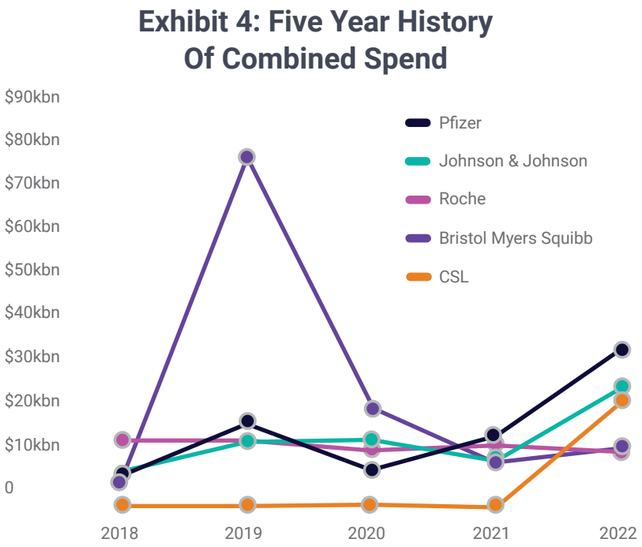
A reasonable question to ask, looking at the amount of money being spent on acquiring assets from outside sources, might be how much value is actually being derived from these deals versus organic assets? Exhibit 5 shows the combined net present value for the five companies split by the origin of the drugs. However, it should be mentioned that the products included in company acquisition or product deals are done so regardless of the stage at which they were acquired. So, a product bought whilst it was still preclinical then developed by the buyer would not be classed as organic.

Exhibit 3: Top Companies By Combined Spend



Source: Evaluate

Licensing values comprised of upfronts only



Source: Evaluate

CSL is the only company in the cohort to have the majority of its current forecast revenues deriving from organically originating assets. This is largely to be expected – as we have seen the company has not been, historically, a big dealmaker in the therapeutics space. Almost half of the company's total NPV is tied up in the immunoglobulin Hizentra.

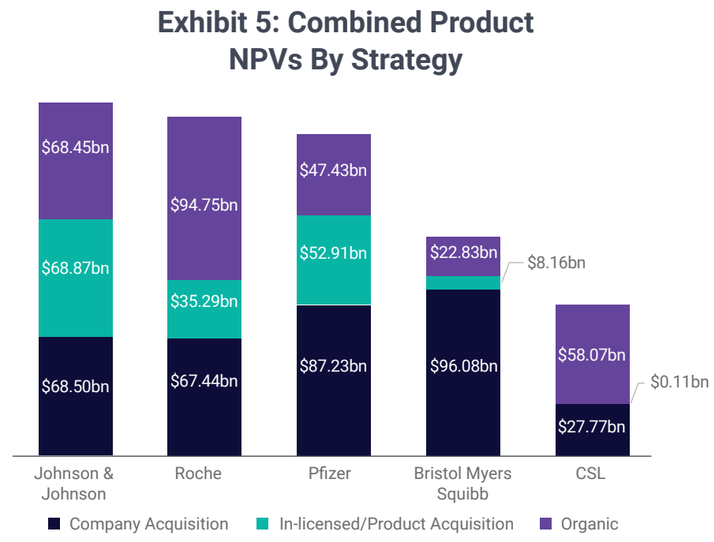
Roche has, very nearly, a fifty-fifty split of organic and non-organic value in its portfolio. Roche's top two forecast assets were both invented in-house: the wet age-related macular degeneration and macular oedema bispecific Vabysmo (faricimab-svoa), and the PD-L1 antibody Tecentriq (atezolizumab). Among the Swiss company's assets which have been brought in from outside sources is Ocrevus (ocrelizumab), which is forecast to be the third largest earner for Roche going forward, the licensing rights to which it acquired with the 2009 purchase of Genentech. The license to sell the hemophilia A drug Hemlibra outside of Japan, Korea and Taiwan – acquired from Chugai – has also proved lucrative for Roche and sits with an NPV of over $17bn.

J&J is unusual in that its largest forecast segment comes from products which have been licensed or individually acquired rather than from company acquisitions. $44bn of this in-licensed revenue is due to come from Darzalex (daratumumab). J&J licensed the CD-38 antibody from Genmab and the cancer treatment has since gain a very broad label. Carvykti (ciltacabtagene autoleucel), the CAR-T therapy, licensed from Legend Biotech in 2017 and launched in 2022 also makes up a substantial portion of this NPV.

Over three-quarters of BMS's NPV is forecast to be from assets which have been acquired through company takeouts. $38bn of this value is derived from Opdivo (nivolumab), which BMS acquired from Medarex in 2009. Other big-ticket drugs acquired though buyouts for BMS include: the factor Xa inhibitor Eliquis (apixaban) which was acquired with DuPont in 2001 and, more recently, the mega-merger with Celgene yielded products including Reblozyl (luspatercept) and Revlemid – although the latter of those drugs is now in decline.

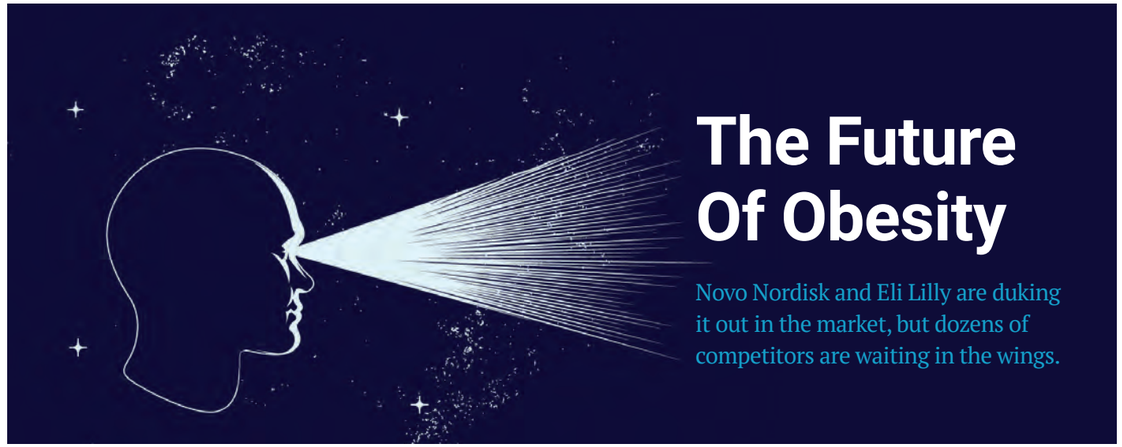
Although Pfizer's COVID franchise sales are waning Comirnaty and Paxlovid still represent the two greatest contributors to the company's NPV at present. Comirnaty was licensed from BioNTech whilst Paxlovid is an organic product. Paxlovid makes up around half of Pfizer's projected organically derived income with the other major contributors being the anti-bacterial Sulperazon (Cefoperazone/sulbactam) and the 2023 approvals of RSV vaccine Abrysvo and multiple myeloma treatment Elrexfio (elranatamab).

Of Pfizer's 2022 acquisitions Nurtec ODT, courtesy of Biohaven, and Etrasimod, gained from the purchase of Arena Therapeutics, add the most value to the projected sales. Whilst neither of these products hold a candle to Pfizer's current top-sellers, the acquisition of Seagen does promise some other drugs which hold larger forecasts. Most notably Padcev (enfortumab vedotin) and Adcetris (brentuximab vedotin) – which should add to Pfizer's potential gains in 2023 if the deal closes by year-end.



Source: Evaluate

Net Present Value (NPV) is the current perceived global value of a product over its remaining lifetime



The Future Of Obesity

Novo Nordisk and Eli Lilly are duking it out in the market, but dozens of competitors are waiting in the wings.

BY **ELIZABETH CAIRNS,** SENIOR WRITER

The recent approval of Eli Lilly & Co.'s Zepbound (tirzepatide) for obesity means two highly effective incretin drugs are now available for the disease. Lilly believes it can supply Zepbound in large quantities from the off, besting Novo Nordisk which has been unable to make Wegovy (semaglutide 2.4mg injection) in sufficient amounts to meet demand.

Novo has other advantages, notably the chance to get a cardiovascular protection claim on Wegovy's label on the basis of the SELECT trial, full data from which showed a sizeable reduction in the risk of death among patients with obesity and cardiovascular disease. But Novo is also ahead of Lilly when it comes to the chances of bringing new obesity products to market. Three formulations of semaglutide are in late-stage trials and Novo could remain the biggest name in obesity for years to come.

Which does not mean that there is not a great deal of competition. Majors like Pfizer Inc., Sanofi and Boehringer Ingelheim have obesity candidates in mid- or late-stage trials, and a variety of mechanisms beyond GLP-1 agonism – which underpins both Wegovy and Zepbound – are under evaluation.

The Next Big Things

Only one obesity candidate is known to be awaiting an approval decision: Tesomet (tesofensine), a neurotransmitter reuptake inhibitor developed by the Danish company Saniona. It has been filed in Mexico as a potential therapy for hypothalamic obesity, a rare condition in which excess weight is gained following an injury to the hypothalamus. The product is a curiosity but will not be anything like a serious competitor to Novo and Lilly's drugs.

And those two players are set to entrench their positions as the leading groups in obesity with forthcoming data readouts. Next year will see Phase III trials data emerge on two crucial variations on the semaglutide theme.

Wegovy is available as a weekly injected dose of 2.4mg – this is a contrast to semaglutide's use in diabetes, where it is approved as a weekly 1mg jab under the name Ozempic. Novo is pursuing a higher dose still, with a pivotal trial of a 7.2mg dose set to yield data by the end of the year. The aim of the STEP UP trial is to improve weight loss over the 12.5% Wegovy managed in its pivotal trial, STEP 1, without increasing toxicity.

Added to the results of the SELECT trial, which could boost Wegovy uptake in patients with cardiovascular risk factors, STEP UP could further expand the reach of the drug, which is expected to sell more than $4bn in 2023.

Another readout is due next year that could be even more commercially significant for Novo. OASIS-4, the final approval trial of the oral formulation of semaglutide in obesity, will report. This formulation is already on the market as Rybelsus for diabetes, and anecdotal evidence suggests that it is already being used off-label for obesity.

Meanwhile Lilly has decided against developing an oral form of Zepbound, and the reasons for this are unclear; perhaps the company has had difficulty reformulating it, or maybe the dose that would be required might mean unmanageable side effects. Instead it has developed a different incretin, orforglipron, whose Phase III program could generate data in 2025.

Bill Coyle, global head of biopharma at the consultancy ZS, believes that obesity pills could see strong sales – eventually.

"The Wegovys and the [Zepbounds] have pretty dramatic results in terms of weight loss. One could imagine for a patient who is heavier, or has been struggling longer with obesity, perhaps [injections are] the right first move, but perhaps they could switch to an oral over time," he says.

But he says there will also, eventually, be direct competition. Some patients will want to avoid needles, whereas others might prefer to avoid a daily pill, opting for the more certain compliance a weekly shot affords.

For now, patient choice is not really a factor. The demand for these powerful weight loss drugs exceeds supply, and many patients are clamoring for therapy regardless of whether it comes in a syringe or a blister pack.

Pills might also be preferable in less developed markets, Coyle said, since the packaging is less delicate and the supply chain simpler. Wegovy syringes must be kept refrigerated, whereas Rybelsus, and Novo's similar version for obesity, is stable at room temperature.

One of the most keenly watched Phase III assets is Lilly's retatrutide. This combines three different mechanisms: the GLP-1 and GIP agonism used by Zepbound, plus glucagon agonism. Retatrutide's results in Phase II were the strongest ever seen for a mid- or late-stage obesity drug, the 22.1% weight loss drawing audible gasps from the audience when the data were presented at the American Diabetes Association's annual meeting in Spring 2023.

Its Phase III trials ought to read out in 2026, and it is fair to say that expectations are very high indeed.

It is worth noting that the only non-incretin at the Phase III stage is, like Tesomet, only intended for a narrow use. Rhythm Pharmaceuticals' melanocortin-4 agonist Imcivree (setmelanotide) is already approved in the US and Europe in patients older than six years with obesity caused by mutations in the POMC, PCSK1 and LEPR genes, as well as in patients with Bardet-Biedl syndrome, another rare disorder that can cause obesity.

Rhythm is seeking to expand into hypothalamic obesity, and its 120 patient Phase III study in this disorder could read out in 2025 (*see Exhibit 1*).

Exhibit 1: The Late-Stage Obesity Pipeline

Product	Company	Mechanism	Route	Status
Filed				
Tesomet (tesofensine)	Saniona	Serotonin, norepinephrine and dopamine reuptake inhibitor	Oral	Awaiting approval in Mexico for hypothalamic obesity
Phase III				
Rybelsus (oral semaglutide)	Novo Nordisk	GLP-1 agonist	Oral	50mg dose caused 15.1% weight loss in Phase III OASIS-1 trial; OASIS-4 25mg dose data due H1 2024
High-dose semaglutide	Novo Nordisk	GLP-1 agonist	Subcutaneous	STEP UP trial of 7.2mg dose in 1,407 patients could report late 2024
Mazdutide (IBI-362)	Innovent Biologics/ Eli Lilly	Glucagon agonist; GLP-1 agonist	Subcutaneous	Phase III trial in 600 patients could report 2024
Cagrisema (cagrilintide + semaglutide)	Novo Nordisk	Amylin receptor agonist + GLP-1 agonist	Subcutaneous	In four Phase III trials; first data could come 2025
Orforglipron	Eli Lilly/Chugai Pharmaceutical	GLP-1 agonist	Oral	In three Phase III trials (ATTAIN-1, -2 and -J); data could come 2025
Ecnoglutide (XW003)	Sanofi/Sciwind Biosciences	GLP-1 agonist	Subcutaneous	Phase III SLIMMER trial in 664 patients could report 2025
Imcivree (setmelanotide)	Rhythm Pharmaceuticals	Melanocortin-4 agonist	Subcutaneous	Phase III trial in 120 patients with hypothalamic obesity could report 2025
Survodutide	Boehringer Ingelheim/ Zealand Pharma	Glucagon agonist; GLP-1 agonist	Subcutaneous	In three Phase III trials (SYNCHRONIZE-1, -2 AND -CVOT); data could come 2026
Retatrutide (LY3437943)	Eli Lilly	GIP agonist; Glucagon agonist; GLP-1 agonist	Subcutaneous	In four Phase III trials (TRIUMPH1-4); data could come 2026

Source: Evaluate Pharma; Biomedtracker

More Variation

The Phase II pipeline contains a wider variety of mechanistic approaches than the later-stage list. Lilly, for example, has the activin type II A and B inhibitor bimagrumab which it obtained via its acquisition of Versanis Bio in July 2023. A Versanis-originated Phase II trial, BELIEVE, is testing bimagrumab alone and in combination with Wegovy (*see Exhibit 2*).

Novo is also playing in the non-incretin space. NN9775 is an analogue of neuropeptide Y, a hormone that regulates appetite. A Phase II trial in combination with Wegovy concluded last year, but no results have been released, and Novo's development plans are unclear.

However, it has another shot on goal with the cannabinoid receptor type 1 inverse agonist INV-202, which it got when it bought Inversago Pharma in August 2023. But there is a precedent for this pharmacology that is not quite ideal; Sanofi's CB1 blocker rimonabant was approved in the EU for obesity as Acomplia, but was withdrawn from market in 2009 after it was linked with depressive disorders, mood alterations and suicidal ideation. Inversago claims INV-202 is safer than its mechanistic forerunner.

That said, incretins are still represented here. Pfizer is going the oral route with danuglipron, and could release mid-stage data before the end of 2023. The US major has been quiet about the asset recently, failing to mention it at all in its Q3 press release or prepared remarks, leading some to deduce that the data might disappoint.

And Altimmune's pemvidutide showed itself to be effective in the Phase II MOMENTUM trial, but worryingly toxic, with high dropout rates. Further data will come by the end of the year and will be scrutinized closely.

For now, drugs based on the two main incretins – GLP-1 and GIP – carry far greater expectations than therapies that use different mechanisms. The fact that the only non-incretins in late-stage development are intended for rare forms of obesity reflects this.

There is still one lingering question about the frontrunners, Wegovy and Zepbound, however: will they work safely over the very long term? It is already known that when patients who lose weight with these drugs come off therapy, they regain that weight. What is not yet known is whether they can resume incretin treatment and lose weight once more – and if they can do this without harm.

The obesity space is at a very exciting point and new developments are coming thick and fast. And it is by no means a mature market. If the safety of therapies like Wegovy and Zepbound remains manageable long-term, Coyle can see a future 15 or 20 years hence when these drugs, and others like them, are used as widely as statins, for example, are now.

Exhibit 2: The Mid-Stage Obesity Pipeline

Product	Company	Mechanism	Route	Status
Bimagrumab	Eli Lilly	Activin receptor 2a blocker	Subcutaneous	Phase IIb BELIEVE trial in 495 patients, alone and in combination with semaglutide, could report 2025
M1Pram	Adocia/Sanofi	Amylin agonist; insulin agonist	Subcutaneous	Phase II trial in 40 patients completed 2022
NN9775 (PYY1875)	Novo Nordisk	Neuropeptide Y agonist	Subcutaneous	Phase II trial in 119 patients completed 2022
Pemvidutide	Altimmune	Glucagon agonist; GLP-1 agonist	Subcutaneous	Phase II MOMENTUM trial hit in Mar 2023 but with high discontinuations; further data due 2023
Danuglipron	Pfizer	GLP-1 agonist	Oral	Phase II trial in 630 patients could report 2023
EMP16	Empros Pharma	Alpha-glucosidase inhibitor; lipase inhibitor	Oral	Phase II trial in 320 patients, in combination with Alli, could report 2024
INV-202	Inversago Pharma/ Novo Nordisk	Cannabinoid receptor type 1 inverse agonist	Oral	Phase II trial in 100 patients could report 2024
S-309309	Shionogi	Monoacylglycerol acyltransferase 2 inhibitor	Oral	Phase II trial in 320 patients could report 2024
APH-012	Aphaia Pharma	Glucose	Oral	Phase II trial in 150 patients could report 2024
ZP7570	Zealand Pharma	GLP-1 agonist; GLP-2 agonist	Subcutaneous	Phase II DREAM trial in 54 patients could report mid-2024
APHD-012	Aphaia Pharma	Jejunal-release dextrose	Oral	Phase II trial in 174 patients could report mid-2024
HRS9531	Jiangsu Hengrui Pharmaceuticals	GIP agonist; GLP-1 agonist	Subcutaneous	Two Phase II trials in a total of 309 patients could report mid-2024
VK2735	Viking Therapeutics	GIP agonist; GLP-1 agonist	Subcutaneous	Phase II VENTURE trial in 125 patients could report mid-2024
AMG 133	Amgen	GIP antagonist; GLP-1 agonist	Subcutaneous	Phase II trial in 570 patients could report late 2024
HU6	Rivus Pharmaceuticals	Unclassified	Oral	Two Phase II trials in a total of 328 patients in patients with obesity and type 2 diabetes; first data could come in late 2024
K-757 and K-833	Kallyope	Nutrient receptor agonists	Oral	Phase II trial in 150 patients could report late 2024
GSBR-1290	Structure Therapeutics	GLP-1 agonist	Oral	Phase I/II trial in 118 patients could report early 2024

Source: Evaluate Pharma; Biomedtracker

BY **HEIDI CHEN,** ASSOCIATE DIRECTOR, RESEARCH & COMM SUPPORT

The Clinical Trials Landscape

In a post-pandemic world, the evolving landscape of clinical trials just got more complex. The year 2022 was one of many adjustments given the incidence of lower trial initiations. The health care industry endured the impacts of geopolitical conflicts, curbed growth in China and stagflation in major markets.

Citeline's latest Clinical Trials Roundup provides an overview of the Phase I-III clinical trials initiated in the prior calendar year (2022) across all therapeutic areas comprehensively covered by Trialtrove, as well as in-depth analyses into the key diseases and geographies.

As of 26 June 2023, Trialtrove curated 9,104 Phase I-III clinical trials (*see Exhibit 1*) investigating at least one drug and with a disclosed start date within the calendar year of 2022. This marks a decline of 12.5%, breaking the upward trend of clinical trial counts for the first time since 2016.

The clinical trial landscape slightly changes when taking a closer look at industry-sponsored trials, which may better represent the current health of the pharmaceutical industry. In 2022, industry-sponsored trials (*see Exhibit 2*) decreased by 7% overall, but if we exclude COVID-19 trials, this reduces to a 4% decline, reflecting the industry's survival mode since 2021.

Exhibit 2 also supports a trending departure of COVID-19 trials research by industry sponsors in 2021 (619 trials) and 2022 (344 trials). Companies such as Roche and Novartis have shifted their focus away from COVID-19 over the last two years, while Pfizer held on like a long-distance champion in this arena. The exclusion of COVID-19 trial count is a way to minimize the COVID effect on the trials landscape, providing a surrogate health check on clinical research. The decrease in trial numbers in 2022 demonstrated a more restrained and cautious environment for clinical research, guided by a complex myriad of factors: the global economy, legislation and overall political climate.

Exhibit 1: Clinical Trial Activity By Volume And Growth

Year Of Trial Initiation	2022	2021	2020	2019	2018	2017	2016
Trial count	9,104	10,410	9,819	7,765	7,606	6,794	6,067
Year-on-year growth (%)	-12.5%	6%	26%	2%	12%	12%	N/A
Trial count (excluding COVID-19 trials)	8,541	9,077	7,424	7,765	7,606	6,794	6,067
Year-on-year growth (excluding COVID-19 trials, %)	-6%	22%	-4%	2%	12%	12%	N/A

Exhibit 2: Industry-Sponsored Trials

Year Of Trial Initiation	2022	2021	2020*	2019*	2018*	2017*	2016*
Industry-sponsored trials	6,151	6,646	6,542	6,211	6,127	5,684	5,089
Year-on-year growth (%)	-7%	2%	5%	1%	8%	12%	N/A
Industry-sponsored trials (excluding COVID-19 trials)	5,807	6,027	5,709	6,202			
Year-on-year growth (excluding COVID-19 trials, %)	-4%	6%	-8%	N/A			

Source: Trialtrove, June 2023
** Data accessed August 2023*

Clinical Trial Activity By Therapeutic Area

The ranking of therapeutic areas by trial initiations in 2022 remained the same as in prior years, albeit most therapeutic areas (TAs) saw a modest decrease in trial counts (*see Exhibit 3*). Infectious disease had a dramatic rise to second place when its trial initiations rose from 760 trials in 2019 to 3,053 trials in 2020, largely contributed by COVID-19 trials. While the pandemic persisted through 2021, the number of ID trial initiations dropped to 2,771 trials, and further decreased to 1,711 (-38%) in 2022, closing the gap of its lead over central nervous system (CNS) trials.

Oncology continued to be the top-ranking TA with a clear lead, even though its trial initiations were down by 10%. The cardiovascular TA experienced a 15% decrease of trial initiations in 2022, while other TAs such as metabolic/endocrinology, autoimmune/inflammation, ophthalmology and CNS held on to their 2021 rebound and saw a smaller reduction ranging between 1% and 3%. Genitourinary is the only TA with growth, posting a 4% rise in 2022.

Top Diseases

Each year Citeline analyzes the top 10 diseases for clinical trial activities to get a glimpse of where research efforts are taking place. After a two-year reign, COVID-19 finally gave up its number one spot back to an oncology disease (unspecified solid tumor, 566 trials), though it continues to exert its presence in a close second place (563 trials). Clearly, the pandemic disruptions to clinical trials have subsided. The makeup of the top 10 diseases has been consistent for several years, with some slight ranking shifts.

Cancer makes up half of the top 10 chart and four out of five diseases within the top five: unspecified solid tumor, non-small cell lung cancer (NSCLC), breast cancer, and non-Hodgkin's lymphoma (NHL). The COVID-19 trials clearly had a major cut from 1,333 (13%) in 2021 to 563 (6%) in 2022. However, the phase distribution of COVID-19 trials in 2022 is more evenly distributed between Phases I, II and III, as opposed to the inflated Phase II trial numbers seen in prior years.

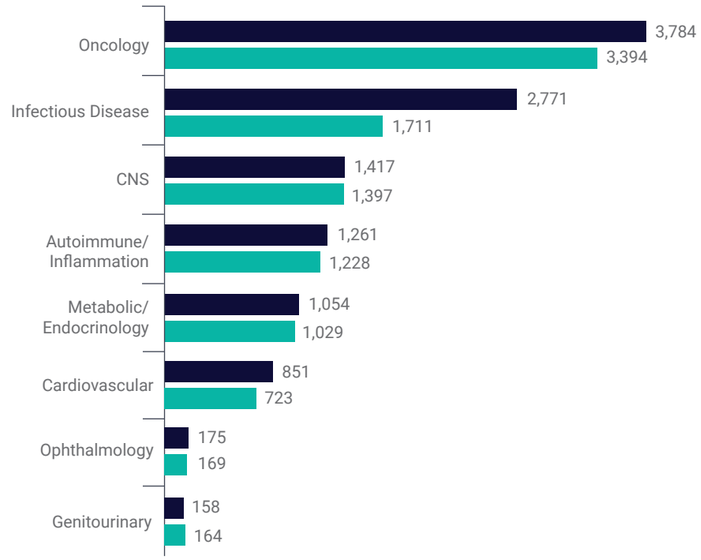
Respiratory vaccines and respiratory infections were the other two indications that rode the wave with the COVID-19 trials, but their numbers also took a dive and moved down the ranks in 2022. Head and neck cancer dropped off the top 10, making way for pain (nociceptive) to rejoin the fold as number 10. Most of the other top diseases had a modest reduction of trial initiations, though their proportion with respect to total trials barely changed. Type 2 diabetes is the disease within the top 10 that had the highest increase in trial initiations, exhibiting rising activity in early-phase development.

The steady upward trend of rare disease R&D also suffered a setback in 2022, with 13% fewer trial initiations than the previous year, wiping away the post-pandemic rebound observed in 2021.

The receding trial initiations in 2022 no doubt impact rare disease trials. The nature of rare disease research inherently faces tougher challenges, as most conditions are debilitating or fatal, particularly in pediatrics. Due to a limited patient pool for rare diseases, clinical trials often had to expand recruitment to multiple countries for suitable patients, resulting in longer trial timelines and higher expenditure. The depressed economic climate for biopharma in 2022 also accentuated the challenges further.

Historically, oncology indications have dominated the rare disease landscape, and 2022 is no different. NHL continues to be the most studied rare disease, while other indications experienced minor decreases in trial counts. Only head and neck and liver cancer experienced notably fewer trial starts in 2022. Outside oncology, the top three rare indications in 2022 were the same as in the previous year: amyotrophic lateral sclerosis (35 trials), tuberculosis (33 trials), and sickle cell disease (28 trials).

Exhibit 3: Clinical Trial Initiations By Therapeutic Area



Source: Trialtrove, June 2023

Geographic Survey Of Trial Activity

China retained its lead in trial initiations with 3,405 trials (vs. 3,795 trials in 2021), with the US in a close second at 2,876 trials (vs. 3,310 trials in 2021). In 2022, we observed a downward trend in trial starts across all regions, with the sharpest decline in Asia (-12%). We have not yet seen the impact of pain points with the new EU Clinical Trials Information System (CTIS) on trial initiations, as that was only made mandatory by the European Medicines Agency (EMA) Clinical Trials Regulation on 31 January 2023. Although frustrations were heard loud and clear as sponsors struggled with CTIS earlier this year, it would be premature to project how this episode might interfere with trial activities in 2023 and the implications this may have on regional differences.

All countries had fewer trials in 2022, reflecting a shared trend of lower trial volume all around.

Ukraine suffered the biggest loss of trial initiations (-154%) due to displacements of trial subjects, and clinical trials in Russia also plunged by 86% compared to 2021. The lack of stability caused by the war extended to Poland and Hungary, where clinical trials went down by 35% and 34%, respectively. Both Poland and Ukraine were considered as up-and-coming locations for clinical trials in recent years. One can expect the low numbers of clinical trials in these regions to continue in 2023 as there has been no sign of armistice.

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The Growing Pains Of Chinese Biotech

The emergence of China from API manufacturer to an innovation leader, fuelled by domestic investments and home-grown talent, has been one of the most remarkable trends of the last decade.

BY **TIMOTHY PANG,** MANAGING VP

BY **DANIEL CHANCELLOR,** DIRECTOR OF THOUGHT LEADERSHIP AND CONSULTING

Around one quarter of active drug development now has a Chinese origin, with particular emphasis in biologics, cell therapies and cancer R&D. While the appetite for these assets among multinational pharmaceutical companies remains strong, the financing crunch that is throttling investment into start-ups is being felt particularly keenly in China. In such a landscape, domestic biotech companies will need to prioritize reliable near-term revenue streams while keeping global ambitions in mind. A domestic Amgen- or Regeneron-like success story may yet be inevitable, although steady progress is far more likely than a sudden growth spurt.

Having broken through the 20,000 mark in 2022, the global biopharma pipeline has continued to grow and now totals more than 22,000 assets under active development. In recent years, while the pace of expansion has moderated in Western markets, China has dramatically increased its R&D footprint.

As shown in Exhibit 1, there are now around 5,000 drugs under active development by China headquartered companies, part of an ecosystem of around 1,700 drug developers. Remarkably, it was only five years ago that Chinese companies collectively possessed just 1,000 drug programs, and 10 years ago the figure was a mere 200. This growth spurt over the last decade has resulted in Chinese companies now laying claim to around one quarter of all global R&D.

Among the totals, China possesses clear strengths in biologics, cell therapies and cancer drug development. In each of these three hot growth areas for research, China has a larger-than-expected footprint. This does not come at the expense of overall diversity, with the presence of emerging domestic gene and RNA therapy platforms and large numbers of clinical trials across the spectrum of therapeutic areas and diseases.

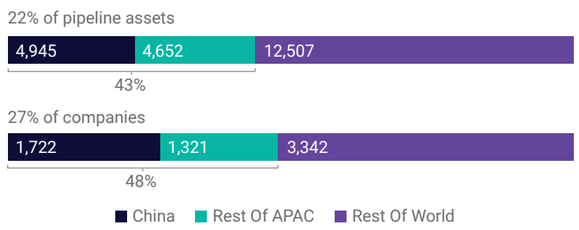
Alliances In Vogue

This engine for new drug creation has allowed the capture of domestic market share, but also attracted the attention of multinational pharmas. Particularly for validated drug classes, Chinese biotechs have been quick to create their own versions using platform technologies. The classic example is in the programmed cell death protein 1/ligand 1 (PD-1/L1) market, where the total now stands at 12 approved China-originated monoclonal antibodies. This pattern is also being played out across a multitude of drug targets, even for those that are still in the developmental stage. Over half of the anti-TIGIT pipeline is Chinese, while home-grown biotechs are often leading the developmental effort for new chimeric antigen receptor (CAR) T-cell designs.

These assets are highly attractive for multinational pharmas that are looking to license their way into emerging drug classes. Exhibit 2 shows the number (line) and value (bars) of such alliances, split by upfront payments and potential milestones. Each year, Chinese biotechs are securing around $2-3bn in upfront fees and milestones of up to $30bn, in addition to any separate financing or product revenue streams. While there has been a slight drop from the peaks of 2021, perhaps relating to the regulatory realities of commercializing assets without US-based trials, demand is still robust.

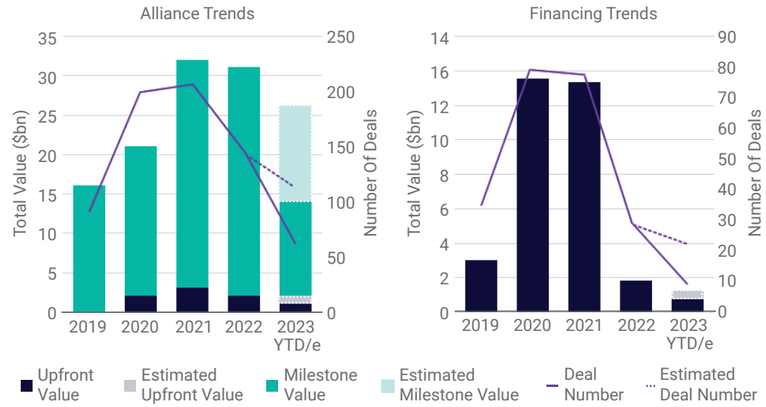
These alliances are even more important to Chinese biotech firms considering the throttling of external investment over the last 18 months. While the biotech downturn has been apparent globally, its effects have been felt keenly in China. Financing peaked in 2020 and 2021 with around $13bn raised in total, although this plummeted to just $2bn in 2022, and 2023 may finish even lower. For the many clinical-stage, pre-revenue biotechs, the stark drop in the capital markets leaves growth ambitions on hold.

Exhibit 1: Chinese Share Of Global R&D



Source: Citeline; Pharmaprojects

Exhibit 2: Chinese Biopharma Deal-Making Trends Since 2019



Source: Citeline; Biomedtracker

Near-Term Challenges

This short-term pressure leaves many forced to consider strategic countermeasures in order to preserve cash runways and chart a path to market for lead assets. Most immediately, those without revenue streams must recalibrate business operations and R&D expenses to bridge the downturn. On the costs side, this can include scaling back of pipelines and headcount, while capital expenditure can be deferred. Short-term funding solutions are also essential, such as scaling alliance structures in a way that eschews milestone payouts in favor of immediate cashflow. Hutchmed recently secured a $400m upfront from Takeda for a vascular endothelial growth factor (VEGF) antibody, while Akeso negotiated $500m upfront as part of a $5bn potential deal with Summit for its PD-1/VEGF bispecific antibody. Companies that have already licensed assets can consider converting milestones and long-term revenue potential with non-traditional investors such as royalty purchasers.

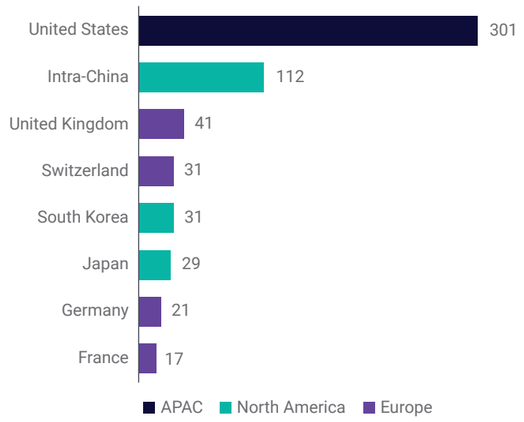
Considering the strength of the local pipeline, there will also be a tremendous amount of value to be made within China's own borders. Indeed, around 16% of alliances signed by Chinese companies since 2019 have involved the exchange of technologies or developmental rights with a domestic partner (*see Exhibit 3*). Companies that are already at the commercial stage can source complementary assets to build a comprehensive portfolio and grow revenues within the China market itself. From this starting point, domestic consumption has the potential to act as a foundation for stable growth. In time, this will allow the development of commercial capabilities in international markets – perhaps the ultimate endgame for the globalization of the Chinese pharma industry.

Rome Wasn't Built In A Day

All of the ingredients are present for the next world-leading biotech company to emerge out of China. This is undoubtedly happening in other high-tech industries, although the slower-moving and highly regulated nature of pharmaceuticals means that patience is required. Coupled with the near-term funding challenges, we are unlikely to see a break-out within the next few years. That said, with the scale of innovation taking place in China, and the vast revenue potential on offer as health care expenditure grows, such a breakthrough would appear to be inevitable. While running hard for the finish line, it remains important for Chinese and other firms to embrace a steady growth trajectory and invest within a company's means, and within its own borders. Solid business fundamentals will enable Chinese companies to develop and retain the next generation of therapeutic breakthroughs.

US companies have captured much of the value of checkpoint inhibitors, while Europe will be able to ride the GLP-1 wave. Perhaps it will be Chinese biotechs that will unlock the commercial potential of cellular or genetic therapies at scale over the next several years.

Exhibit 3: Top Partner Location For Chinese Alliances



Source: Citeline; Biomedtracker

WORLD VIEW

Latin America And Caribbean Move Towards Creating A New Regional Regulator

BY **FRANCESCA BRUCE,** SENIOR WRITER

Industry support for a new regional regulator for Latin America and the Caribbean is cautious and experts warn that it could harm competitiveness of the region.

Countries from Latin America and the Caribbean have this year formally started talks on creating a new regional medicines and devices regulator. The initiative has the potential to bring benefits for companies and patients, including reduced regulatory burden, an easier route to market and increased safety, quality and efficacy for products. However, experts warn that it could harm competitiveness of the region with increased bureaucracy and costs if the initiative is poorly managed.

Cofepris, Invima and Cecmed, regulators from Mexico, Colombia and Cuba respectively, formalized talks for a new Latin American and Caribbean Medicines Agency (AMLAC) in April 2023 when they signed the Acapulco Declaration. Alejandro Svarch Pérez, director of Cofepris, described the declaration as a "major milestone" in the path to establishing a new regulator.

The signing followed proposals tabled in January at a summit of the Heads of State and Government of the Community of Latin American and Caribbean States. According to the proposals, a new regulatory agency would work towards:

- regulatory convergence and mutual recognition of authorizations to guarantee effective access to health products and supplies;
- stimulating and enabling R&D of innovative products and provide regulatory certainty throughout the region;
- supporting local production and integration of local supply chains; and
- exploring public procurement mechanisms for medicines to guarantee access and sustainable financing. These would prioritize "self-sufficiency," such as contracts with regional manufacturers.

Bolivia, Dominica, Ecuador, El Salvador, Honduras, Jamaica, and the Dominican Republic have expressed support for a new agency. Most recently, Argentina, Brazil and Chile, entered the discussions in July. Regulators in Argentina and Brazil are two of the region's most developed regulatory agencies.

However, there has been some doubt over whether Brazil will officially join the potential new agency. The country has already taken steps to strengthen its regulator, Anvisa, and may therefore have different priorities or concerns relating to participating in a regional regulatory agency, explained Bruna Rocha, a partner at the law firm Campos Mello Advogados Life Sciences, Healthcare and Cannabis in Latin America.

Model

There is so far little detail on how the new agency will take shape. However, Fifarma, the Latin American Federation of the Pharmaceutical Industry, has expressed cautious support for a new agency. A regional regulator would be "desirable and necessary" if it aims to strengthen regulatory systems and pursue the harmonization and convergence of regional regulatory frameworks and align them with international regulations, it commented.

A regulatory model based on the European Medicines Agency (EMA) would be preferable, the federation added. "From our experience in Latin America and the Caribbean, this is the most desirable approach to increasing the regulatory level in the region," it said.

Some markets in the region already consider EMA rules as a reference for implementing their own guidance and standards, pointed out Pharmalex, a pharmaceutical and biotech consultancy.

"Drawing inspiration [from the agency] could be desirable [because it has] a track record of harmonizing regulations and ensuring access to safe and effective medicines," said Rocha. Whether it is a suitable model for Latin America and the Caribbean will depend on regional needs.

Priorities And Benefits

Among the priorities the agency should focus on, according to Fifarma, is a centralized authorization process that cuts the timelines for granting access to innovative medicines. For example, the EU operates a system where a company can secure authorization in all EU member states through a centralized authorization evaluated by the EMA.

Fifarma would also like to see the agency focus on improving work-sharing between regulators, and improved pharmacovigilance and patient safety activities.

Rocha also thinks centralized approvals, along with harmonized regulations, should be a priority for the agency. "Centralized approvals can streamline the process for granting access to innovative medicines, which is especially important during health emergencies." Harmonized regulations could also cut complexity, improve cooperation between national authorities and "create a more cohesive regulatory landscape," she said. However, she noted that there will be hurdles to clear, particularly when it comes to centralized authorizations owing to "national sovereignty considerations."

A new agency could also benefit industry if the agency pursues standardized requirements for clinical trials, labeling and packaging as well as post-marketing surveillance, added Pharmalex.

Risks

On the other hand, a new regional regulator could bring risk for industry. Poorly-managed harmonization processes could increase regulatory complexity, warned Rocha. Overly stringent or costly requirements may also impact the region's competitiveness. "Industry players will need to adapt to the new regulatory landscape and ensure compliance with AMLAC's standards, which could involve adjustments to their business practices," she said.

Pharmalex, also noted that a regional regulator could "become overly bureaucratic" and stifle innovation if it imposed "excessively burdensome requirements." Compliance with regional regulations may mean added costs and resources for companies, including hiring new staff to manage regulatory processes and conduct additional tests, it commented.

The new regulator will have to balance regional harmonization with the unique needs of each participating country. Open collaboration and communications across member states, regulatory bodies and industry will be crucial, said Rocha.

Engagement with industry will be key to the initiative's success, she said. "It is common practice in the development of regulatory agencies to involve industry stakeholders. Inclusion of industry input can help ensure that the agency's regulations and processes align with industry practices while maintaining a focus on safety and efficacy. That is why I'm of the view that once the initiative matures, industry involvement is likely."

Industry should be "deeply involved" in any discussions on creating a new regulator in the region, said Pharmalex. However, it cautioned that industry input must be balanced with "the interests of other stakeholders," including governments, health care professionals and patients.

Although industry has "valuable expertise and knowledge" of drug development, manufacturing and distribution, it also has "a commercial interest in the regulation of pharmaceutical products," which means their involvement must not "undermine public health and safety or compromise the independence of the regulatory authority," advised Pharmalex.

Fifarma said earlier this year that it has offered technical support to authorities in Mexico and Colombia with regard to setting up the new agency. However, it has not yet been invited to contribute to the initiative.

Timeline

As yet, no time line for the regulator has been issued, though it will likely take several years before it becomes operational. Rocha pointed out that creating a regulatory agency involves numerous processes, including developing legal and institutional frameworks, recruiting staff, harmonizing regulations and striking agreements among participating countries.

"Ensuring cooperation and alignment among member states will be a significant challenge." Differences in national interests, regulatory frameworks and legal systems could lead to areas of disagreement and legal barriers, she commented. "Countries may have different views on issues like intellectual property, data protection and decision-making processes within the agency."

Fifarma also warned that it may also be challenging to get the new agency off the ground and ensure that all regional authorities were on board. It could be difficult for them to reach a "consensus about the key elements for the constitution of a regional agency. For example, [there could be discrepancies involving] the legal basis, the status of independence and sovereignty of the national authorities, the essential activities to be handled, financing and economic resources and the drafting of regional sanitary regulation and guidelines," it said.

Status Quo

Latin American markets currently have their own regulatory health authorities. Some countries have their own dedicated regulators, while in other countries health ministries are responsible for certain activities, including regulatory approval and post-marketing surveillance.

Regulatory consultants at Pharmalex point out that the Pan American Health Organization (PAHO) offers these authorities technical support and promotes regional cooperation and harmonization. Regional efforts to strengthen regulatory cooperation have been made, for instance, through the Southern Common Market (MERCOSUR) and the Andean Community. "These organizations have established mechanisms for harmonizing regulatory requirements and procedures for medicines. However, no relevant benefits have been implemented in terms of regulatory harmonization and each country involved with the initiative continues to have their own requirements," said Pharmalex.

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