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Outlook 2024: Biopharma Embraces New Markets And New Tech

by Lucie Ellis-Taitt

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?

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.

Exhibit 1. 2024 Drivers And Brakes

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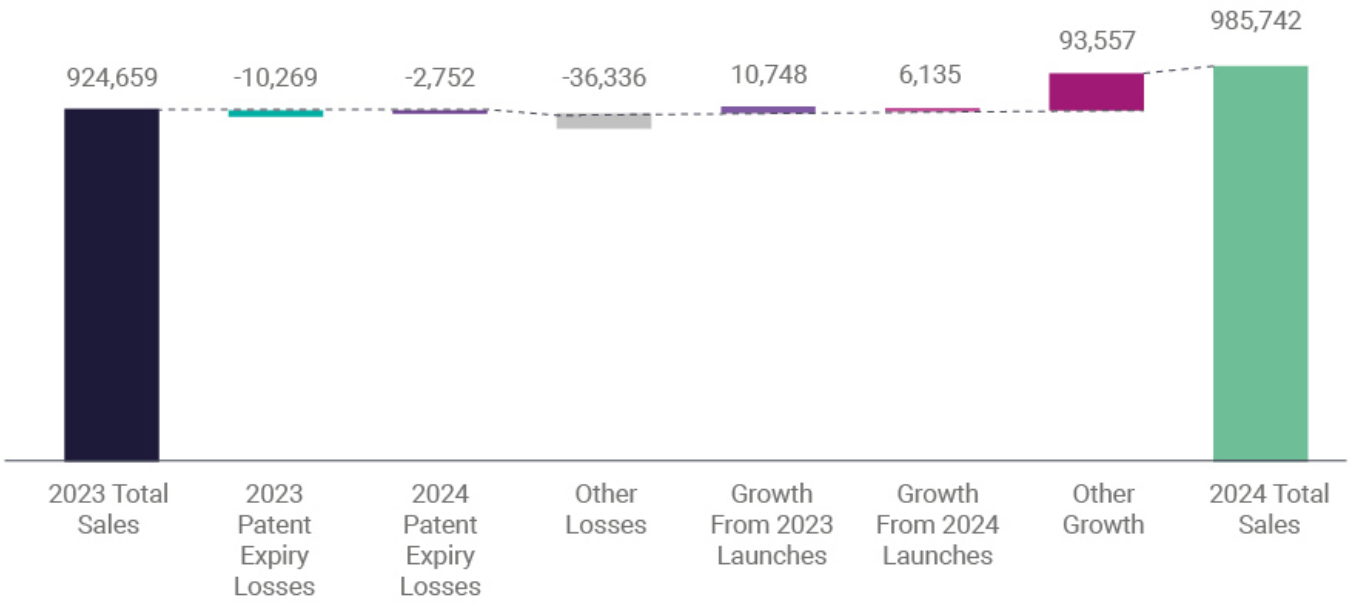

Source: Evaluate Pharma

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 dealmaking 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 SA*'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."

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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.

In the first half of 2023, sales of *Novo Nordisk A/S*'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. (Also see "*A Cardio Comeback: CV Market Back In The Spotlight*" - In Vivo, 11 Oct, 2023.)

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.

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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.

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The landmark, yet controversial, US approval of *Biogen, Inc.* and *Eisai Co., Ltd.*'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 and Company*'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

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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 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).

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., Inc.*'s Keytruda (pembrolizumab) plus *Seagen Inc.* '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

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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 see "*ESMO 23: Pluvicto Fulfils Promise For Prostate Cancer Label Expansion*" - Scrip, 18 Oct, 2023.)

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*.

Other late-stage oncology trial data readouts to watch for in H1 2024:

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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.

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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 Inc.*/*BioNTech SE*'s Comirnaty and *Moderna, Inc.*'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."
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.

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Looking ahead into the first half of 2024, *AstraZeneca PLC* 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;

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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.

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."

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