Biopharmaceutical Sector

Weekly Update – September 18, 2023

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Recent issues in case you missed and want to read:
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Join Us at These Upcoming Events

1

Biotech Hangout held its latest event on September 15th.

The next event will be on September 22, 2023.

Please join us.

To Learn More
https://www.biotechhangout.com/

2

SACHS ASSOCIATES

Basel | September 20-21, 2023 (Movenpick Hotel)

23RD ANNUAL BIOTECH IN EUROPE FORUM

The conference will feature more than 15 hours of high-level keynotes and panel discussions. In addition, there will be a global company showcase of 60+ presentations by established public, private, emerging and seed companies, offering innovative solutions and seeking investment and partnering opportunities.

To Learn More
https://www.sachsforum.com/23bef-about.html

3

biofuture™

New York City | October 4-6, 2023

Innovators & Investors Come Together to Shape the Future of Healthcare

At this year's summit, BioFuture attendees will be exploring the exciting mashup between rapidly evolving fields including biopharma, digital medicine, big data, AI, healthcare systems, payors, and more. The coming decade will dramatically accelerate the transformation of the healthcare ecosystem. Be part of the discussions that will shape and transform the future of healthcare.

To Learn More
https://biofuture.com/

Macro Update

Despite Rising Gas Prices, Americans Feel More Optimistic About Inflation's Future

Brian Mena, CNN, Sep 15, 2023 (excerpt)

Rising gas prices haven't taken their toll on the American consumer just yet, amid growing optimism that inflation is easing, according to the latest consumer sentiment survey from the University of Michigan.

The university's latest consumer survey released Friday showed that Americans' expectation of inflation rates in the year ahead fell to a 3.1% rate in September, down from 3.5% in the prior month, marking "the lowest since March 2021 and just above the 2.3-3.0% range seen in the two years prior to the pandemic," according to a statement.

Meanwhile, inflation expectations in the next five to 10 years dropped to a 2.7% rate, "falling below the narrow 2.9-3.1% range for only the second time in the last 26 months."

Source: https://www.cnn.com/2023/09/15/economy/consumer-sentiment-september/index.html

Core Inflation Coming Under Control in the U.S.

Greg Iacurci, CNBC, Sep 13, 2023 (excerpt)

Inflation rose in August on the back of higher gasoline prices, according to the consumer price index. But there's good news for Americans: That increase is likely temporary, economists said. Aside from energy, there are signs that inflation continued its broad retreat in August, they said.

"This should just be a temporary interruption of the downward trend," said Andrew Hunter, deputy chief U.S. economist at Capital Economics.

"Broadly, we're already seeing pretty clear signs the situation is approaching normal again," he added.

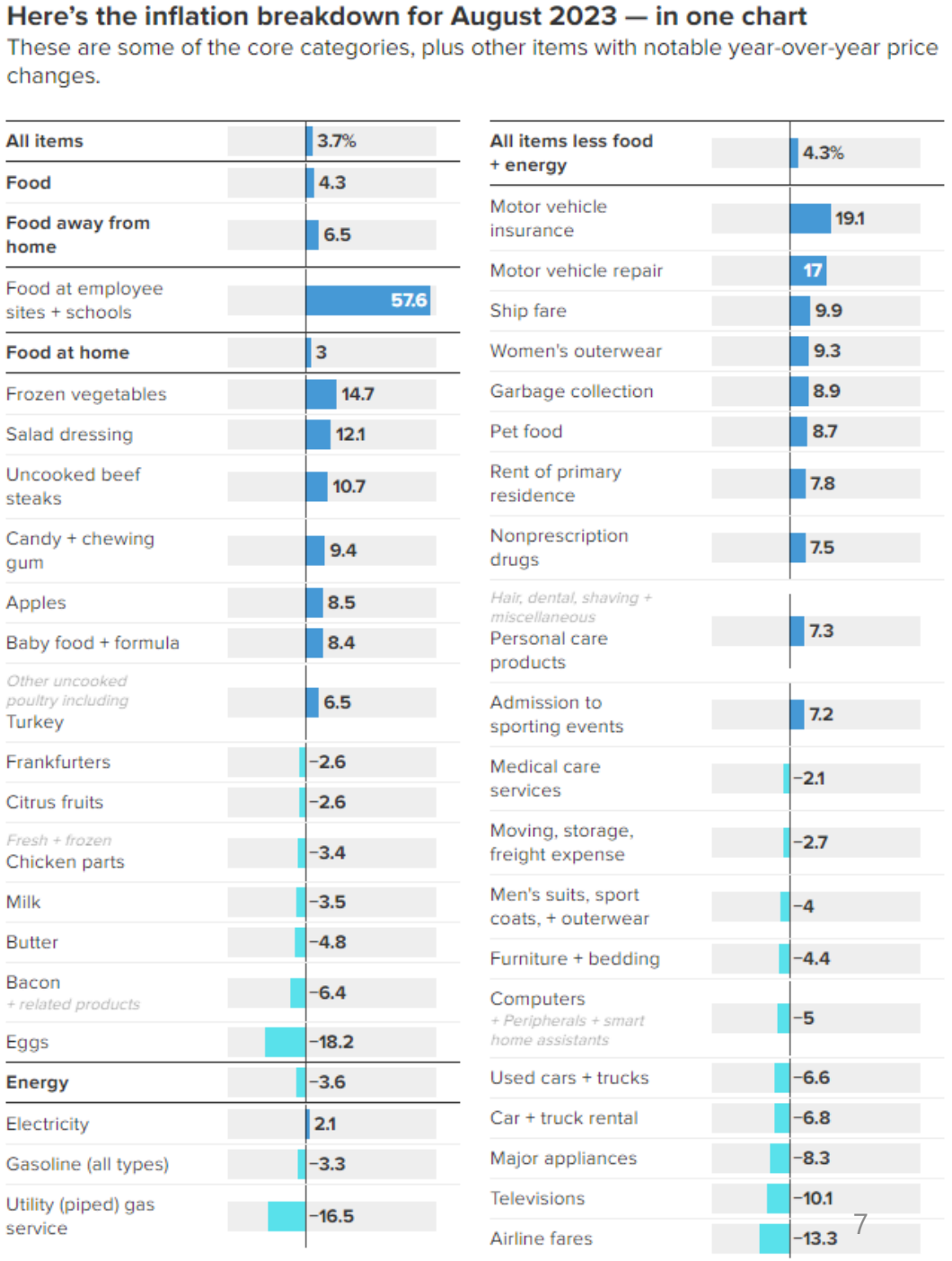
When assessing underlying inflation trends, economists generally like to look at one measure that strips out energy and food prices, which tend to be volatile from month to month. This pared-down measure — known as "core" CPI — fell to an annual rate of 4.3% in August from 4.7% in July.

On a monthly basis, core inflation rose slightly, to 0.3% in August from 0.2% in July. The economy would need consistent monthly core CPI readings of 0.2% to get the U.S. back to its pre-pandemic baseline, a time when inflation was low and stable, economists said.

The increase in monthly core CPI "is a little bump in the road," said Kayla Bruun, senior economist at Morning Consult.

"It doesn't mean it's turning around and going in the other direction," Bruun said. "Overall, most of the pieces are headed in the right direction."

Source: https://www.cnbc.com/2023/09/13/heres-the-inflation-breakdown-for-august-2023-in-one-chart.html



Fed Policy: Higher for Longer

By Michael Mackenzie and Edward Bolingbroke, Bloomberg, Sep 16, 2023 (excerpt)

Treasury yields have settled into tight ranges this month near the highest levels in more than a decade as data show a resilient economy and inflation still well above the Fed's 2% target.

The Fed is widely expected to leave its policy rate unchanged next week after lifting it in July for the 10th time in an aggressive hiking cycle that began in March last year. It's also seen significantly raising its forecast for growth and indicating another rate increase this year in its so-called dot plot. The rate outlook for 2024 remains up for debate. In June, the median projection showed a full percentage point cut by the end of next year.

It's very reasonable to see lower yields in an economic environment heading into a downturn, according to Vanguard's Hallam. But the picture for bond buyers gets complicated should higher energy prices stall the recent disinflationary trends.

"Sticky inflation would make it very difficult for the Fed to ease next year," he said.

This article appeared in Bloomberg last Saturday and notes that the Fed has one more rate rise in store this year.

The authors predicts that the Fed will then be watching economic activity more than inflation in deciding what to do in 2024. The author's term the Fed's current approach as "higher for longer".

It is this Fed approach that is impacting the markets, including biotech stocks.

Source: https://www.bloomberg.com/news/articles/2023-09-16/fed-s-higher-for-longer-mantra-has-doubters-in-bond-market

Biopharma Market Update

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Mixed Mood

Investors remained active last week with several key investor conferences taking place in New York. Our offices in New York had many visitors in town for the various confabs.

And, yet the mood remained distinctively mixed. Excitement is coupled with trepidation. Fundamental investors are engaged and energized but are also acutely aware that generalists are not coming into the market.

We think a recovery won't arrive until the Fed is well along in easing rates. One would think that generalist and retail entry should be triggered by anticipation of lower rates, but if you can get 5% by investing in cash it's hard to reallocate to high-risk asset classes.

Importantly, we saw two major IPO's launch with heavy oversubscription. Key long funds came into each stock. This is an excellent sign of underlying health in the market.

We spoke to a number of funds last week and can report: (1) many of them on the hunt for attractive PIPE deals, (2) on the venture side it's all about quality and sizzle at a good value, (3) many investors spoke about the importance of deep research and understanding of stories.

We like this focus on fundamentals. It's that sort of market right now, where you have to get the story right to thrive.

Biotech Stocks Down Last Week

The XBI was down last week by 2% and is now down 7% for the year. The overall market, measured by the S&P 500, was flat last week in light of an unwelcome slight spike in inflation.

Biotech Stocks Down Last Week

Return: Sep 9 to Sep 15, 2023

Nasdaq Biotech Index: -0.6%
Arca XBI ETF: -2.0%
Stifel Global Biotech (EV): 2.1%*
S&P 500: 0.0%

Return: Jan 1 to Sep 15, 2023

Nasdaq Biotech Index: -3.7%
Arca XBI ETF: -7.1%
Stifel Global Biotech: -8.2%*
Stifel Global Biotech (adjusted): -5.4%*
S&P 500: +15.9%

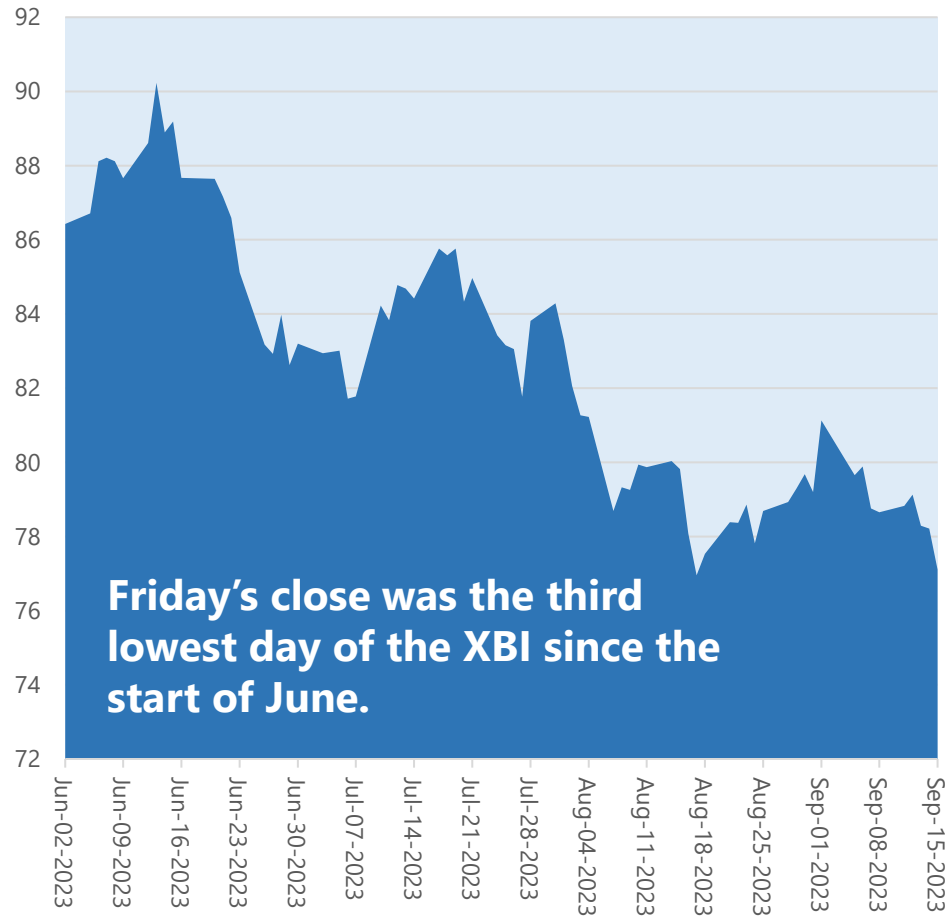
VIX Flat

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
May 26: 18.0%
July 21: 13.6%
Aug 18: 17.3%
Sep 8: 13.8%
Sep 15: 13.8%

10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
May 26: 3.8%
July 21: 3.84%
Aug 18: 4.25%
Sep 8: 4.26%
Sep 15: 4.33%

XBI, June 1, 2023 to Sep 8, 2023

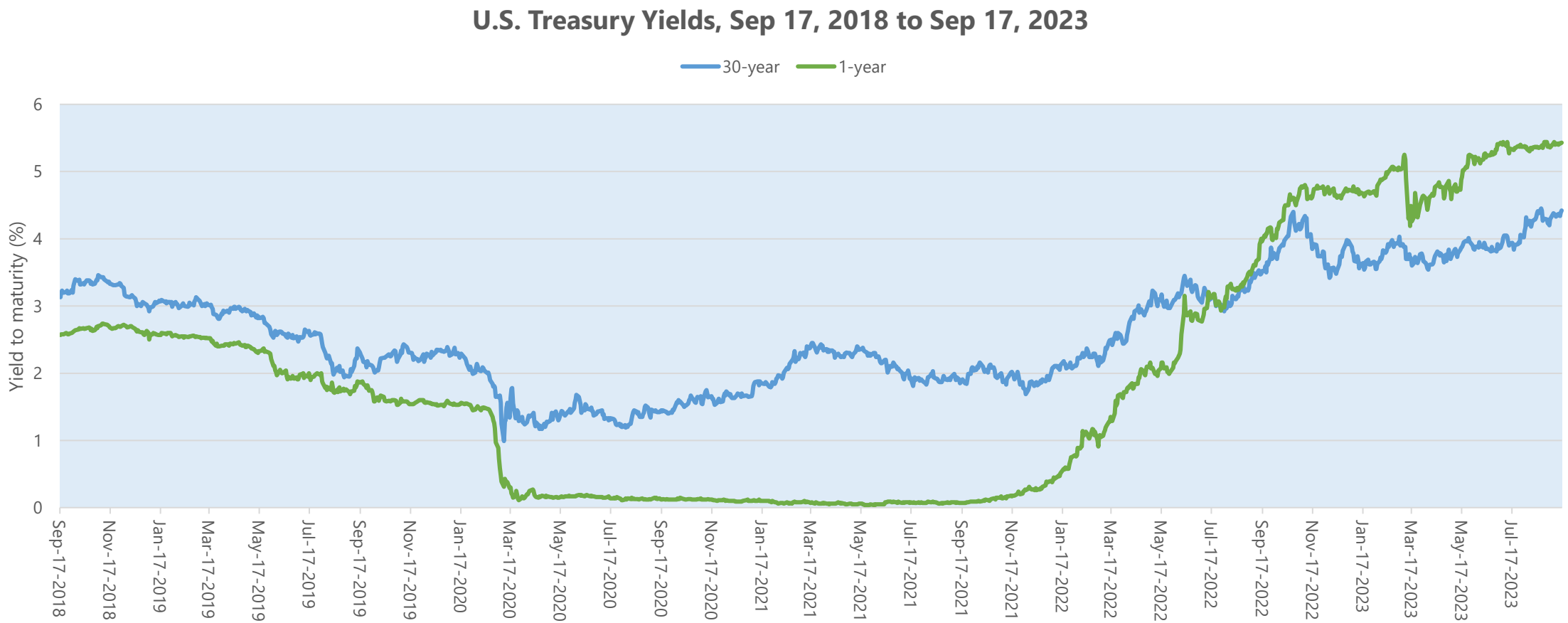


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. This week would have been up only slightly had we not added in Neumora and Rayze to the global biotech group.

Source: S&P Capital IQ and Stifel analysis

U.S. Treasury Yields Continue to Rise

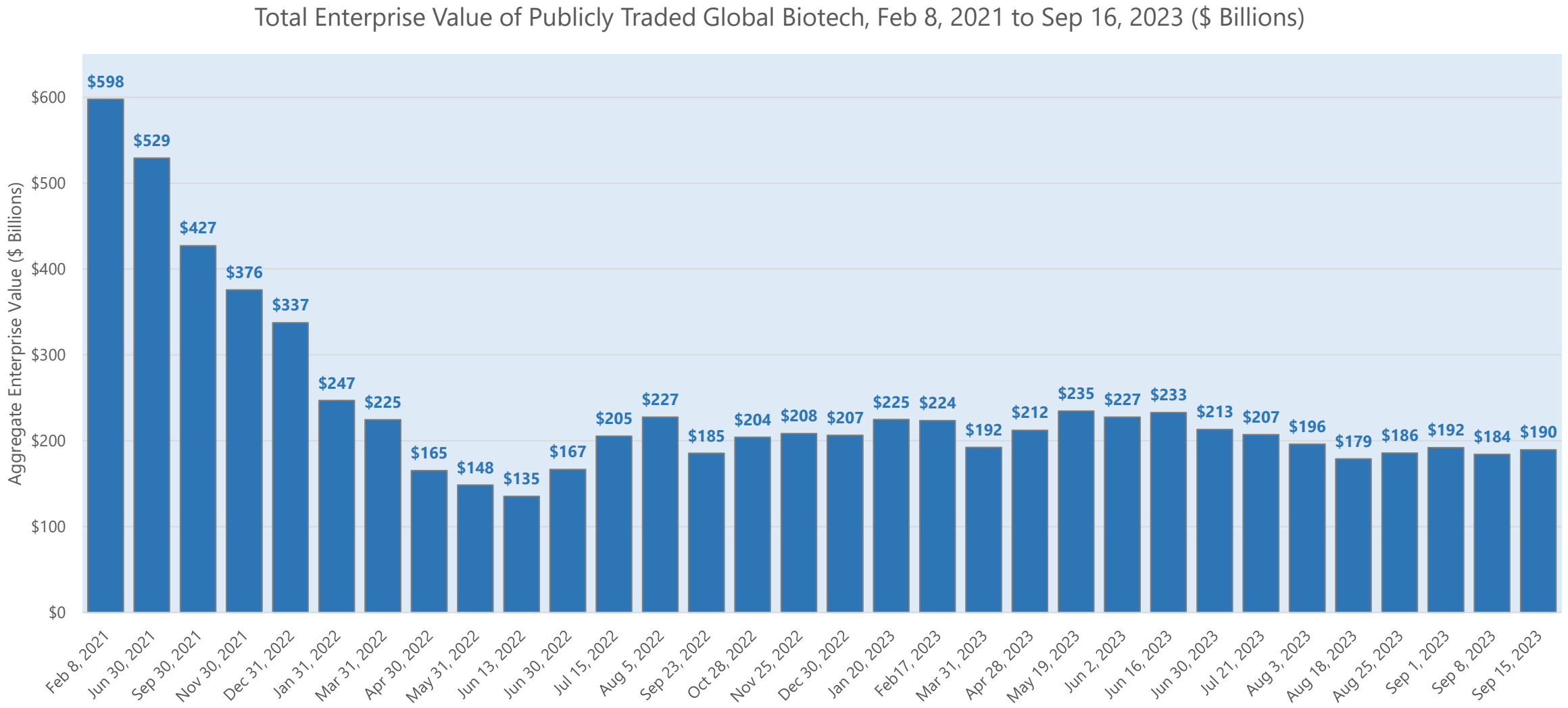
Short-term Treasury yields give one a picture of near-term inflation expectations while long-term rates reflect investor's perceptions of long-term inflation. This all feeds into markets for risky assets (such as biotech stocks). Notably, 30-year Treasury yields have been rising for the last six months, indicating investor's pessimism about the prospects for getting inflation down. We believe that we are going to need to see inflation ease up and Treasuries move the other way for biotech to rally in a meaningful way.



Source: CapitalIQ.

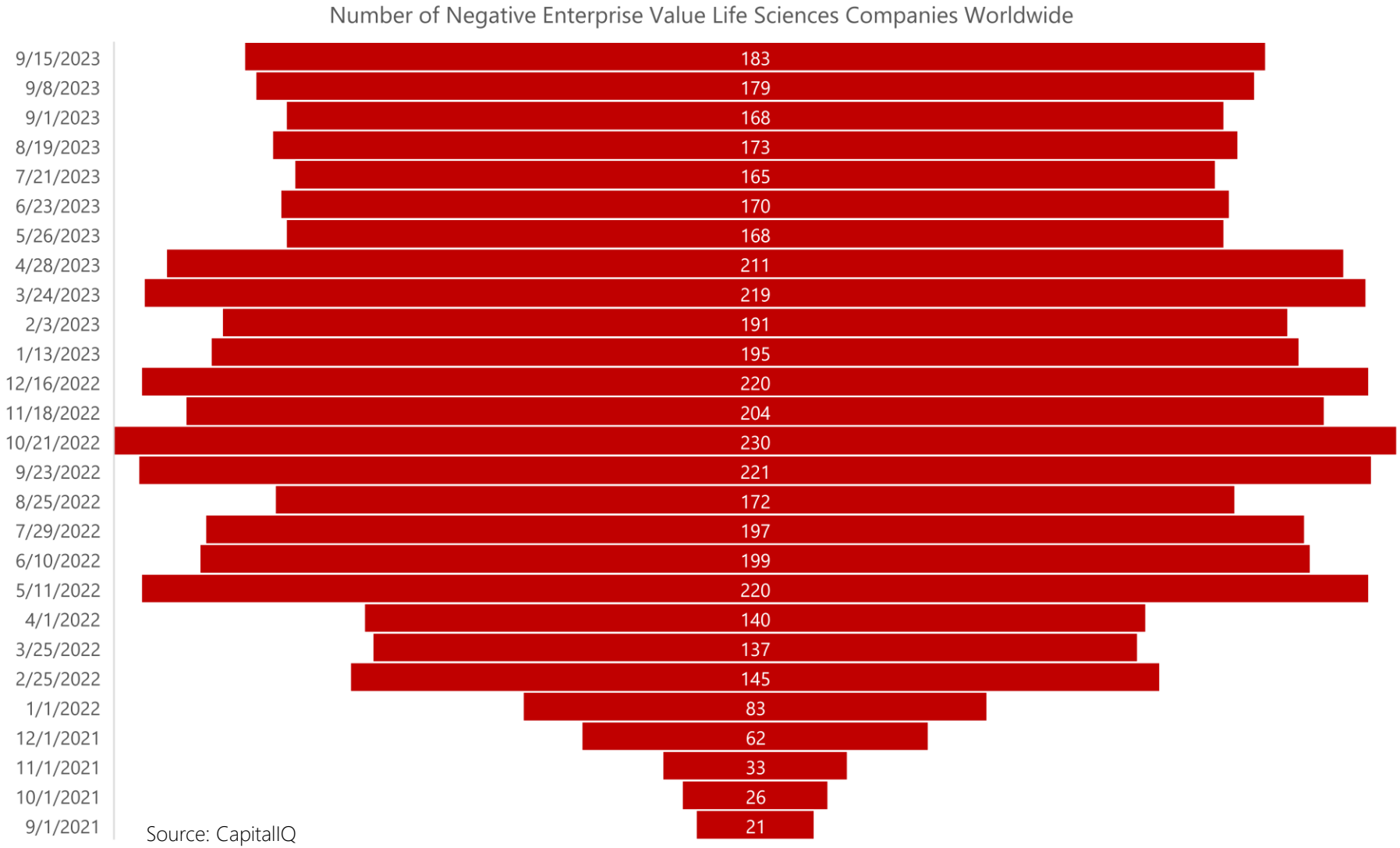
Total Global Biotech Sector Up Last Week

The total value of the global biotech sector rose 2.1% last week. Had we not added in Neumora and Rayze, the biotech group value would have been close to flat week-on-week.



Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Number of Negative Enterprise Value Life Sciences Companies Rose to 183 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 179 a week ago to 183 last Friday.

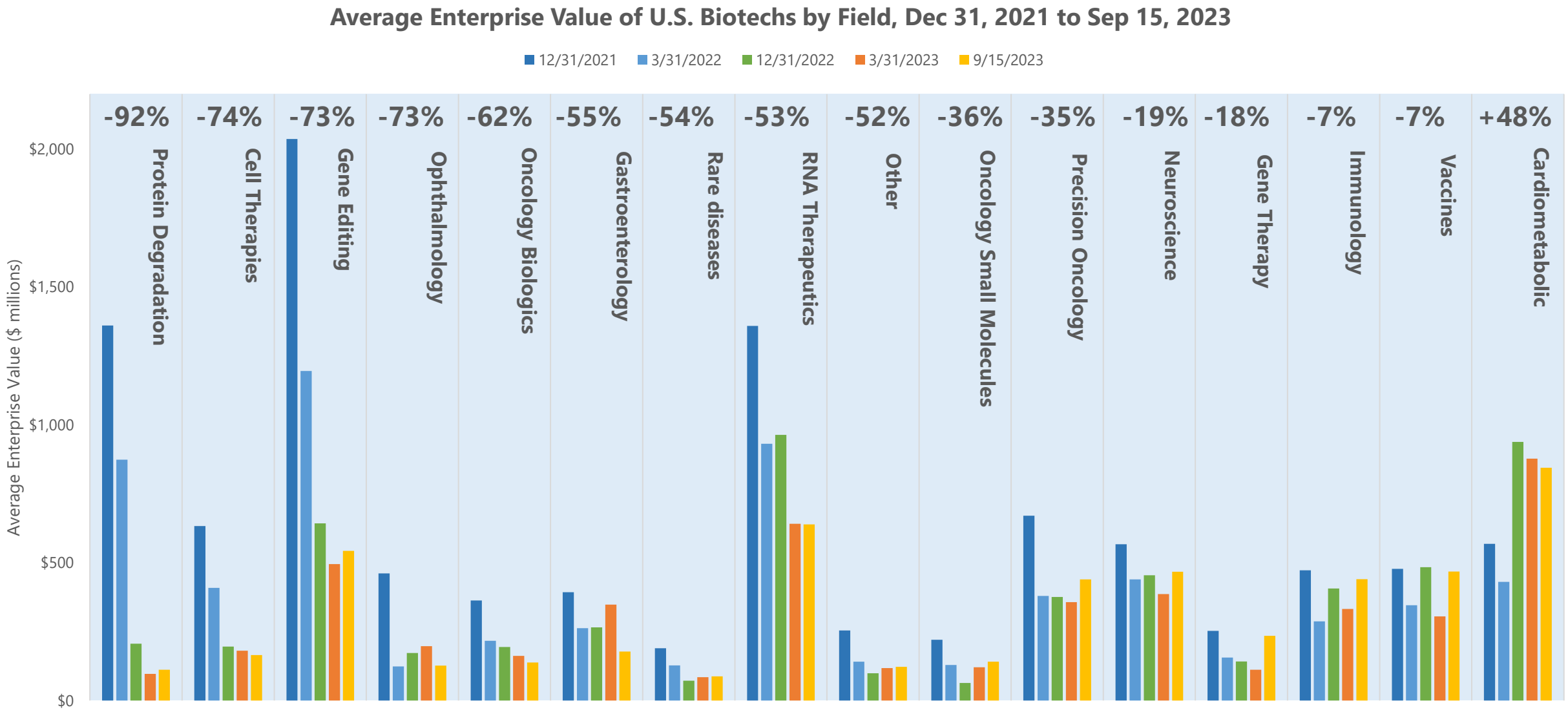
Public Life Sciences Sector Value Rose Last Week

The total enterprise value of the publicly traded life sciences sector rose by 0.5% last week ($53 billion). The sectors that rose the most were API, CDMOs, biotech and pharma services. The commercial pharma sector role by 0.5% in value.

Sector	Firm Count	Enterprise Value (Sep 15, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$80,795	3.1%	2.9%	-2.4%
Biotech	818	$190,191	2.1%	2.7%	-5.1%
CDMO	40	$168,035	2.5%	0.8%	-6.9%
Diagnostics	83	$239,561	-1.3%	-5.1%	6.5%
OTC	32	$30,449	1.6%	-2.1%	8.2%
Commercial Pharma	725	$5,904,483	0.5%	-0.3%	11.3%
Pharma Services	41	$211,490	1.9%	0.0%	5.4%
Life Science Tools	54	$691,022	1.0%	-1.8%	-7.6%
Medical Devices	181	$1,576,407	0.3%	-0.6%	1.9%
HCIT	11	$22,946	-0.2%	-5.1%	-13.9%
Total	**2066**	**$9,116,379**	**0.5%**	**-0.5%**	**6.7%**

Source: CapitalIQ

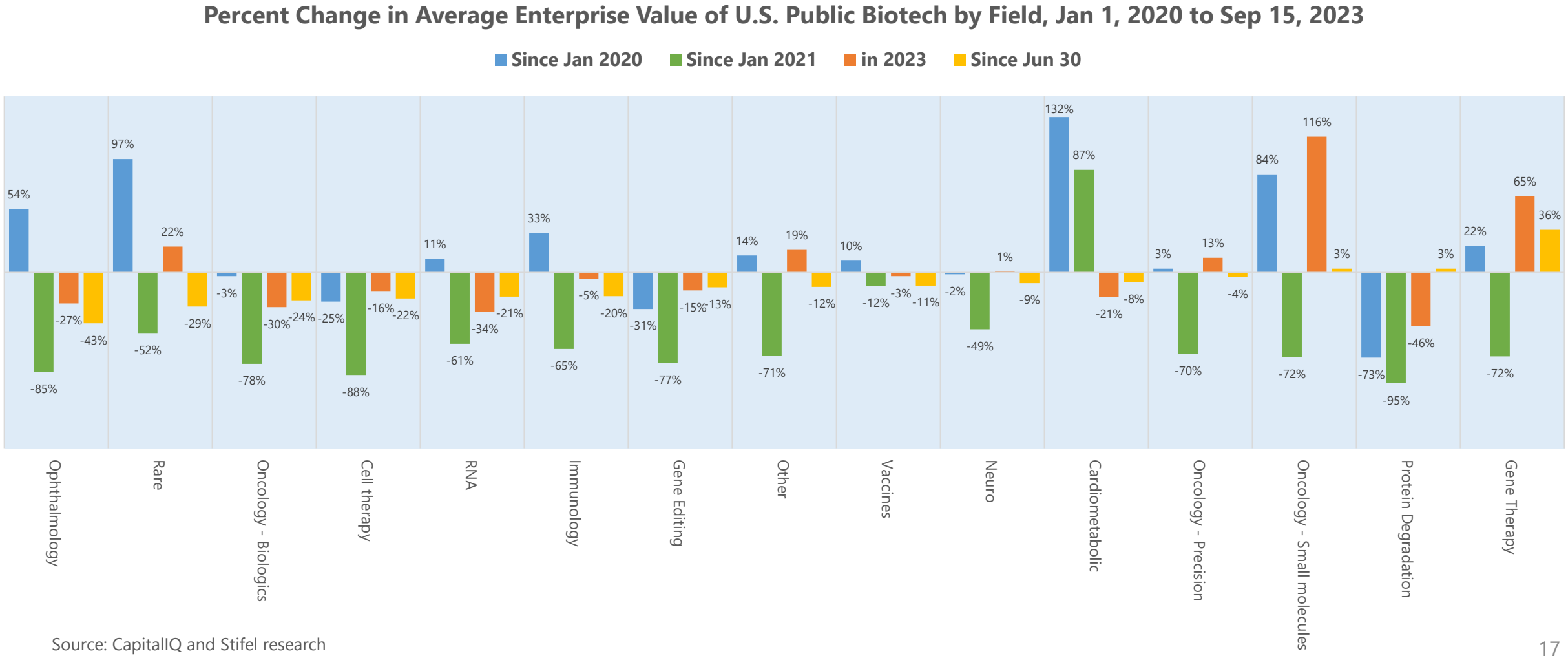
Biotech Valuation Change from Dec 31, 2021 to Sep 15, 2023 by Field



Source: CapitalIQ and Stifel research

Biotech Valuation Change from Dec 31, 2021 to Sep 15, 2023 by Field

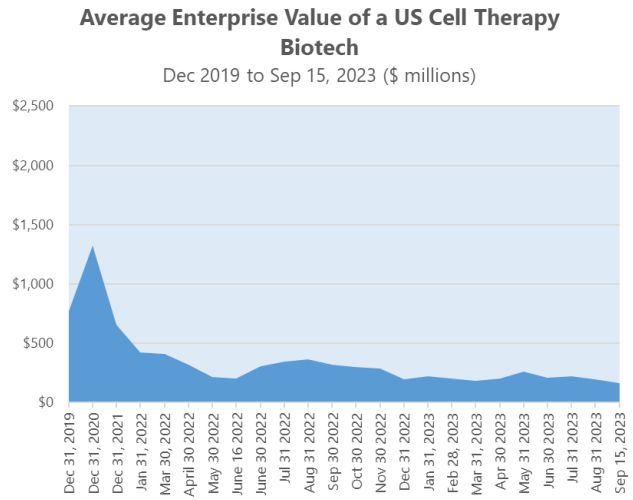
The story of changing biotech valuations since mid-year is a recovery in gene therapy stocks (led by Taysha) and continued weakness in rare disease, oncology biologics, cell therapy (mainly oncology), RNA therapeutics and ophthalmology biotech stocks. Immunology stocks have seen some weakness as well, in part due to the major decline last week in Acelyrin.

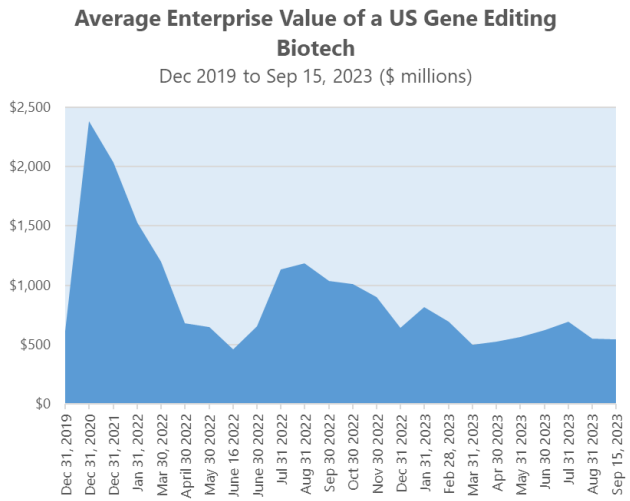


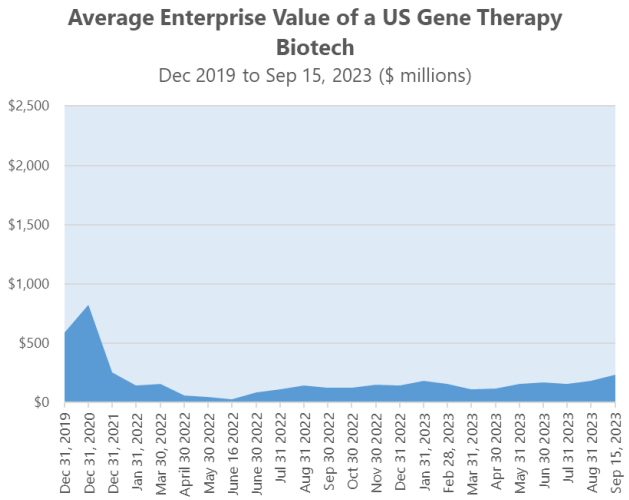
Source: CapitalIQ and Stifel research

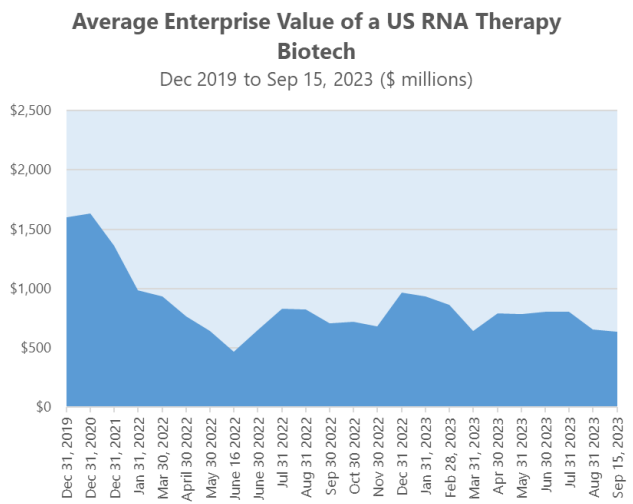
Biotech Valuations By Platform Area, Dec 2019 to Sep 2023

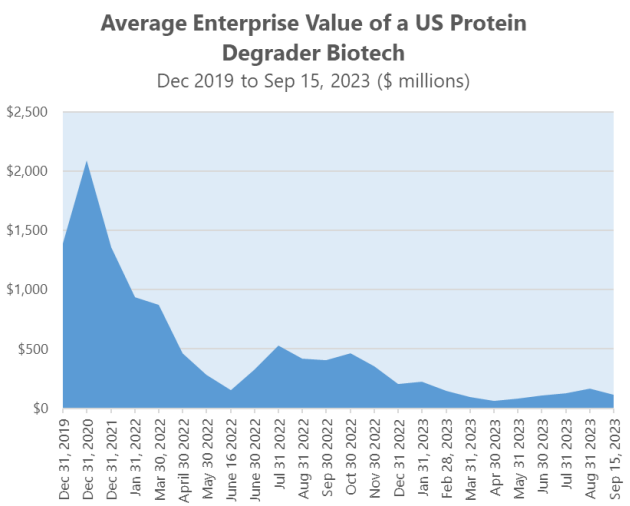
One can see a major jump during the Pandemic in once hot fields like protein degraders, gene editing and cell therapies. These stocks have all experienced major declines since then. Interestingly, gene edit stocks and RNA therapeutics stocks have held up during most of 2023 with average enterprise values pegged at around $600mm.

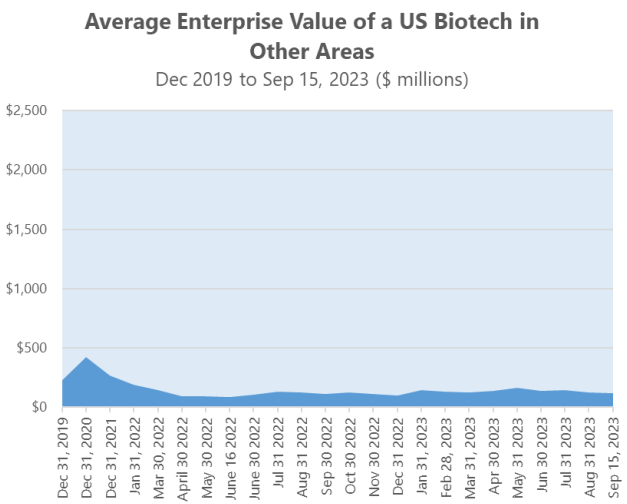










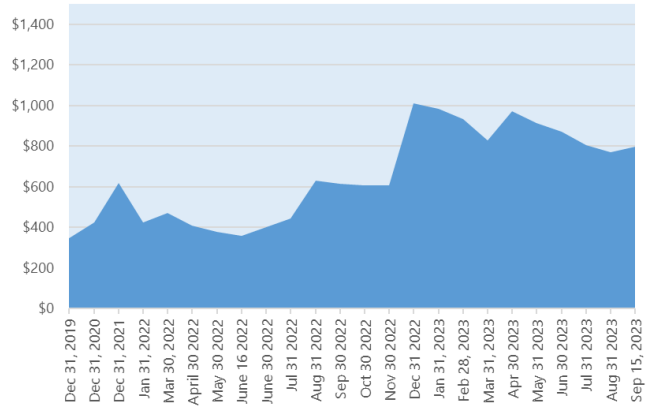


Source: CapitalIQ and Stifel research

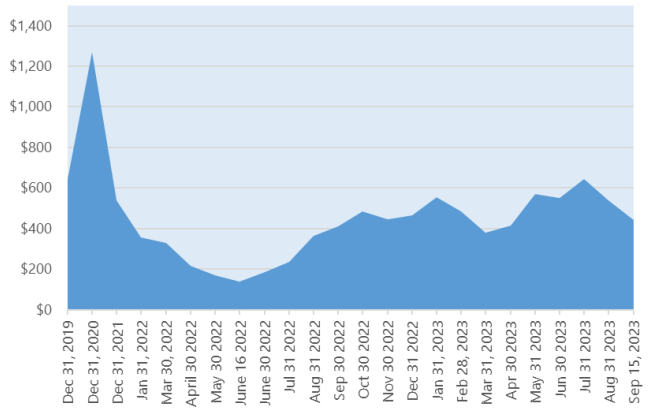
Biotech Valuations By Therapeutic Area, Dec 2019 to Sep 2023

This chart shows the strength in cardiometabolic, neuro, vaccines and immunology stocks versus rare disease, ophtha and rare disease biotechs. Despite some weakness this year, the market continues to view cardiometabolic biotech stories favorably.

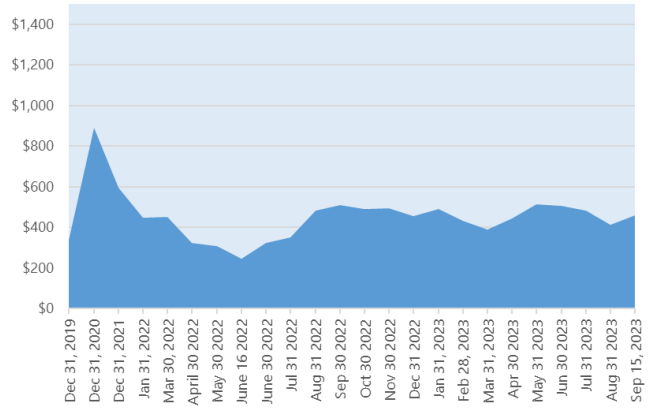
Average Enterprise Value of a US Cardiometabolic Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



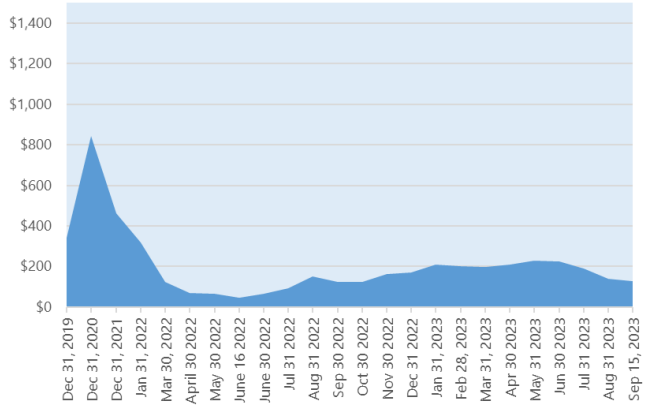
Average Enterprise Value of a US Immunology Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



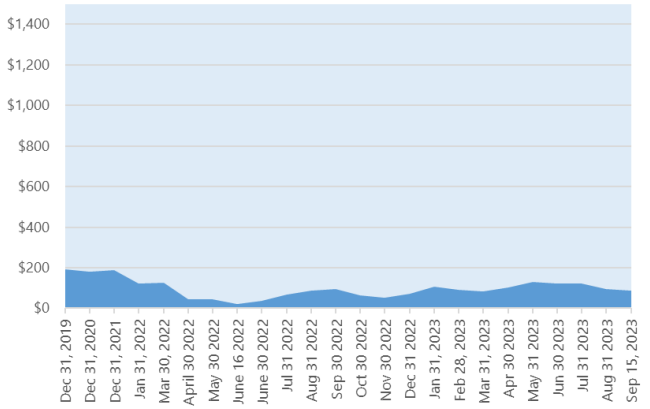
Average Enterprise Value of a US Neuroscience Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



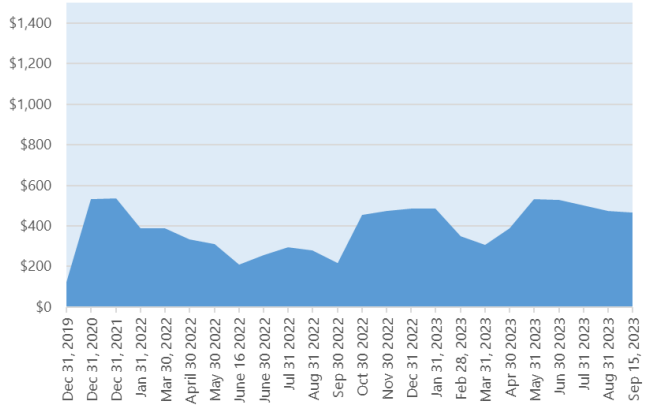
Average Enterprise Value of a US Ophthalmology Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



Average Enterprise Value of a US Rare Disease Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



Average Enterprise Value of a US Biotech in Vaccines
Dec 2019 to Sep 15, 2023 ($ millions)

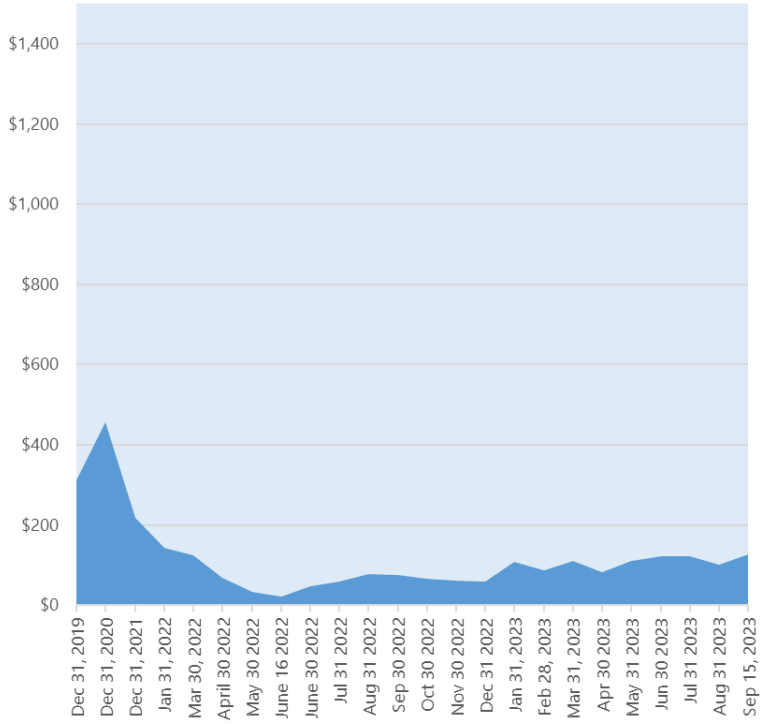


Source: CapitalIQ and Stifel research

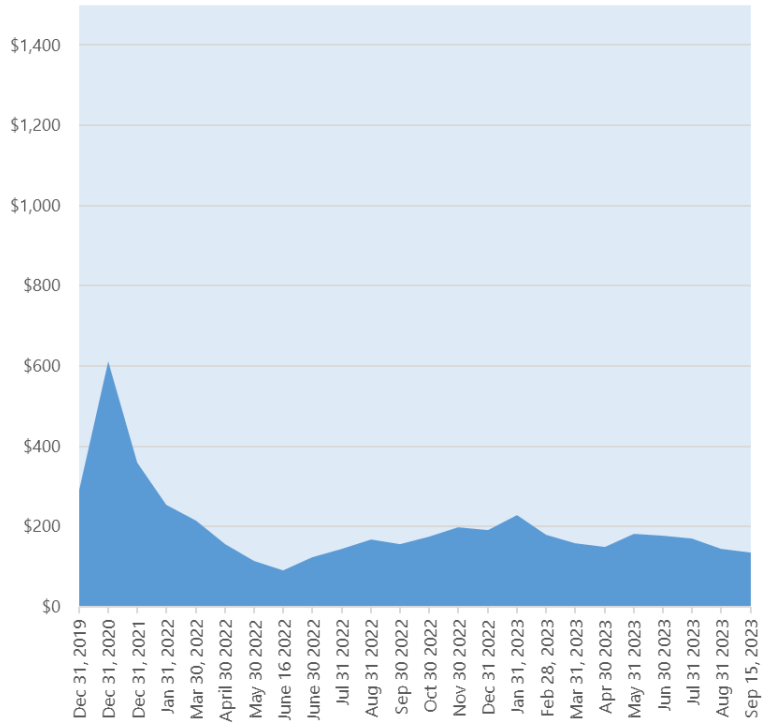
Oncology Biotech Valuations, Dec 2019 to Sep 2023

During the Pandemic the market was most excited by precision oncology stories and least excited by conventional small molecule oncology stories (particularly those involving cytotoxics). Since then, we have seen the value of precision oncology companies plummet and then slowly recover since mid-June of 2022. There has been ongoing weakness in both traditional small molecule and biologic stories in oncology since the Pandemic period.

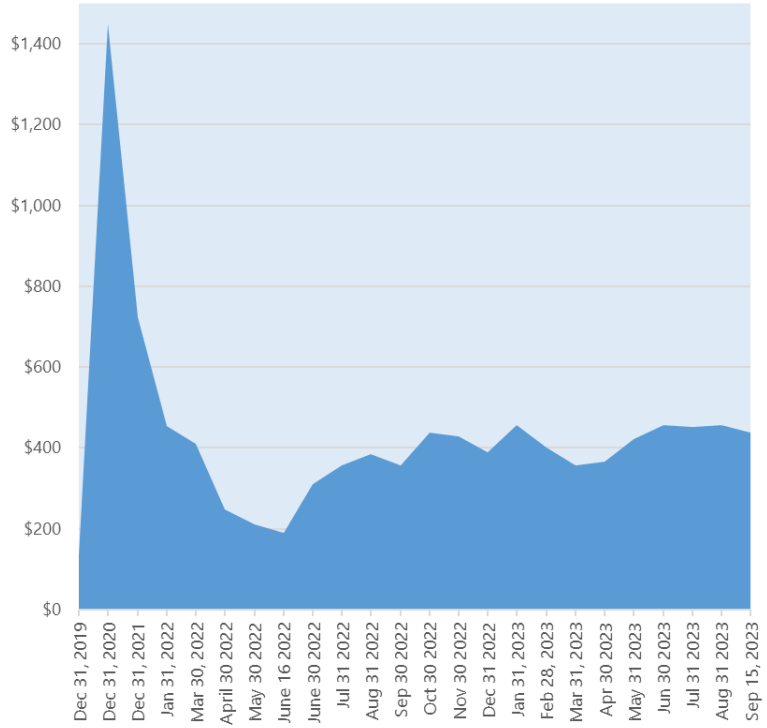
Average Enterprise Value of US Small Molecule Oncology Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



Average Enterprise Value of a US Oncology Biologics Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



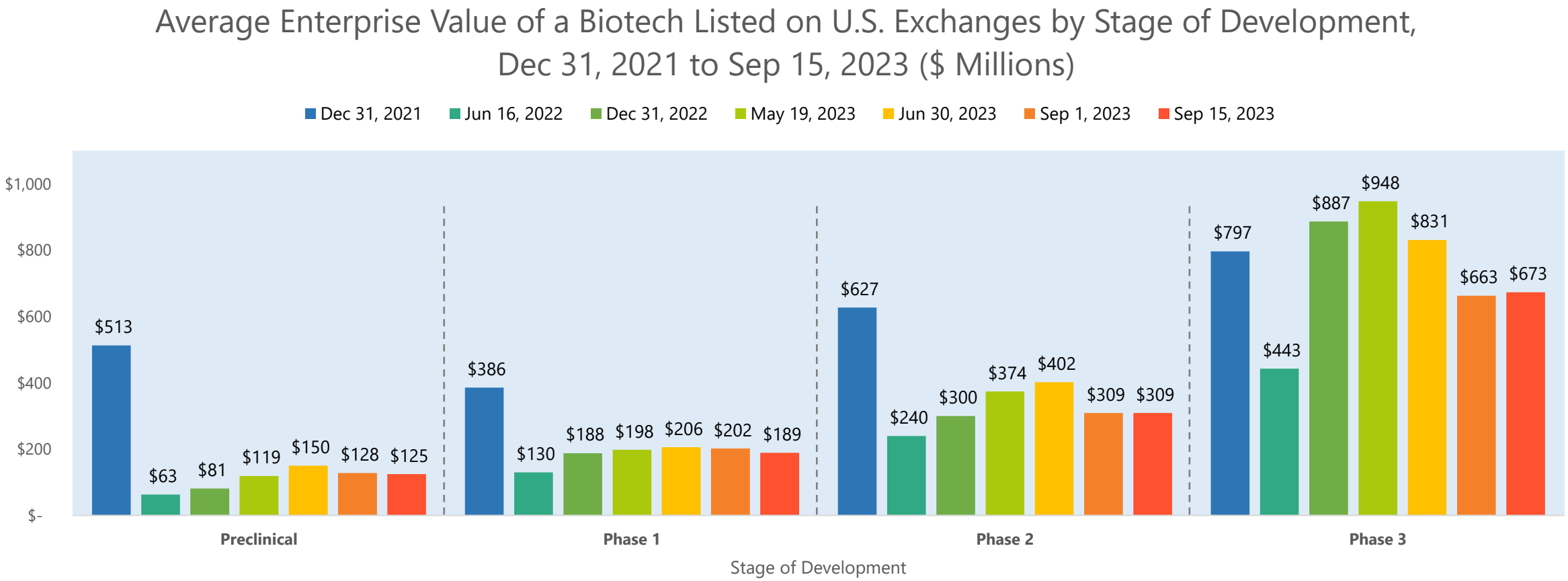
Average Enterprise Value of a Precision Oncology Biotech
Dec 2019 to Sep 15, 2023 ($ millions)



Source: CapitalIQ and Stifel research

U.S. Biotech Average Valuations by Stage of Development of Lead Compound, Last 18 Months

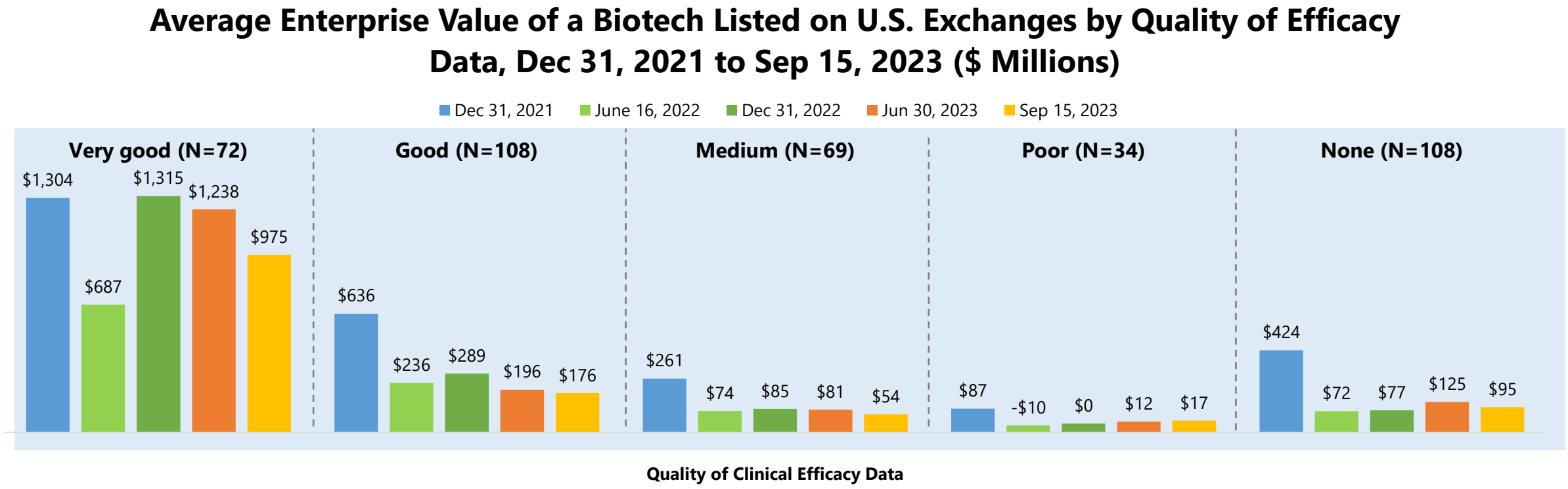
Recent weeks have seen preclinical and Phase 1 companies continue to lose value while those that are later stage have gained in value (slightly). Among other things, this is a reflection of the rate environment – which rewards later stage assets.



Notes: These data are sourced from CapitalIQ and based on Stifel research on the company's development stage. We required that the company have data in that stage. So, for example, if a company was dosing a Phase 1 study but had not yet reported data, we classified the company as preclinical.

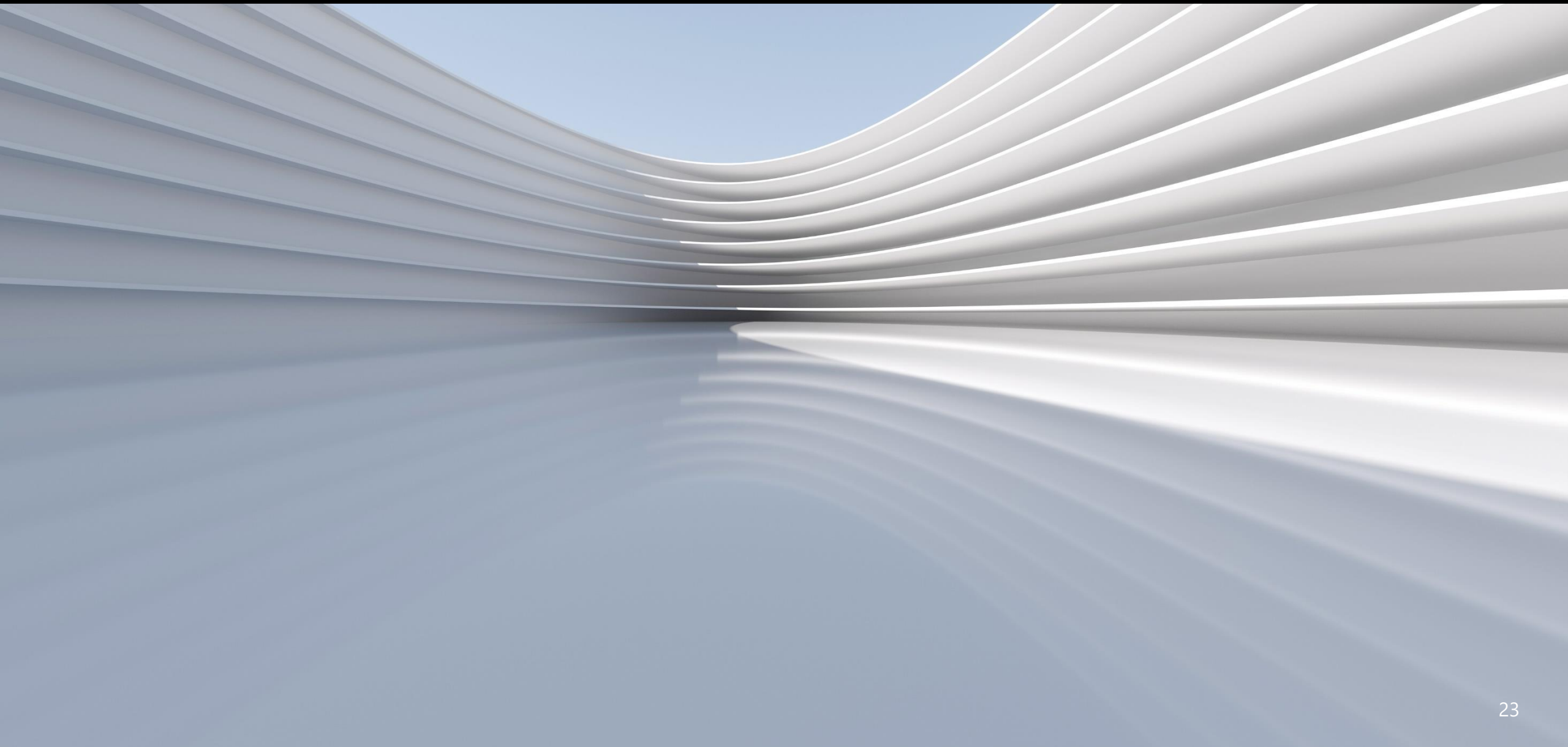
U.S. Biotech Average Valuations by Quality of Data for Lead Compound, Last 18 Months

Companies with very good datasets have held their value since the Pandemic period. There has been a bit of a drop in the value associated with having a great dataset in the last year. Companies with good, medium or poor datasets saw a big drop off in value between the end of 2021 and the middle of 2022. The recovery in value of platform companies that was seen in the first half of 2023 has reversed itself. The market remains focused on companies with very good datasets.



Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

Industry News



Pharma's Procedural Attack Opens New Front in Drug Price War

Ian Lopez, *Bloomberg Law*, September 13, 2023 (excerpt)

The pharmaceutical industry is expanding its attack on President Joe Biden's plan to lower Medicare drug prices into allegations that the administration violated procedural norms in implementing the program, a tactic legal experts say will run into roadblocks but that could ultimately prevail.

AstraZeneca PLC and Boehringer Ingelheim are suing the Biden administration, alleging it violated the Administrative Procedure Act by trying to institute the drug pricing program via agency guidance rather than the formal regulatory process.

The APA claims mark important additions to "the litigation saga" unfolding around drug pricing, said Margaux Hall, partner in Ropes & Gray LLP's health-care practice.

"If an agency can implement a statute through guidance alone and functionally rewrite the terms of the statute through that guidance, that seems to present broader, potential enduring harms," Hall said.

The companies are among the first to have drugs subject to Medicare price negotiations. They join five other pharmaceutical giants and several lobbying groups suing in federal courts to block the program, a litigation strategy that's expected to grow.

AstraZeneca and BI, however, take their attacks into the procedural realm. In its complaint filed in the US District Court for the District of Delaware, AstraZeneca says the Centers for Medicare & Medicaid Services guidance took steps to make certain drugs eligible for negotiations when they wouldn't otherwise be. That, the company says, violates the APA.

Meanwhile, in a separate lawsuit, BI told the US District Court for the District of Connecticut that the drug program guidance was actually a legislative rule, meaning it required the agency to give stakeholders an opportunity to weigh in before enactment.

Source: https://news.bloomberglaw.com/health-law-and-business/pharma-cries-procedural-foul-in-next-front-of-drug-price-war

In China, a Completely Different Approach to Lowering Healthcare Costs

Chun Hang Weong and Clarence Leong, *Wall Street Journal*, Sep 13, 2023

SINGAPORE—China is carrying out a massive anticorruption purge across its healthcare sector, in an effort to bring down medical costs and revive the country's flagging economy.

Communist Party enforcers have steamrolled through hospitals and medical institutions across China, detaining at least 190 hospital party chiefs, directors and deputy directors—incumbent and former—so far this year, according to a Wall Street Journal review of government disclosures. A retired provincial party chief, who held a top government role overseeing healthcare reforms from 2010 to 2015, was detained in late August for allegedly committing "severe violations of discipline and law"—a euphemism for corruption.

Beijing has long sought to combat rising costs in housing, education and healthcare—often described in China as the "three big mountains" that contribute most heavily to many households' living expenses, and which economists say have exacerbated wealth inequality, weighed on consumption and dragged down birthrates.

More than 95% of China's population has basic health insurance, but it offers only bare-bones coverage. About one-third of healthcare spending in China was paid out of pocket in 2020, the latest year for which World Health Organization data is available. That was about three times the share that Americans paid.

"Chinese leaders understand when people do not have affordable healthcare, it will threaten social stability," said Winnie Yip, a Harvard professor and an expert on Chinese health policy.

Source: https://www.wsj.com/world/china/in-china-a-completely-different-approach-to-lowering-healthcare-costs-f5a8ebba

U.S. and Other Foreign Venture Firms Pull Back From China's Biotech Sector

Brian Gormley, *Wall Street Journal*, Sep 14, 2023

Venture capitalists from the U.S. and other countries have reduced investment in Chinese drugmakers, denting momentum in China's developing biotechnology industry.

Their retreat reflects a global pullback in venture investment as well as China's faltering economy and rising geopolitical tensions, analysts said.

"China biotech had as big or bigger of a biotech bubble than we had in the U.S., and that is in the process of deflating," said Les Funtleyder, healthcare portfolio manager for E Squared Capital Management. The U.S.-based family office backed some Chinese biotechs last decade, but hasn't made life-sciences deals in China recently, he added.

Biotech venture investment in China, as in the U.S., jumped in the years leading to 2021. Venture funding for Chinese biotechs rose from $1.2 billion in 2015 to $19.3 billion in 2021, then fell to $8.9 billion last year, according to market tracker PitchBook Data.

Cross-border investment, including from the U.S., has been an important source of capital for China's biotech industry, said Scott Moore, a political scientist at the University of Pennsylvania and author of "China's Next Act," a book discussing the nation's biotech sector.

"The Chinese VC landscape is maturing very rapidly, but access to financing, particularly for early-stage biotech startups, is not at the volume or the level of sophistication as it is in the U.S.," he added.

Source: https://www.wsj.com/articles/u-s-and-other-foreign-venture-firms-pull-back-from-chinas-biotech-sector-318839cc

J&J Changes Logo and Removes Janssen Name

Johnson & Johnson Marks New Era as Global Healthcare Company with Updated Visual Identity

"Brand and visual identity demonstrate the best of Johnson & Johnson's care and humanity, while capturing the Company's passion and determination to improve the health of people worldwide"

Johnson&Johnson

New Brunswick, N.J., Sept. 14, 2023 – For more than 135 years, Johnson & Johnson (NYSE: JNJ) has provided health care products and solutions to people worldwide. Now, with its exclusive focus on healthcare innovation and tackling the toughest health challenges, the Company is updating its brand and uniting both its medtech and pharmaceutical segments under the Johnson & Johnson brand name to demonstrate its collective power in healthcare.

"Our exclusive focus on Innovative Medicine and MedTech solutions enables us to innovate across the full spectrum of healthcare in ways no other company can," said Joaquin Duato, Chairman of the Board and Chief Executive Officer. "Uniting our diverse businesses under an updated Johnson & Johnson brand reflects our unique ability to reimagine healthcare through transformative innovation, while staying true to Our Credo values and the level of care that patients and doctors expect of us."

Moving forward, the Company's two segments will be more connected to the Johnson & Johnson brand. Over time, Janssen, the Company's pharmaceutical segment, will be named Johnson & Johnson Innovative Medicine, and the medical technology segment will continue to be named Johnson & Johnson MedTech.

Source: https://www.jnj.com/johnson-johnson-marks-new-era-as-global-healthcare-company-with-updated-visual-identity

A New Era at J&J

"The announcement marks the next era for Johnson & Johnson, which is leveraging its expertise in innovative medicine and medical technology to prevent, treat and cure complex diseases and introduce solutions that are smarter, less invasive and more personalized."

Source: https://www.jnj.com/johnson-johnson-marks-new-era-as-global-healthcare-company-with-updated-visual-identity

The Focus is On Innovation

"Our exclusive focus on Innovative Medicine and MedTech solutions enables us to innovate across the full spectrum of healthcare in ways no other company can."

Joaquin Duato

Chairman of the Board and Chief Executive Officer

The brand refresh announcement is more than window dressing:

"At Johnson & Johnson, we believe health is everything. Our strength in healthcare innovation empowers us to build a world where complex diseases are prevented, treated and cured, treatments are smarter and less invasive, and solutions are personal."

The above language identifies strategic themes for the present and future including personalization, intelligence, disease cures and disease prevention. We look forward to seeing what the great people of J&J will be bringing to society in the decades to come.

Source: https://www.jnj.com/brand-announcement

Johnson & Johnson

Our Credo

We believe our first responsibility is to the patients, doctors and nurses, to mothers and fathers and all others who use our products and services. In meeting their needs everything we do must be of high quality. We must constantly strive to provide value, reduce our costs and maintain reasonable prices. Customers' orders must be serviced promptly and accurately. Our business partners must have an opportunity to make a fair profit.

We are responsible to our employees who work with us throughout the world. We must provide an inclusive work environment where each person must be considered as an individual. We must respect their diversity and dignity and recognize their merit. They must have a sense of security, fulfillment and purpose in their jobs. Compensation must be fair and adequate and working conditions clean, orderly and safe. We must support the health and well-being of our employees and help them fulfill their family and other personal responsibilities. Employees must feel free to make suggestions and complaints. There must be equal opportunity for employment, development and advancement for those qualified. We must provide highly capable leaders and their actions must be just and ethical.

We are responsible to the communities in which we live and work and to the world community as well. We must help people be healthier by supporting better access and care in more places around the world. We must be good citizens — support good works and charities, better health and education, and bear our fair share of taxes. We must maintain in good order the property we are privileged to use, protecting the environment and natural resources.

Our final responsibility is to our stockholders. Business must make a sound profit. We must experiment with new ideas. Research must be carried on, innovative programs developed, investments made for the future and mistakes paid for. New equipment must be purchased, new facilities provided and new products launched. Reserves must be created to provide for adverse times. When we operate according to these principles, the stockholders should realize a fair return.

J&J's brand refresh announcement prominently refers to staying true to its Credo.

Johnson & Johnson expects its senior executives and employees to live by its Credo which talks about the primacy of the physician customer, the patient and importance of the employee, the community and the business side.

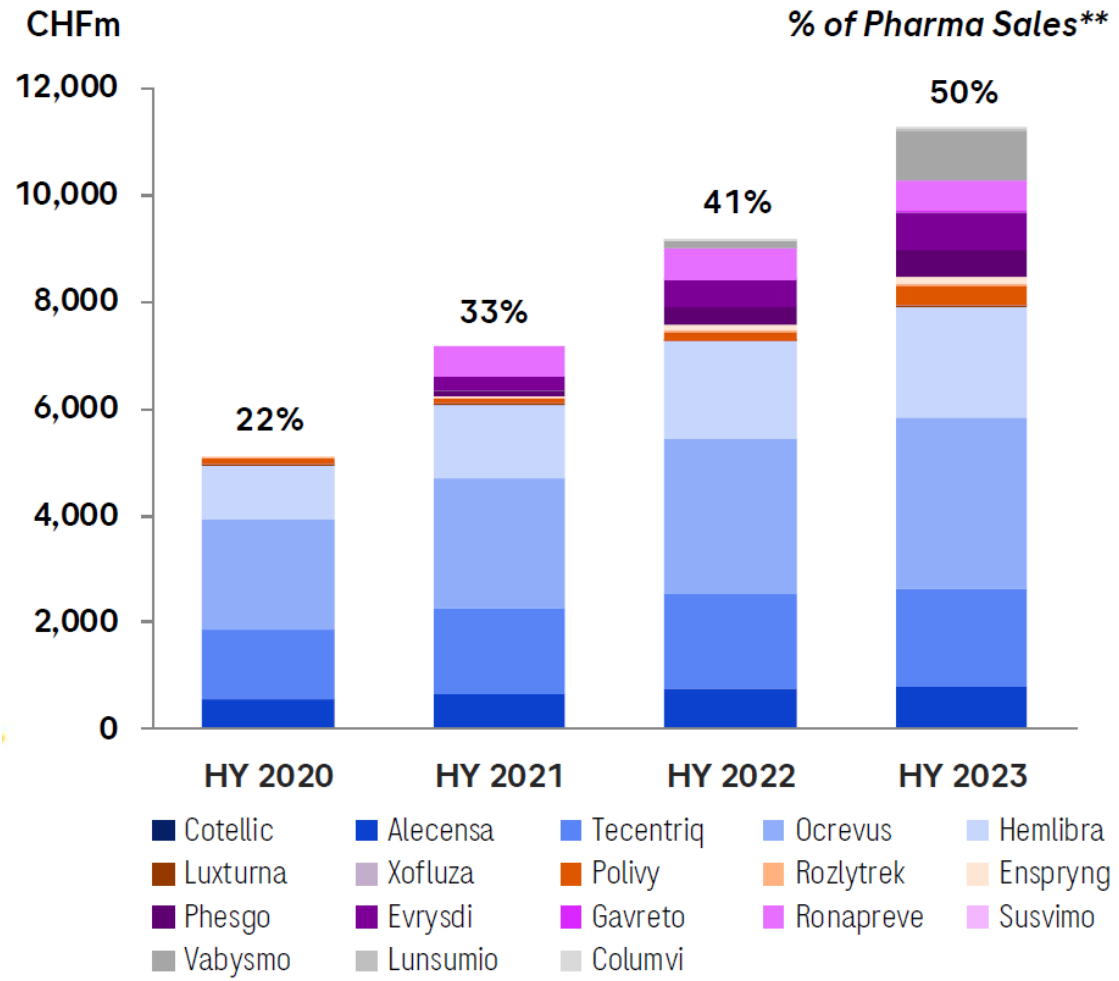
Written by Robert Wood Johnson in 1943, the Credo is refreshing in an era where society decries pharma pricing. Somewhat uniquely, the Credo talks about the importance of equal opportunity and a strong balance sheet.

Roche

Roche Pharma Day 2023

London, 11 September 2023

Young portfolio of NME's delivering for Roche

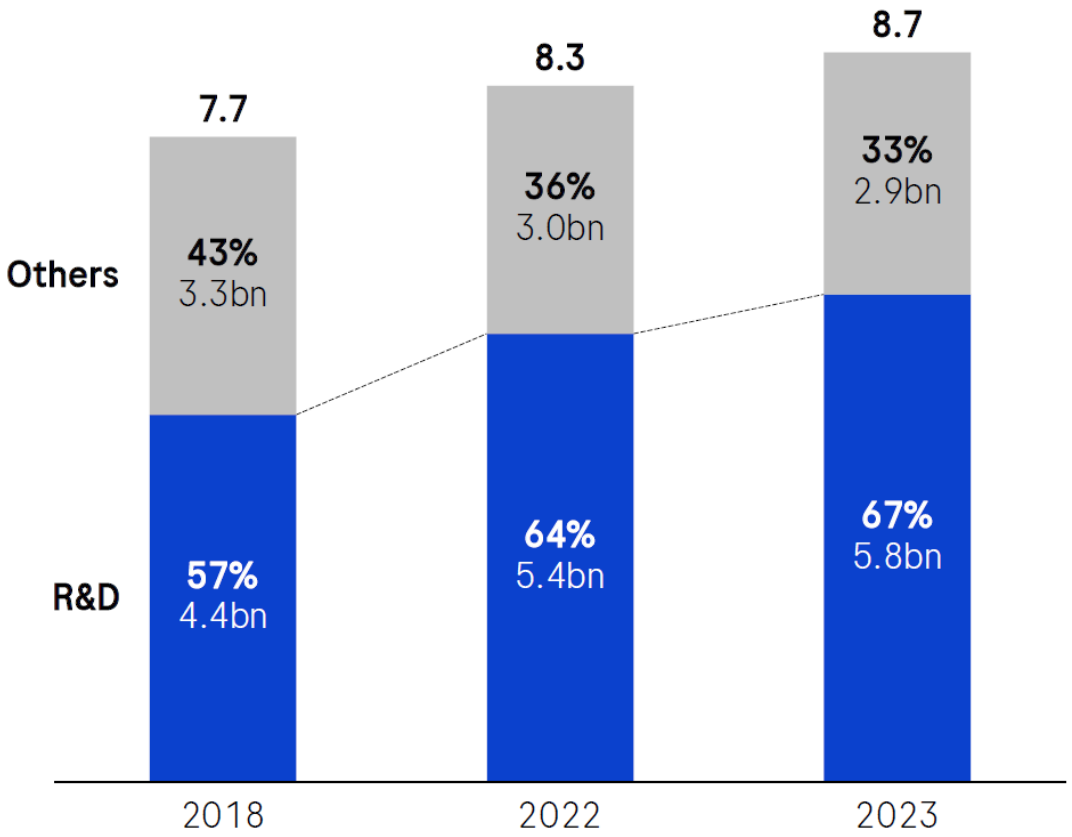


Source: https://assets.roche.com/f/176343/x/72a34572bc/pharma-day-2023.pdf

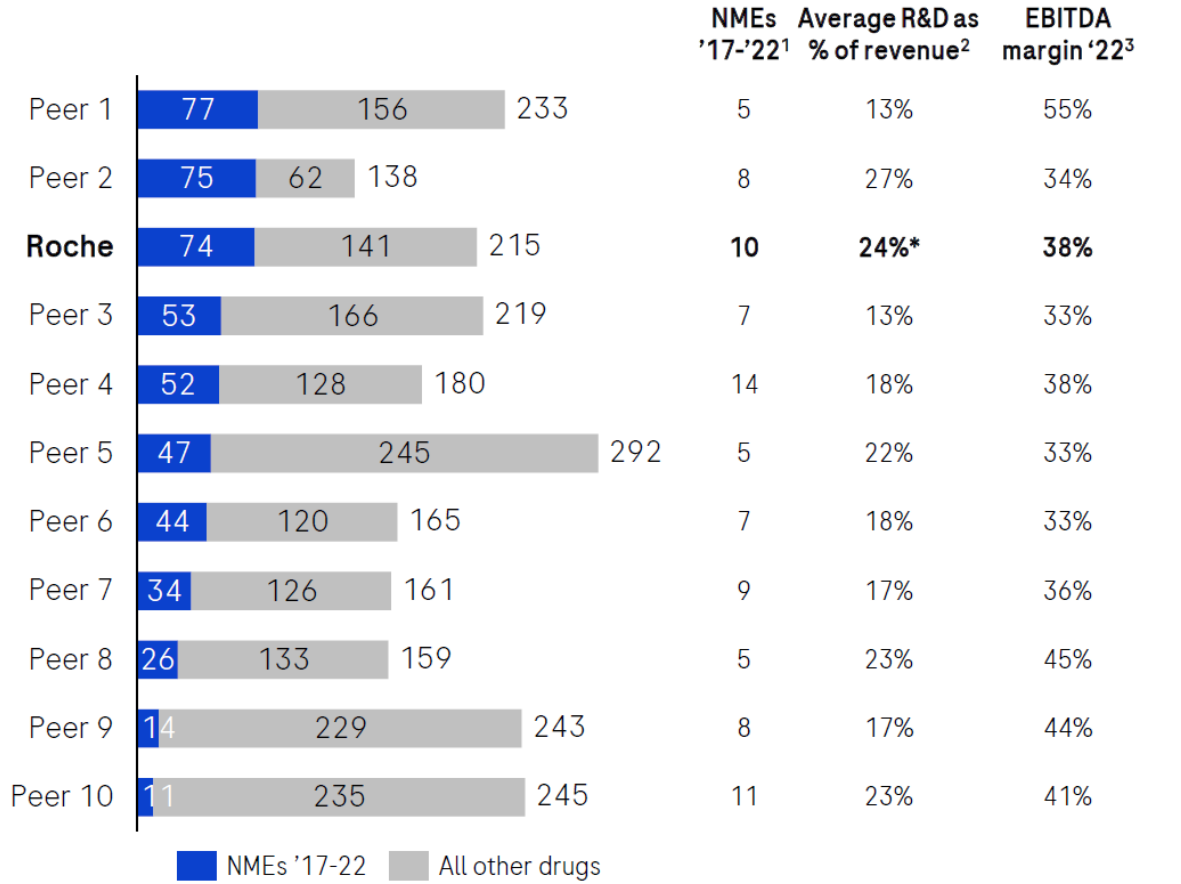
Commitment to innovation

After reallocating resources to R&D, focus is now on 'R&D Excellence'

HY Roche Pharma R&D investment allocation (2018-2023, % of OPEX, CHF bn)



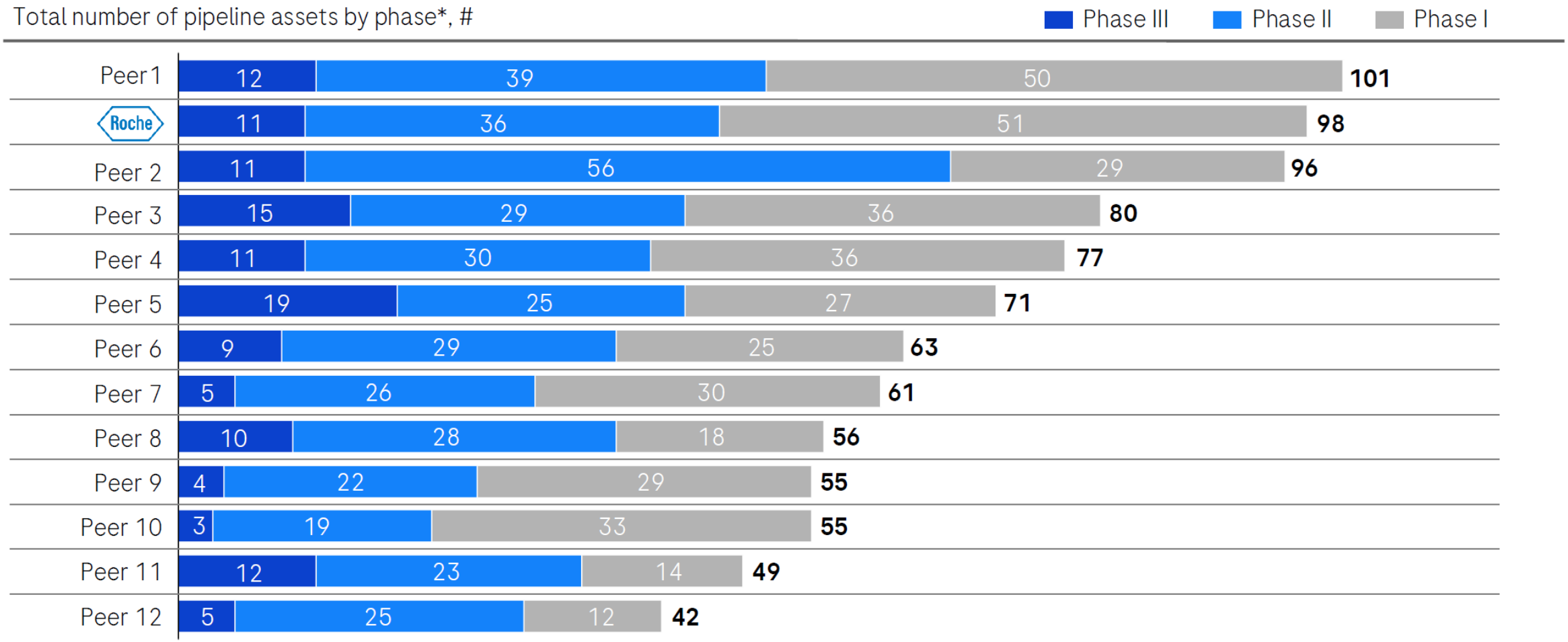
R&D investment and profitability[1] Recently approved NME share of NPV (2022, USD bn)



1 Evaluate Pharma, 2017-H1 2022 data; 2 Company financial reports 2018-2022; 3 Bloomberg; *Roche Pharma only

Number of pipeline assets in Phase I to III

Roche ranks #2 in total pipeline volume

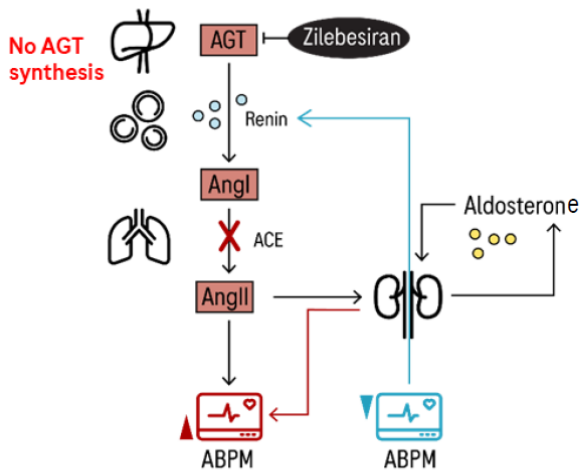


*Excludes pipeline products in pre-registration, registration and filed; Peer 1-12 are other large-cap Pharma
Source: Pharmaprojects (February 2023), McKinsey attrition analytics

Zilebesiran with best-in-disease potential in hypertension

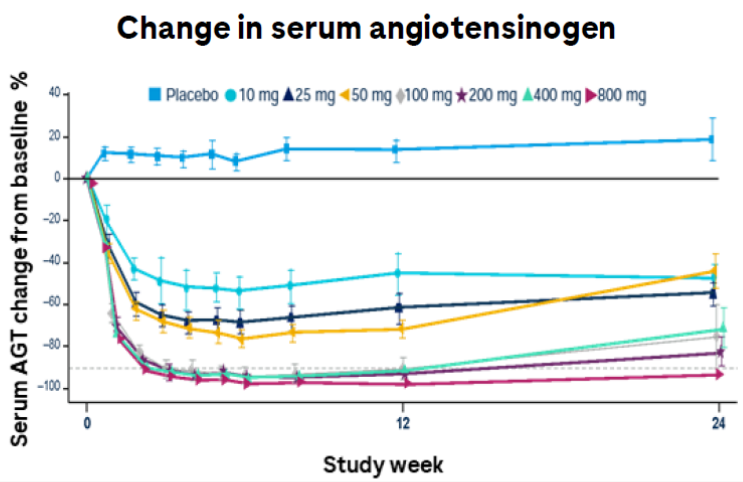
New MoA with tight upstream blockade of AGT pathway and strong early results

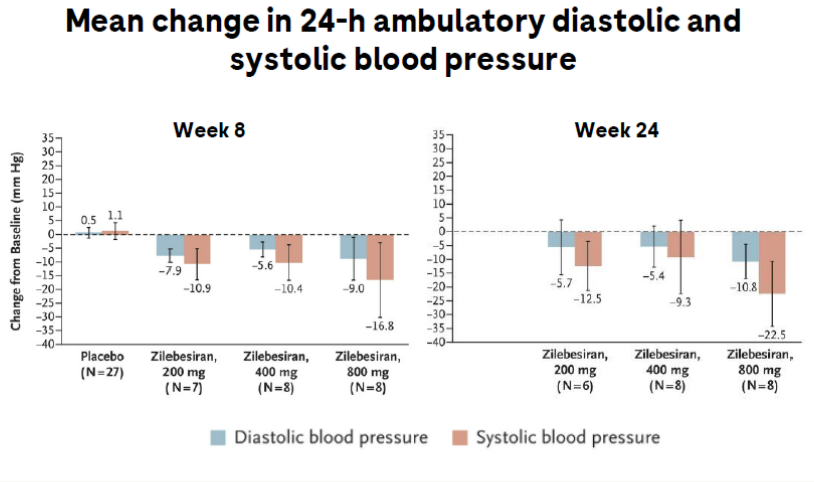
Zilebesiran (siRNA targeting AGT)



- siRNA targeting angiotensinogen, the precursor of all angiotensin peptides may avoid RAAS escape
- Consistent + durable blood pressure control with potential for improved adherence

Ph I results in hypertension[1]





- Positive Ph I results:
  - >90% reduction of serum AGT for up to 6 months at single SC dose of zilebesiran ≥100mg
  - Decreases in systolic blood pressure (>10 mm Hg) and diastolic blood pressure (>5 mm Hg) by week 8 and sustained at 24 weeks at single SC dose of zilebesian ≥200mg
- Well tolerated, only mild-to-moderate injection site reactions and no TRAEs, hypotension or significant alterations of renal/liver function

1 Desai et al. N Engl J Med 2023;389:228-38; MoA=mode of action; siRNA=small interfering RNA; SC=subcutaneous; RAAS=renin angiotensin aldosterone system; AGT=angiotensinogen; AngI/II=angiotensin I/II; ACE=angiotensin-converting enzyme; ABPM=ambulatory blood pressure monitoring; SoC=standard of care; TRAEs=treatment related serious adverse events; zilebesiran in partnership with Alnylam Pharmaceuticals

BMS R&D Day Highlights Growth Ahead

Research & Development Day

September 14, 2023

Bristol Myers Squibb™

Numerous levers to drive long-term growth

Strong Base Business with unrecognized durability

Increasingly de-risked New Product Portfolio

Expanding registrational pipeline from **6** to **12** new assets over next 18 months

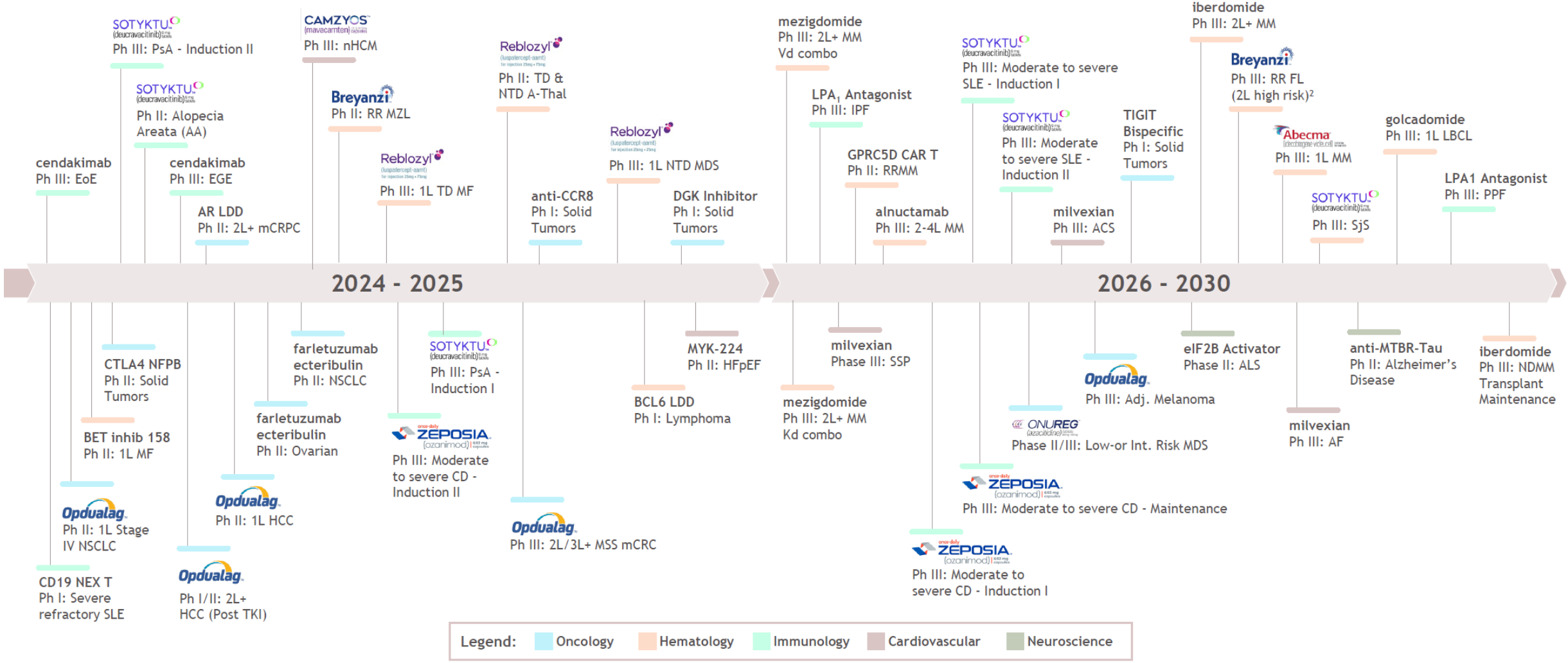
Robust early pipeline with **30+** assets & opportunity to deliver **~10** INDs a year

Increased R&D productivity

Strategic optionality from Business Development

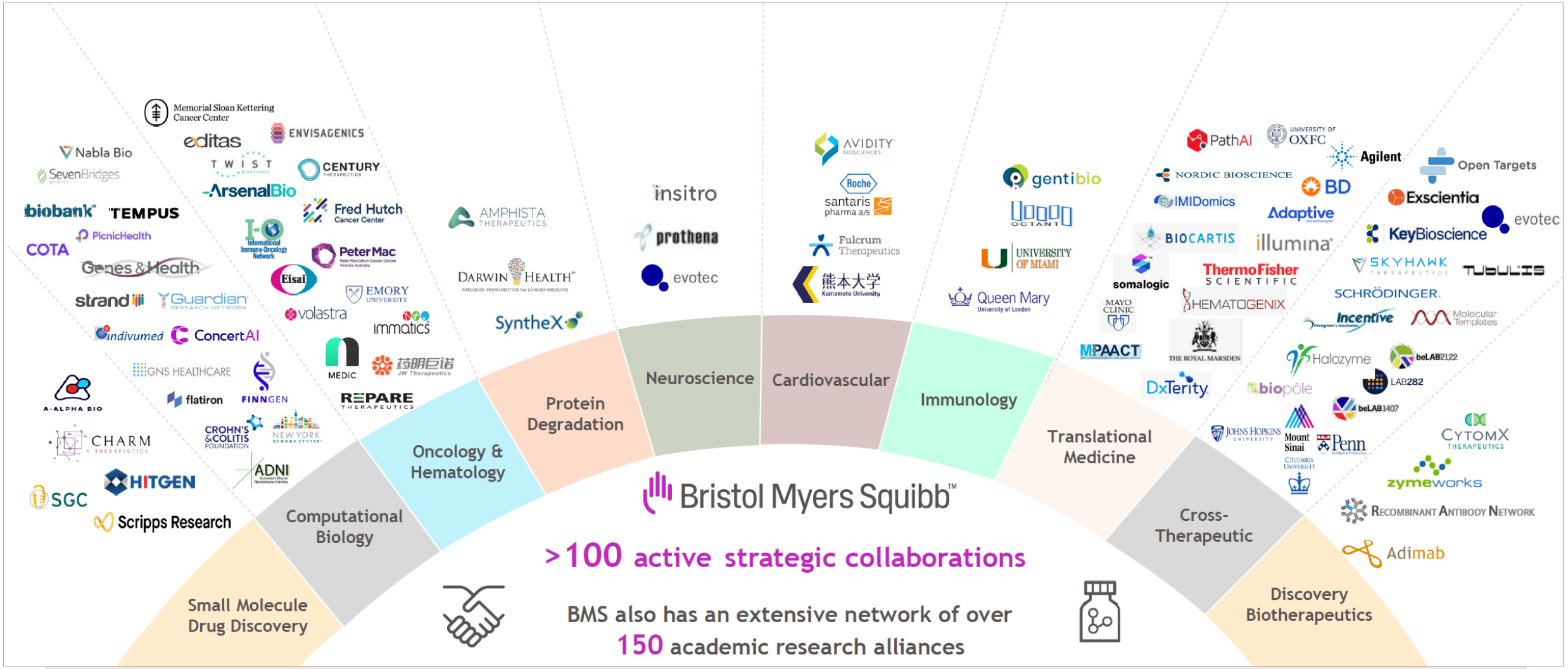
Source: https://www.bms.com/assets/bms/us/en-us/pdf/r-and-d-day/2023/bmy-r-and-day-presentation.pdf

BMS Has Impressive Group of Catalysts Ahead



Source: https://www.bms.com/assets/bms/us/en-us/pdf/r-and-d-day/2023/bmy-r-and-day-presentation.pdf

Internal R&D strengths are amplified through extensive network of external partnerships



moderna

Expanding the field of mRNA medicine

R&D day and business updates

September 13, 2023

Moderna's platform for harnessing the power of mRNA is being realized

Respiratory vaccines

3/3 positive Phase 3 programs

- **COVID:** Approved
- **RSV:** Filed
- **Flu:** Positive Phase 3 data

Latent + other vaccines

CMV: Phase 3 fully enrolled in adults

Oncology therapeutics

- **INT:** Positive Phase 2 data
- **INT:** Phase 3 in adjuvant melanoma enrolling
- **INT:** Phase 3 in NSCLC to begin in 2023

Rare disease therapeutics

3/3 programs with positive clinical signals

PA, MMA & GSD1a: Encouraging early data and preparing to move towards registrational studies

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Source: https://investors.modernatx.com/events-and-presentations/events/event-details/2023/Investor-Event---RD-Day-and-Business-Updates-2023-R6Uethcocx/default.aspx

Anticipating up to 15 product launches over the next 5 years

Our mRNA platform is delivering across cancer, rare disease, and infectious diseases

	Respiratory vaccines	Latent/other vaccines	Oncology	Rare disease
by 2025	**RSV** (older adults) mRNA-1345 **Seasonal Flu** mRNA-1010 **Flu/COVID** mRNA-1083 **NextGen COVID** mRNA-1283			
by 2028	**Flu/COVID/RSV** NextGen **RSV/hMPV** (older adults) mRNA-1365 **RSV** (2-18Y) mRNA-1345 **Pandemic Flu** mRNA-1018 **NextGen Flu** mRNA-1011/-1020 **Endemic hCOV** mRNA-1287	**CMV** mRNA-1647 **Norovirus** (older adults) mRNA-1403/-05 **EBV (IM)** mRNA-1189 **Lyme** mRNA-1975/-82 **VZV** mRNA-1468 **HSV** mRNA-1608	*Subject to regulatory discussions*[1] **INT** (adjuvant melanoma) mRNA-4157 **INT** (undisclosed indication) mRNA-4157 **INT** (adjuvant NSCLC) mRNA-4157	**MMA** mRNA-3705 **PA** mRNA-3927 **PKU** mRNA-3210 **GSD1a** mRNA-3745

Note: Subject to positive clinical data and regulatory discussions/approvals
1 Subject to future regulatory discussions, there may be potential for accelerated or conditional approvals in some markets

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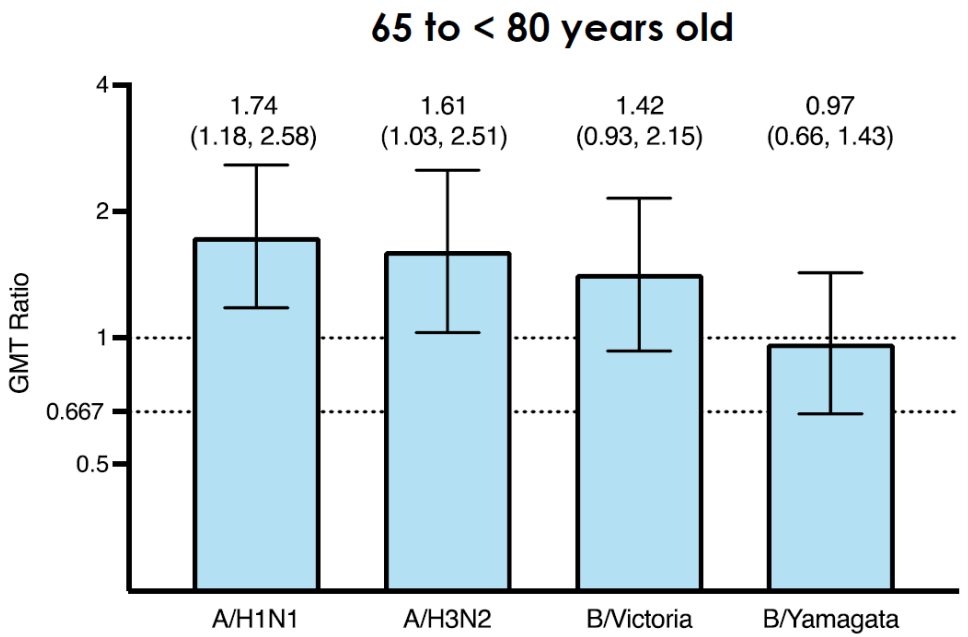
moderna

Moderna Flu Data Look Good

mRNA-1010 elicited similar or numerically higher titers compared to Fluzone® HD in a Phase 1/2 study

- mRNA-1010 was compared to a preferentially recommended enhanced vaccine for older adults (Fluzone® HD) in a clinical study
- Approximately 50 participants in each study arm
- Titers were similar or numerically higher than Fluzone® HD
- Supports future Phase 3 studies to formally compare immune responses to enhanced influenza vaccines



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Source: https://investors.modernatx.com/events-and-presentations/events/event-details/2023/Investor-Event---RD-Day-and-Business-Updates-2023-R6Uethcocx/default.aspx

Biomarin R&D Day Highlights Large Opportunities in R&D Portfolio

Proven R&D strategy & capability as a foundation for the future

History of R&D Success → **Four for Four on Major De-risking Events Over the Last Two Years** → **8 Approved Products**

100%

Commercialization rate for BioMarin Phase 3 assets

- VOXZOGO EU Approval
- VOXZOGO US Approval
- ROCTAVIAN EU Approval
- ROCTAVIAN US Approval

*Market Opportunities > $1 billion annual revenue

ROCTAVIAN® (valoctocogene roxaparvovec) Solution for intravenous infusion

Palynziq® (pegvaliase-pqpz) Injection

VOXZOGO® (vosoritide) for injection

VIMIZIM™ (elosulfase alfa)

KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution

Brineura™ (cerliponase alfa)

Naglazyme® (GALSULFASE)

ALDURAZYME® (LARONIDASE)

High Probability of Success for Clinical Programs

Sustained Credibility of Scientific Innovation

Strong Foundation of Commercial Success for Further Expansion and Growth

Source: https://investors.biomarin.com/image/2023+R%26D+Day_Final+1735ET.pdf

Indegene Survey: Most Pharma Executives Don't Feel Future Ready

Beth Snyder Bulik, Endpoints News, Sep 15, 2023 (excerpt)

"Pharma is not ready for the future. Only 10% say they're 'future ready,' according to a recent survey of pharmaceutical leaders by Indegene. That's a big decline from just two years ago when close to 60% told the commercial consulting group they felt well prepared for the future.

What's causing all the uncertainty? Two key changes — the emergence of generative AI and the passage of the Inflation Reduction Act — are disrupting pharma management peace of mind.

Leadership is pretty much insecure and saying 'we just don't know,' said Gaurav Kapoor, Indegene EVP and president of global operations. 'Not only around digital and technology maturity, but overall, 'are we mature enough?' More than half (53%) of the 110 executives surveyed 'strongly agree' that being ready for the future is an important business goal this year, while another 44% said they "somewhat agree."

Source: https://endpts.com/pharma-companies-arent-future-ready-as-pressure-mounts-from-ai-advances-and-ira-legislation-survey-finds/

Future Ready Healthcare | Indegene Digital Summit

Summit, Sep 21 to 22, 2023

Future Ready Healthcare

Future Ready Healthcare is an independent platform for inspiring conversations and thought-provoking content to build capabilities and culture for the future. Through avenues such as industry councils, thought leadership papers, and Indegene Digital Summit, healthcare leaders explore topics of common interest on the platform. They bring diverse perspectives and share personal stories to provoke and inform their strategy and operations. Indegene is proud to orchestrate these conversations that drive the future of healthcare. For any queries, contact the organizing team digitalsummit@indegene.com

https://digitalsummit.indegene.com/

2seventy bio Announces Strategic Restructuring to Prioritize Growth of Abecma, Streamline Pipeline Advancement and Preserve Financial Runway

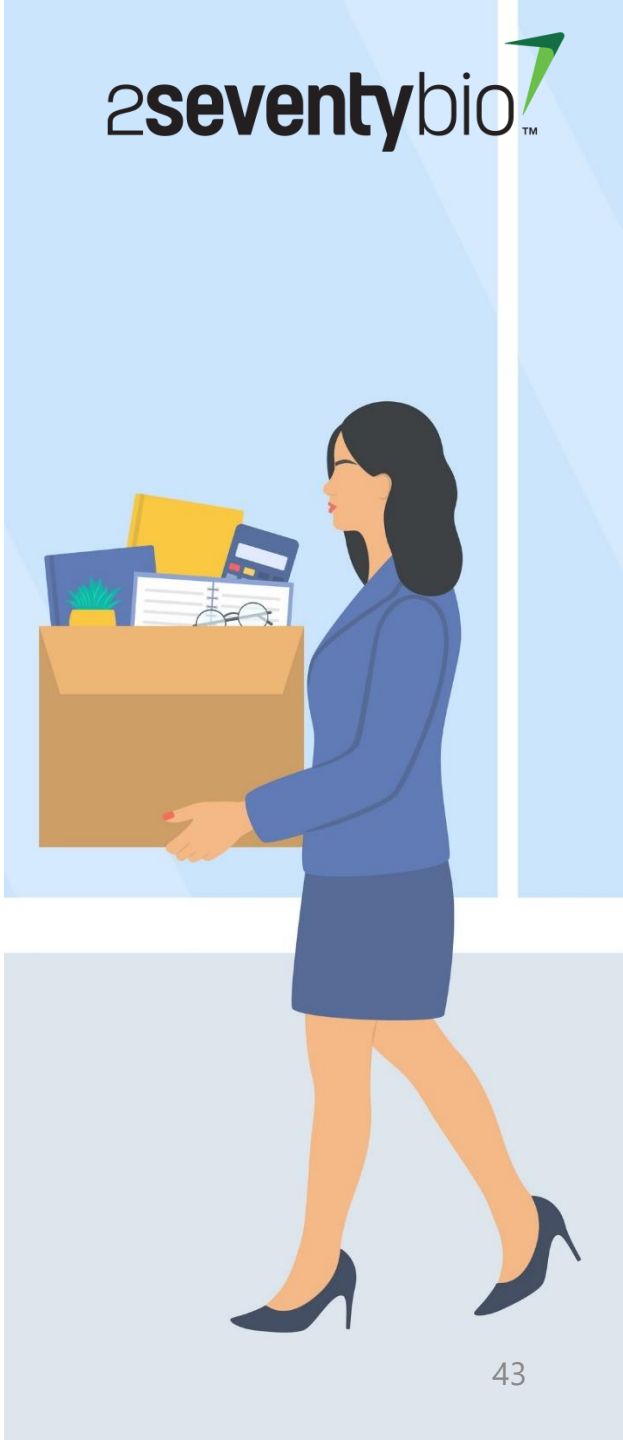
CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 12, 2023

2seventy bio, Inc. (Nasdaq: TSVT), today announced a restructuring of its business operations and research and development model to significantly reduce costs while supporting the execution of a prioritized plan for the long-term growth of the company.

"2seventy's mission remains the same: to unleash the power of the T-cell and develop un-incremental treatments for people living with cancer," said Nick Leschly, chief kairos officer. "However, the macro environment for oncology cell therapy companies and the near-term headwinds we have seen in our own business have led us to examine how we pursue our mission. Today we are taking hard but necessary steps to streamline our team and optimize our R&D approach and cost structure. In this process, we have focused on how to move efficiently and more cost effectively to develop innovative therapies for patients and create value for shareholders. Unfortunately, we will be saying goodbye to many highly talented and committed members of our team. I want to thank each of them for their amazing dedication to 2seventy and our mission to help those in need, doing everything we can to deliver more TIME."

"The difficult but necessary changes we are making to our workforce, our programs and our cost structure reflect our commitment to advancing our pipeline and achieving value creating milestones with existing cash," said Chip Baird, chief operating officer. "Our U.S. Abecma collaboration provides a source of revenue to offset investment in our pipeline programs, and while we continue to be optimistic about Abecma's future, particularly given the potential third-line label expansion at the end of the year, we are planning conservatively. We expect today's changes will preserve runway into at least 2026, and we will continue to focus on careful expense management and thoughtful capital allocation while staying true to our mission of driving programs forward for patients in need. I echo Nick's gratitude to the members of our team who will be departing 2seventy and look forward to continuing to uphold 2seventy's unwavering focus on patients as we move into a new chapter."

Source: https://ir.2seventybio.com/news-releases/news-release-details/2seventy-bio-announces-strategic-restructuring-prioritize-growth



Latecomer Amgen Takes ‘Platform Approach' in Obesity as PhII Data Loom

Amber Tong, *Endpoints News*, Sep 15, 2023

As Amgen catches up with leaders in the burgeoning obesity space, it’s underscoring a “platform approach” and shooting for “broad optionality” in the design of its Phase III.

Speaking at the Bank of America Merrill Lynch Global Healthcare Conference, Amgen CFO Peter Griffith spotlighted two of its obesity programs: AMG 133, a Phase II program that’s been named maridebart cafraglutide, or mari; and the Phase I candidate AMG 786. Mari is “enrolling well,” he noted; the study is tentatively set to read out in late 2024.

“We see obesity as an evolving market,” he said, according to a transcript provided by AlphaSense. “So we’re very excited about what we have to contribute to that evolving market and the patients that suffer from obesity.”

As Novo Nordisk’s Wegovy and Eli Lilly’s Mounjaro rake in megablockbuster revenue that promises to keep soaring, obesity treatments — particularly those that target the GLP-1 receptor — are in hot demand. In fact, the topic has come up in “almost all” of Amgen’s meetings with investors, according to Justin Claeys, vice president of investor relations.

“We feel like it’s very early days here,” he said at the conference, adding later: “We’re going to learn a lot more as the data comes out, and we’re certainly leaning hard into this.”

AMG 133 is bispecific, with an agonist of glucagon-like peptide-1 (GLP-1) and antagonist of the glucose-dependent insulinotropic polypeptide receptor (GIPR). But unlike the current options, it’s an antibody instead of a peptide. Early data have suggested signs of durability, and it’s currently in Phase II trials designed to enroll more than 570 patients — a broad program that Amgen hopes will lead to rich data and offer “optionality” when it comes time to start Phase III.

Then there’s AMG 786, which Claeys notes is an oral compound that “looks differently to other products that are on the market.” Phase I data are expected in the first half of next year.

Source: https://endpts.com/amgen-takes-platform-approach-in-obesity-as-phii-data-loom/

The Promise of MultiModal AI in Medicine

Eric Topol, *Science*, Sep 15, 2023 (excerpt)

Although most of the progress in image interpretation is attributable to supervised learning, which requires fully annotated inputs and ground truths, a major requirement to progress to multimodal AI was the use of self-supervised and unsupervised forms of learning. This preempted the laborious need for data annotation that would not be possible with the massive scale of inputs, as seen with large language models (LLMs, also known as generative AI). But it wasn't just the difference in types of learning or massive inputs that was needed to achieve LLMs such as ChatGPT. This required a new model architecture known as transformers, introduced by Vaswani and colleagues in 2017, to go beyond recurrent neural networks that rely on feedback from one time step to the next (like each word in a sentence), to encompass all the data (e.g., all the words in the sentence). The progression of these LLMs ultimately led to GPT-4, which is multimodal and thus capable of working with all forms of data, including text, audio, speech, and images. This was no small feat. For GPT-4, it took over 1 trillion model parameters (the number of connections between neurons), over 24,000 graphic processing units, >1024 floating point operations per second of computer performance, 45 gigabytes of training data, and self-supervised learning. Notably, the inputs for GPT-4 and the other major base models today, such as Bard, LLaMa, and PALM-2, were derived from Wikipedia, the Internet, and tens of thousands of books. There were no specific medical data used for training—that requires supervised fine-tuning, which is being intensely pursued for many of the use cases I describe below.

Now that LLMs are multimodal, no longer constrained to solely text inputs and outputs, their name should be considered a misnomer—as is "generative AI," because these models perform and excel at many other functions beyond generating, such as editing text. The inability to accurately name these models reflects their broad functionality, a concept that is further accentuated when their use cases in medicine are considered. And whatever model we are assessing today represents a work in progress, with substantial refinements to be expected, such as the capacity for providing updated medical knowledge in real time and improvement in the accuracy and quality of performance.

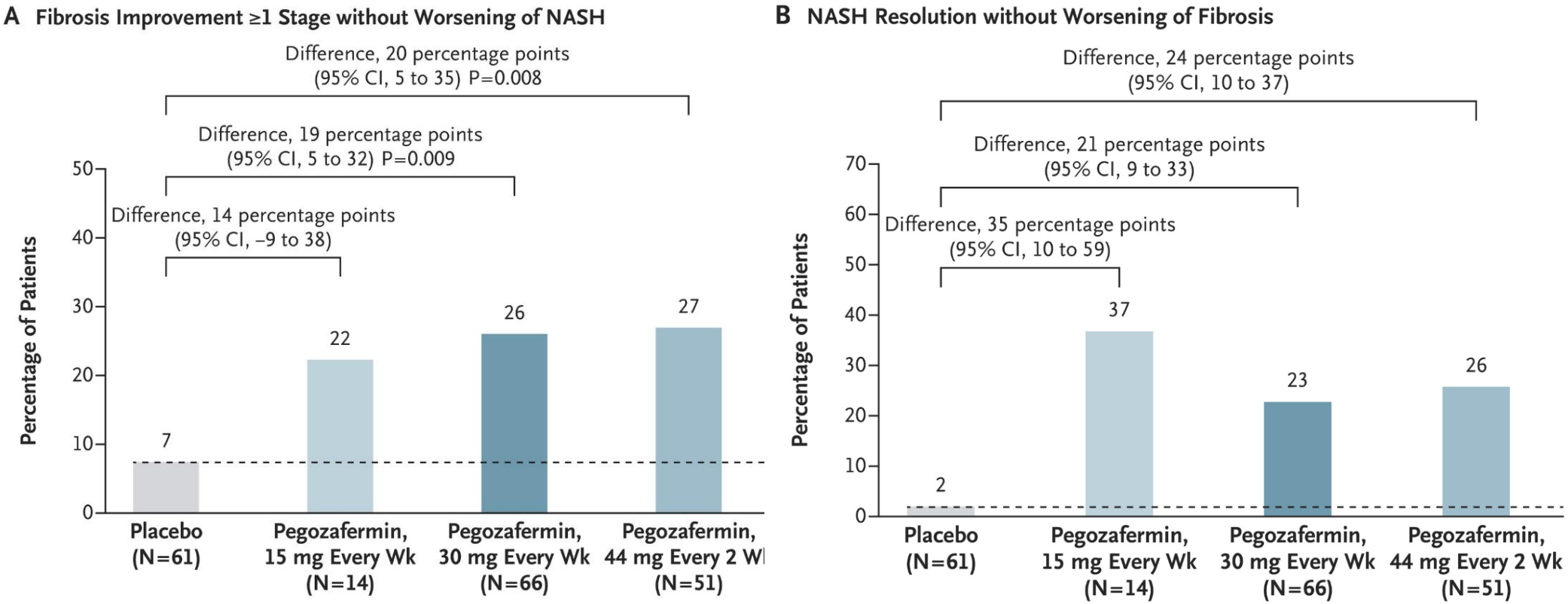
This multimodal AI has the potential for a wide range of data-driven applications. For people at risk for developing chronic medical conditions, a virtual health assistant could provide frequent feedback about their data to achieve prevention or better manage preexisting conditions. Take the example of a person who has high blood pressure and diabetes, and has a high polygenic risk score for developing heart disease. The virtual assistant would not only help achieve blood pressure and glucose control, to diminish the toll of these modifiable risk factors, but also analyze and coach the person on the basis of their physical activity, sleep, stress, retinal photos, unstructured text from medical records, and the latest medical literature. There are already virtual AI chatbot health assistants for specific conditions such as diabetes, hypertension, obesity, and depression, but none have yet become holistic or preventive.

Source: https://www.science.org/doi/full/10.1126/science.adk6139

Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH

Rohit Loomba, M.D., M.H.Sc. et.al., *New England Journal of Medicine*, September 14, 2023

The two primary end points were an improvement in fibrosis (defined as reduction by ≥1 stage, on a scale from 0 to 4, with higher stages indicating greater severity), with no worsening of nonalcoholic steatohepatitis (NASH) at 24 weeks, and NASH resolution (defined as the total absence of ballooning and absent or mild inflammation) without worsening of fibrosis (increase of ≥1 stage) at 24 weeks. Patients were assigned to receive placebo or pegozafermin at a dose of 15 mg every week, 30 mg every week, or 44 mg every 2 weeks.



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2304286

MDMA-Assisted Therapy for Moderate to Severe PTSD: a Randomized, Placebo-controlled Phase 3 Trial

Mitchell JM, Ot'alora G M, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, Paleos C, Nicholas CR, Quevedo S, Balliett B, Hamilton S, Mithoefer M, Kleiman S, Parker-Guilbert K, Tzarfaty K, Harrison C, de Boer A, Doblin R, Yazar-Klosinski B; MAPP2 Study Collaborator Group. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med. 2023 Sep 14.

This multi-site, randomized, double-blind, confirmatory phase 3 study evaluated the efficacy and safety of 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) versus placebo with identical therapy in participants with moderate to severe post-traumatic stress disorder (PTSD). Changes in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score (primary endpoint) and Sheehan Disability Scale (SDS) functional impairment score (key secondary endpoint) were assessed by blinded independent assessors. Participants were randomized to MDMA-AT (n = 53) or placebo with therapy (n = 51). Overall, 26.9% (28/104) of participants had moderate PTSD, and 73.1% (76/104) of participants had severe PTSD. Participants were ethnoracially diverse: 28 of 104 (26.9%) identified as Hispanic/Latino, and 35 of 104 (33.7%) identified as other than White. Least squares (LS) mean change in CAPS-5 score (95% confidence interval (CI)) was -23.7 (-26.94, -20.44) for MDMA-AT versus -14.8 (-18.28, -11.28) for placebo with therapy (P < 0.001, d = 0.7). LS mean change in SDS score (95% CI) was -3.3 (-4.03, -2.60) for MDMA-AT versus -2.1 (-2.89, -1.33) for placebo with therapy (P = 0.03, d = 0.4). Seven participants had a severe treatment emergent adverse event (TEAE) (MDMA-AT, n = 5 (9.4%); placebo with therapy, n = 2 (3.9%)). There were no deaths or serious TEAEs. These data suggest that MDMA-AT reduced PTSD symptoms and functional impairment in a diverse population with moderate to severe PTSD and was generally well tolerated. ClinicalTrials.gov identifier: NCT04077437 .

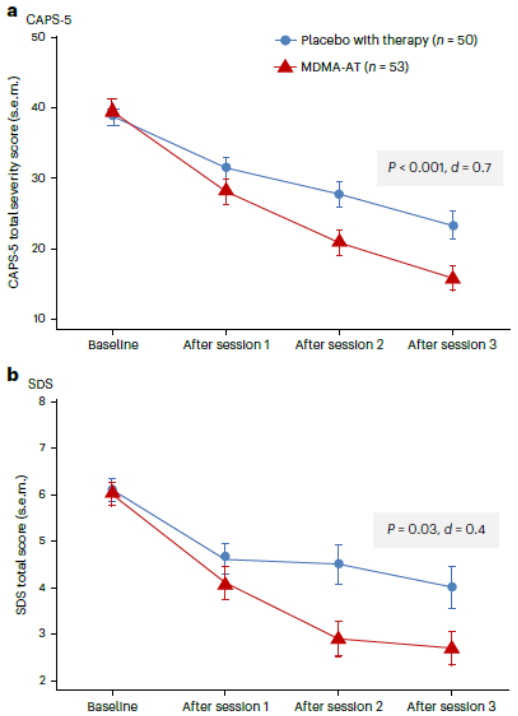


Fig. 2 | Measures of efficacy in the MDMA-AT and placebo with therapy groups. a, LS mean change (±s.e.m.) in CAPS-5 total severity score from baseline to after session 3 (primary outcome) for placebo with therapy ($n = 50$) versus MDMA-AT ($n = 53$, $P < 0.001$, Cohen's $d = 0.7$). **b**, LS mean change (±s.e.m.) in SDS total score from baseline to after session 3 (key secondary outcome) for placebo with therapy ($n = 50$) versus MDMA-AT ($n = 53$, $P = 0.03$, Cohen's $d = 0.4$).

Source: https://pubmed.ncbi.nlm.nih.gov/37709999/

Early Diabetes Especially Deadly

Emerging Risk Factors Collaboration. Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation. *Lancet Diabetes Endocrinol.* 2023 Sep 11:S2213-8587(23)00223-1.

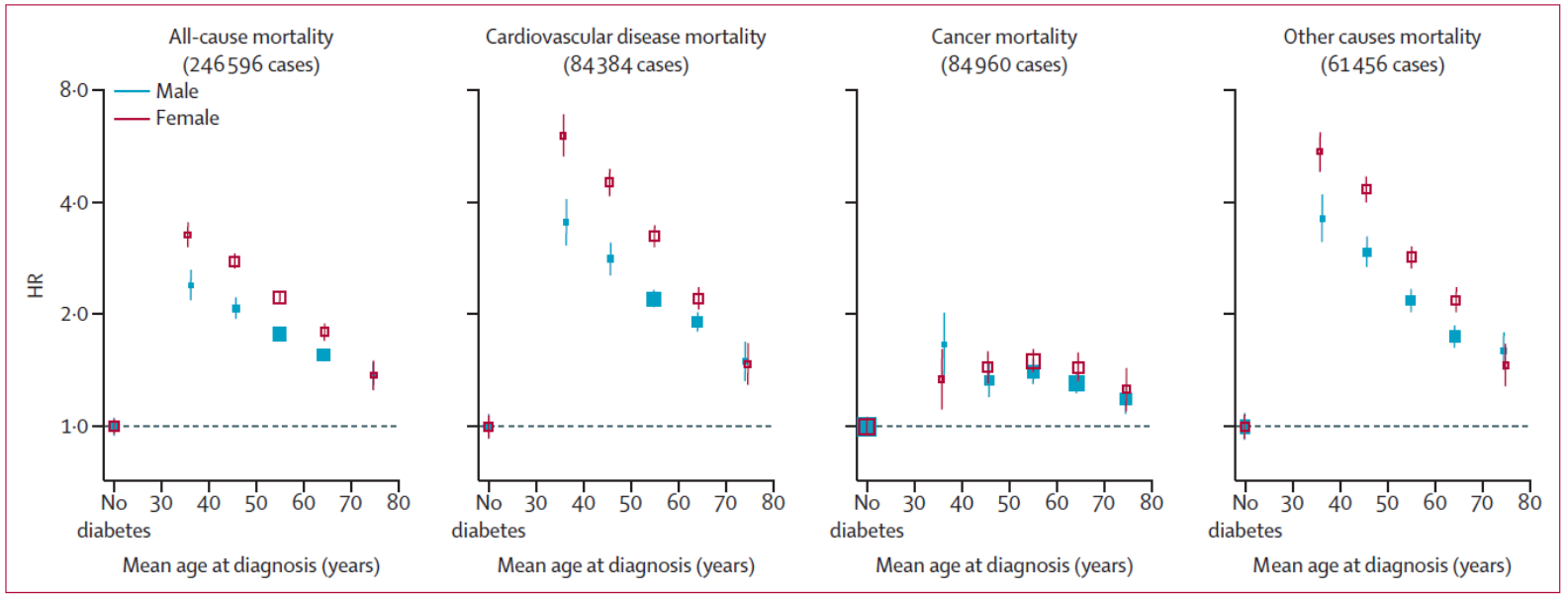


Figure 1: **Sex-specific HRs for all-cause and cause-specific mortality according to age at diagnosis of type 2 diabetes**
The mean age at diagnosis for the categories 30 to <40 years, 40 to <50 years, 50 to <60 years, 60 to <70 years and ≥70 years is plotted on the x axis. HRs are adjusted for age, and the reference (1·0) is people without diabetes. Studies with fewer than ten events of any outcome were excluded from the analysis of that outcome. The sizes of the boxes are proportional to the inverse of the variance of the log-transformed HRs. Vertical lines represent 95% CIs. HR=hazard ratio.

Every decade of earlier diagnosis of diabetes was associated with about 3-4 years of lower life expectancy, highlighting the need to develop and implement interventions that prevent or delay the onset of diabetes and to intensify the treatment of risk factors among young adults diagnosed with diabetes.

Source: https://pubmed.ncbi.nlm.nih.gov/37708900/

Quantifying the Causal Impact of Biological Risk Factors on Healthcare Costs

Lee J, Jukarainen S, Karvanen A, Dixon P, Davies NM, Smith GD, Natarajan P, Ganna A. Quantifying the causal impact of biological risk factors on healthcare costs. *Nat Commun*. 2023 Sep 13;14(1):5672.

Understanding the causal impact that clinical risk factors have on healthcare-related costs is critical to evaluate healthcare interventions. Here, we used a genetically-informed design, Mendelian Randomization (MR), to infer the causal impact of 15 risk factors on annual total healthcare costs. We calculated healthcare costs for 373,160 participants from the FinnGen Study and replicated our results in 323,774 individuals from the United Kingdom and Netherlands. Robust causal effects were observed for waist circumference (WC), adult body mass index, and systolic blood pressure, in which a standard deviation increase corresponded to 22.78% [95% CI: 18.75-26.95], 13.64% [10.26-17.12], and 13.08% [8.84-17.48] increased healthcare costs, respectively. A lack of causal effects was observed for certain clinically relevant biomarkers, such as albumin, C-reactive protein, and vitamin D. Our results indicated that increased WC is a major contributor to annual total healthcare costs and more attention may be given to WC screening, surveillance, and mitigation.

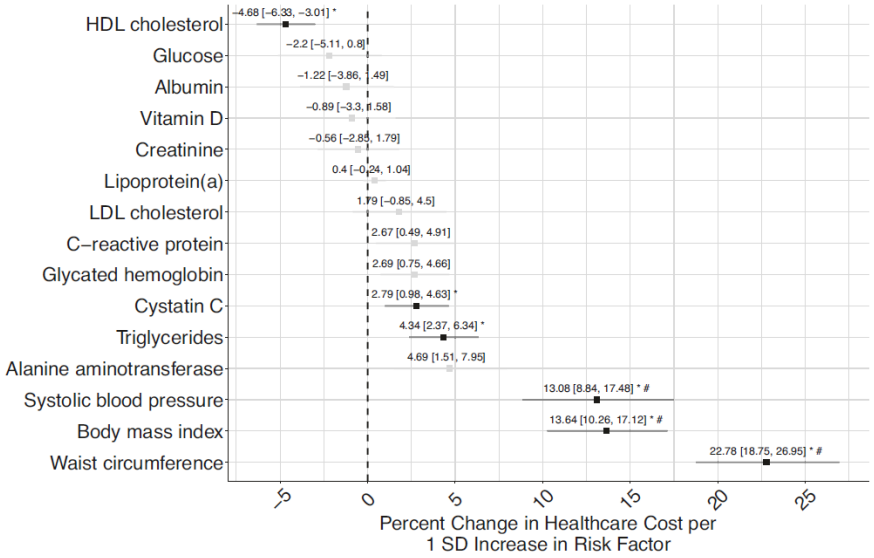


Fig. 3 | Mendelian randomization on 15 biological risk factors on annual total healthcare costs for 373,160 FinnGen participants using the two-sample, inverse variance weighted approach. HDL cholesterol (P=7.23×10−8), cystatin C (P=2.35×10−3), triglycerides (P = 1.24×10−5), systolic blood pressure (P=2.80×10-10), body mass index (P = 1.06×10−16), and waist circumference (P = 1.90×10−33) had a significant, causal effect on annual total healthcare costs. Two-sided p values were calculated from the effect estimates and standard errors of the Mendelian Randomization model and adjusted for multiple hypothesis testing. Bars indicate 95% confidence interval. Black bars and the * symbol indicate biological risk factors that are statistically significant at the Bonferroni-corrected significance level (P<3.33×10−3).

Source: https://pubmed.ncbi.nlm.nih.gov/37704630/

‘Inverse Vaccine’ Could Help Tame Autoimmune Diseases

Mitch Leslie, *Science*, Sep 15, 2023

Vaccines rile up the immune system against pathogen invaders. But in autoimmune diseases, the immune system becomes the enemy. Scientists have now figured out a way to tamp down this self-destructive response in mice by attaching sugars to molecules that provoke immune cells. This “inverse vaccine,” reported this month in *Nature Biomedical Engineering*, could potentially lead to new ways to combat autoimmune diseases such as multiple sclerosis (MS) and lupus.

“It’s a strong piece of work,” says Lawrence Steinman, a neuroimmunologist at Stanford Medicine who wasn’t connected to the study. The work, he says, offers “a cool new way” to potentially defuse self-destructive immune attacks. But Steinman and others caution that many other promising methods for taming the immune system in autoimmune diseases have faltered.

The immune system responds to molecules—or pieces of them—known as antigens. Most of the time they come from dangerous invaders like viruses and bacteria. But some immune cells react to self-antigens, molecules from our own cells. And in autoimmune diseases, these misguided immune cells turn against patients’ own tissues.

A team led by immunoengineer Jeffrey Hubbell, immunologist Andrew Tremain, and biomedical engineer Rachel Wallace of the University of Chicago has been exploring a new approach: directing potential self-antigens to the liver. The organ is crucial for establishing tolerance. Immune cells there pick up self-antigens and then stifle T cells that could target these molecules. The researchers came up with a way to steer antigens to the liver by affixing them to a chain of sugars.

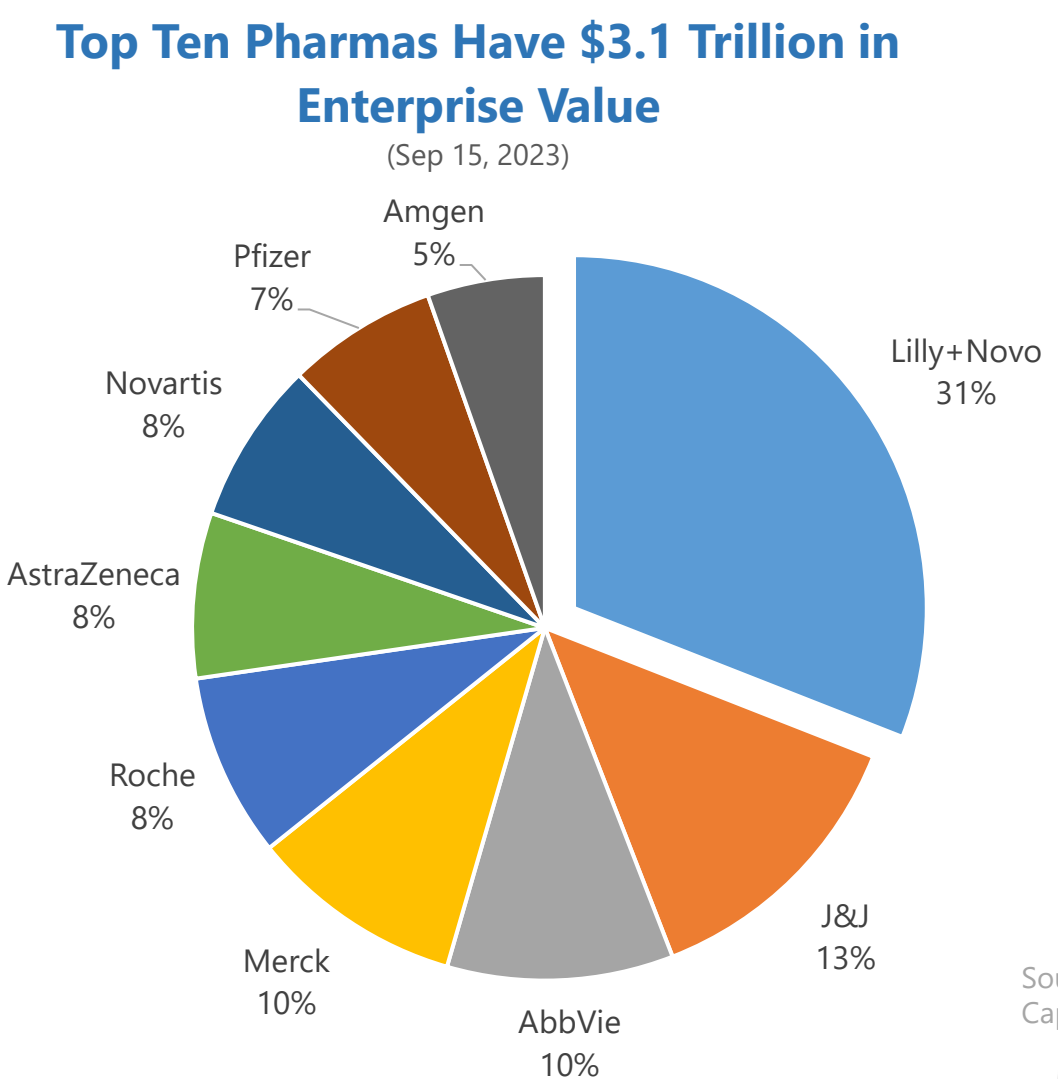
When researchers inject an egg white protein into mice, it normally spurs a strong immune reaction. To gauge the capability of their approach, Hubbell and colleagues first asked whether it could curb this response. The team injected the protein into mice and then gave the animals three doses of the antigen attached to the sugar chain. When the scientists later analyzed the rodents’ lymph nodes and spleen, they found that the inverse vaccine weeded out and suppressed T cells that targeted the protein. These changes “all work together to reestablish immune balance,” Wallace says.

Source: https://www.science.org/content/article/inverse-vaccine-could-help-tame-autoimmune-diseases

The Grand Game in Pharma

The Grand Game in Pharma: An Essay

Last week we wrote at some length about recent developments in health systems in the United States, noting that new entrants such as Amazon, CVS and Optum are in the process of disrupting a well-developed marketplace occupied largely by regional non-profit systems like Ascension, Advent and Intermountain. We also noted that two once middle ranked large pharmaceutical companies account for over 30% of the total value of the top ten pharmaceutical companies in the world (see chart). The dynamism of the relative value rankings in the pharma industry has been high for decades. The data very clearly show that the industry has witnessed ongoing "creative destruction" and rivalry that belies the recent picture given by the FTC of a static, consolidated and anticompetitive industry (see table on next page).



Source: CapIQ

Continual Change in Big Pharma Rankings

The list of the top 15 big pharmas of 1974 is barely recognizable today, containing only 6 companies that remain independent. The ranks of the top players in the industry are highly dynamic as the advent of new products and modalities and patent expiries on the old, drive dramatic change. Also notable is the decline in the EU pharma sector – once the source of most industry sales. Noteworthy is the industry's massive long-term growth (6% revenue growth after inflation, on average since 1974 – far above GDP growth).

Top 15 Pharma Players Ranked by Revenue $mm, 1974-2027

1974

Company	Revenue ($mm)
Roche	$1,386
Merck	$1,197
Hoechst	$1,174
Ciba-Geigy	$1,063
Bayer	$862
Sandoz	$847
Eli Lilly	$789
American Home Products	$758
Pfizer	$740
Upjohn	$683
Warner-Lambert	$611
Rhone-Poulenc	$595
Sterling	$566
Abbott	$551
Boehringer-Ingelheim	$506
Sales of Top 15	$12,328
Sales in 2023 dollars	$77,419

1988

Company	Revenue ($mm)
Merck	$4,984
Glaxo	$4,213
Hoechst	$3,868
Bayer	$3,628
Ciba-Geigy	$3,466
American Home Products	$3,218
Sandoz	$3,089
Takeda	$3,076
Eli Lilly	$2,680
Abbott	$2,599
Pfizer	$2,539
Warner Lambert	$2,509
Bristol-Myers	$2,509
Eastman Kodak	$2,500
Roche	$2,365
Sales of Top 15	$47,243
Sales in 2023 dollars	$123,638

2005

Company	Revenue ($mm)
Pfizer	$44,280
GlaxoSmithKline	$33,960
Sanofi-Aventis	$32,340
Novartis	$24,960
AstraZeneca	$23,950
Johnson & Johnson	$22,320
Merck	$22,010
Wyeth	$15,320
Bristol-Myers Squibb	$15,250
Eli Lilly	$14,650
Abbott	$12,900
Roche	$12,900
Amgen	$12,020
Boehringer-Ingelheim	$10,840
Takeda	$8,530
Sales of Top 15	$306,230
Sales in 2023 dollars	$426,048

2014

Company	Revenue ($mm)
Novartis	$53,717
Pfizer	$49,605
Sanofi	$41,287
Roche	$40,129
Merck	$36,042
Johnson & Johnson	$32,213
GlaxoSmithKline	$28,939
AstraZeneca	$26,095
Gilead Sciences	$24,890
Amgen	$20,063
AbbVie	$19,960
Eli Lilly	$19,616
Bristol-Myers Squibb	$15,879
Novo Nordisk	$14,434
Boeheringer Ingelheim	$13,424
Sales of Top 15	$436,292
Sales in 2023 dollars	$570,663

2022

Company	Revenue ($mm)
Pfizer	$92,951
Merck	$57,869
AbbVie	$53,729
Novartis	$52,222
Sanofi	$50,194
Roche	$50,013
Bristol-Myers Squibb	$45,848
Johnson & Johnson	$45,572
AstraZeneca	$43,840
GlaxoSmithKline	$32,818
Takeda	$30,297
Eli Lilly	$27,691
Gilead	$27,483
Novo Nordisk	$27,459
Amgen	$26,190
Sales of Top 15	$664,177
Sales in 2023 dollars	$702,525

2027 (est.)

Company	Revenue ($mm)
Merck	$72,550
Pfizer	$68,900
AbbVie	$60,770
Sanofi	$60,100
AstraZeneca	$59,600
Novartis	$59,390
Eli Lilly	$55,940
Novo Nordisk	$53,880
Johnson & Johnson	$51,000
Roche	$50,000
Bristol-Myers Squibb	$47,900
GlaxoSmithKline	$44,280
Amgen	$32,680
Gilead	$29,770
Takeda	$27,650
Sales of Top 15	$774,410
Sales in 2023 dollars	$819,123

Sources: CapitalIQ and 2022 Torreya Pharma 1000 report data for 2014 to 2022 period. Harvard Business School for 1974 to 2005 data (see https://www.hbs.edu/ris/Publication%20Files/09-118.pdf). CapitalIQ analyst consensus average revenue estimates taken for 2027 revenue except for J&J and Roche where analyst reports were analyzed to take the pharma division revenue estimate average for 2027. U.S. CPI index used to inflation adjust numbers to 2023 (https://www.minneapolisfed.org/about-us/monetary-policy/inflation-calculator/consumer-price-index-1913-).

Competitive Dynamics are Changing

We expect to see increasing convergence of players across the healthcare spectrum in time. That is, it is likely that care providers like Amazon or CVS will enter the pharma space (either directly or by partnership) and it is also likely that pharma will become involved in the provision of care. But this entry will be spearheaded by the introduction of innovation to care packaged with drugs rather than by buying hospitals etc.

We wish to aver from further discussion of convergence today issue as we have amply touched on this topic in past issues of this weekly market report.

Rather, we wish to talk about how competition between pharma companies might unfold in the next ten to twenty years. We will call this emerging competitive dynamic the “grand game” of the industry and wish to outline what we see as some the key rules of play.

Redefining the Concept of a "Blockbuster" Drug

In past issues we have noted that the four pharma companies that have added the most value since the Pandemic began are those pursuing "pipeline-in-a-pill" or polyindication drug opportunities. Drugs that address a fundamental aspect of human physiology (e.g., removing a key checkpoint that halts immune attack on a tumor) have numerous applications and obvious substantial positive implications for human health. The next page identifies some of the many large polyindication opportunities today.

The rules of the game in the industry are evolving insofar as the old days of aiming for $1 billion revenue "blockbusters" are increasingly quaint. Value is being driven by products that can generate revenue of $25 billion or more. These giant drugs are far and few between. The analysis at right shows the characteristics of 168 drugs approved in the 2011 to 2020 decade. Only 36 of these had sales over $1bn, but these accounted for 70% of the revenue.

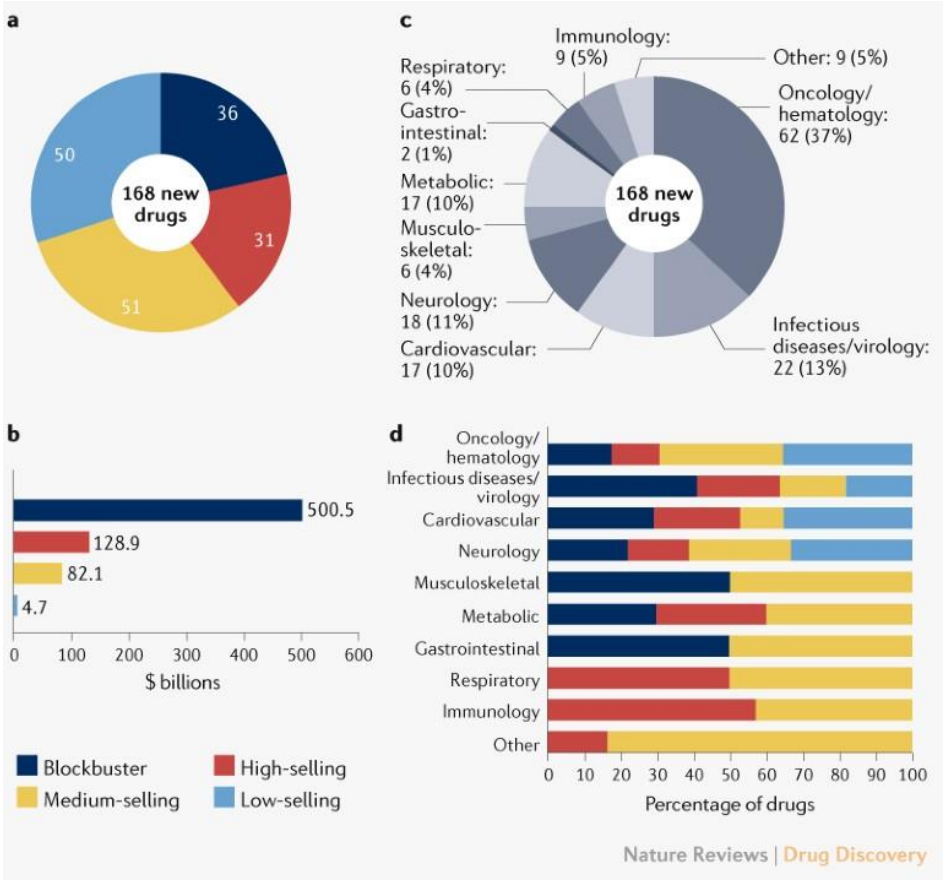


Fig. 1 | Characteristics of 168 new drugs launched by the top 20 pharmaceutical companies from 2011–2020. a, Number of new drugs in four categories based on their mean average annual sales since entering the market: blockbusters (>US$1.000 billion); high-selling drugs ($0.5–0.999 billion); medium-selling drugs ($0.1–0.499 billion); and low-selling drugs (<$0.1 billion). **b**, Total sales of the drugs in each category from 2011–2020. **c**, Distribution of the drugs based on their primary therapeutic area. **d**, Number of drugs in the four sales categories in each therapeutic area.

Source: Schuhmacher A, Hinder M, Boger N, Hartl D, Gassmann O. The significance of blockbusters in the pharmaceutical industry. Nat Rev Drug Discov. 2023 Mar;22(3):177-178.

Emerging PiP or PolyIndication Drug Areas

What each of these drug areas have in common is that they are no longer focused on a single phenotypic condition but instead address some type of *fundamental* physiology.

	B-cell Driven Disease	Fibrotic Disease	Auto-Inflammation
Disease Description	Diseases caused by IgG Autoantibodies	Excess deposition of collagen from fibroblasts	Excess expression of IL-1β, IL-6 and IL-18
Key Mechanism	FcRn: Prevention of transcytosis of IgG	Inhibition of factors that trigger fibrosis	NLRP3: Downregulation of IL-1b, IL-6, IL-18
Number of Diseases / Revenue Potential	Over 100 diseases / $100 Billion+	Over 50 diseases / $50 Billion+	Over 100 diseases / $100 Billion+
Key Players Today (those with positive PoC data)	Argenx Immunovant J&J UCB	Boehringer Ingelheim Pliant Therapeutics	Novartis Roche Ventyx Zydus Cadila

The “Go Big or Go Home” Mindset

Even more importantly, these blockbuster drugs account for the bulk of the profitability after adjusting out the cost of R&D. Perhaps this is a triviality. Products that do better make more money.

Our point is a slightly different one. Relatively few pharma companies have approached the market designing their business to produce giant products. Some companies are built around vertical areas of expertise like dermatology; other companies have a technology edge (perhaps making humanized antibodies); others have good biology or chemistry departments.

We would suggest that going forward it will be increasingly important to design a corporate mindset designed around transformational drugs that present very large market opportunities. There are a number of good reasons to take this “go big or go home” approach.

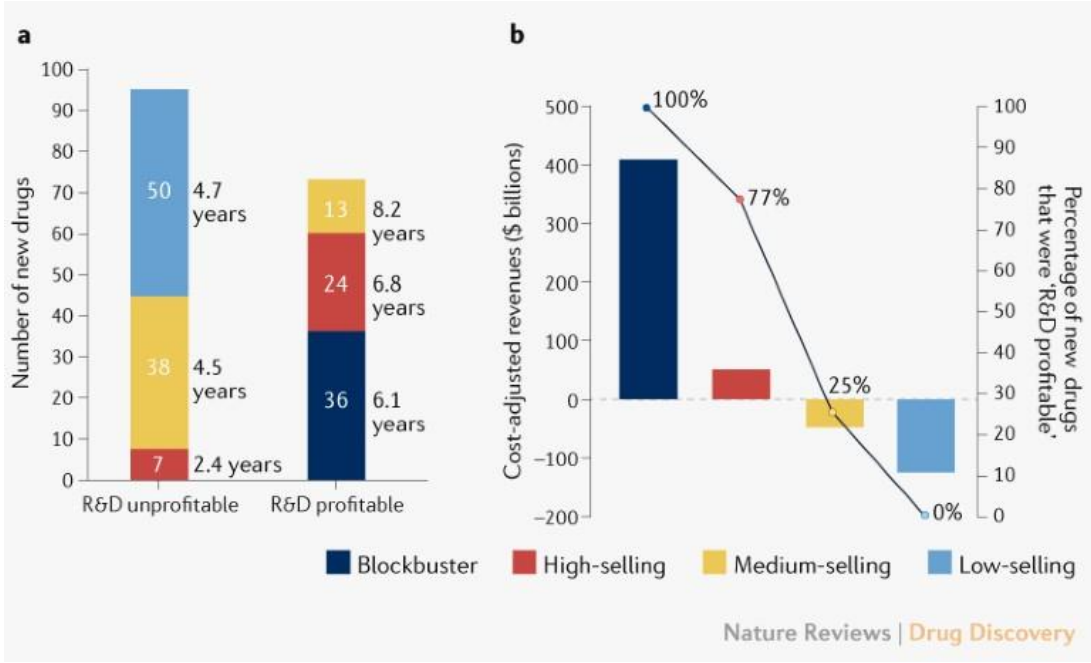


Fig. 2 | Estimated return on investment from new drug launches by the top 20 pharmaceutical companies from 2011–2020. Using a benchmark of US$2.6 billion as the capitalized cost of bringing a new drug to market, the 168 drugs grouped into the four sales categories defined in Fig. 1 were assigned into two subcategories: drugs that reached at least $2.6 billion in cumulative sales since launch (‘R&D profitable’) or drugs that did not (‘R&D unprofitable’). **a**, Number of ‘R&D profitable’ and ‘R&D unprofitable’ new drugs per sales category. The average number of years on the market for drugs in each category since approval is shown next to the bars. **b**, Contribution of the revenue from drugs in each sales category to the overall estimated return on R&D investment in the group of 168 new drugs, based on the assumption that each new drug cost $2.6 billion to bring to market, and the percentage of new drugs in each product category considered to be ‘R&D profitable’.

Source: Schuhmacher A, Hinder M, Boger N, Hartl D, Gassmann O. The significance of blockbusters in the pharmaceutical industry. Nat Rev Drug Discov. 2023 Mar;22(3):177-178.

R&D Strategies Focused on Smaller Market Opportunities Have Low Payoffs

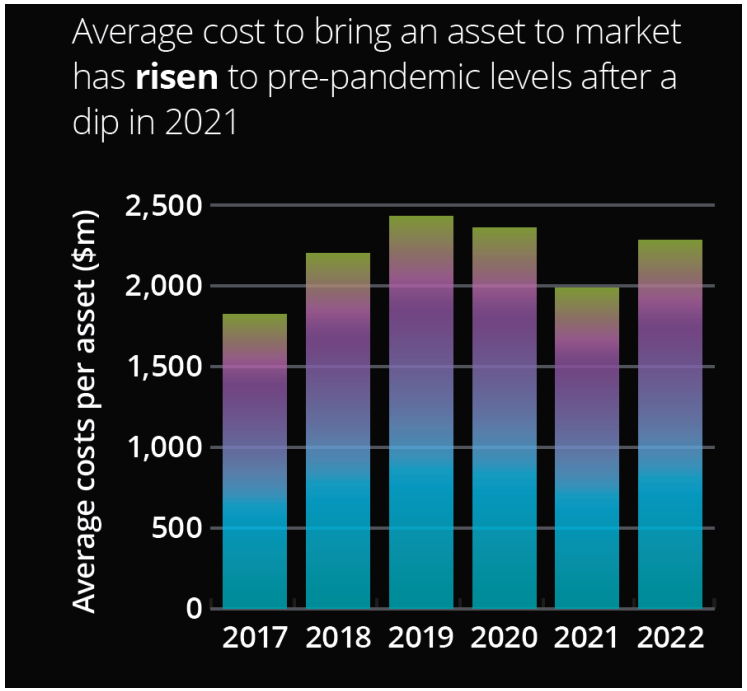
First, approval probabilities are low. Less than three percent of preclinical drugs are ever approved. Second, the cost of R&D is rising. It's just expensive. Deloitte estimates that the average cost to bring a drug to market today is over $2 billion. See chart at right.

Third, exclusivity periods are short. A new drug usually doesn't get close to 20 years of exclusivity. The average time for arrival of branded competition is seven years. On average, sales start to decline twelve years after launch.[1]

Fourth, returns on R&D are not good. As shown on the previous page, returns on R&D for smaller products are particularly low. The average return on pharma R&D investment has been close to zero.[2] A recent report by Deloitte estimates the return on late-stage pharma R&D and finds that in 2022 it was less than one percent. Lest this not sound terrible, bear in mind that pharma companies have an opportunity cost of capital that should be somewhere in low double digits given where Treasuries are. Put another way, most R&D spend is causing shareholders to lose money.

Deloitte.

Report on pharma innovation, Jan 2023



Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

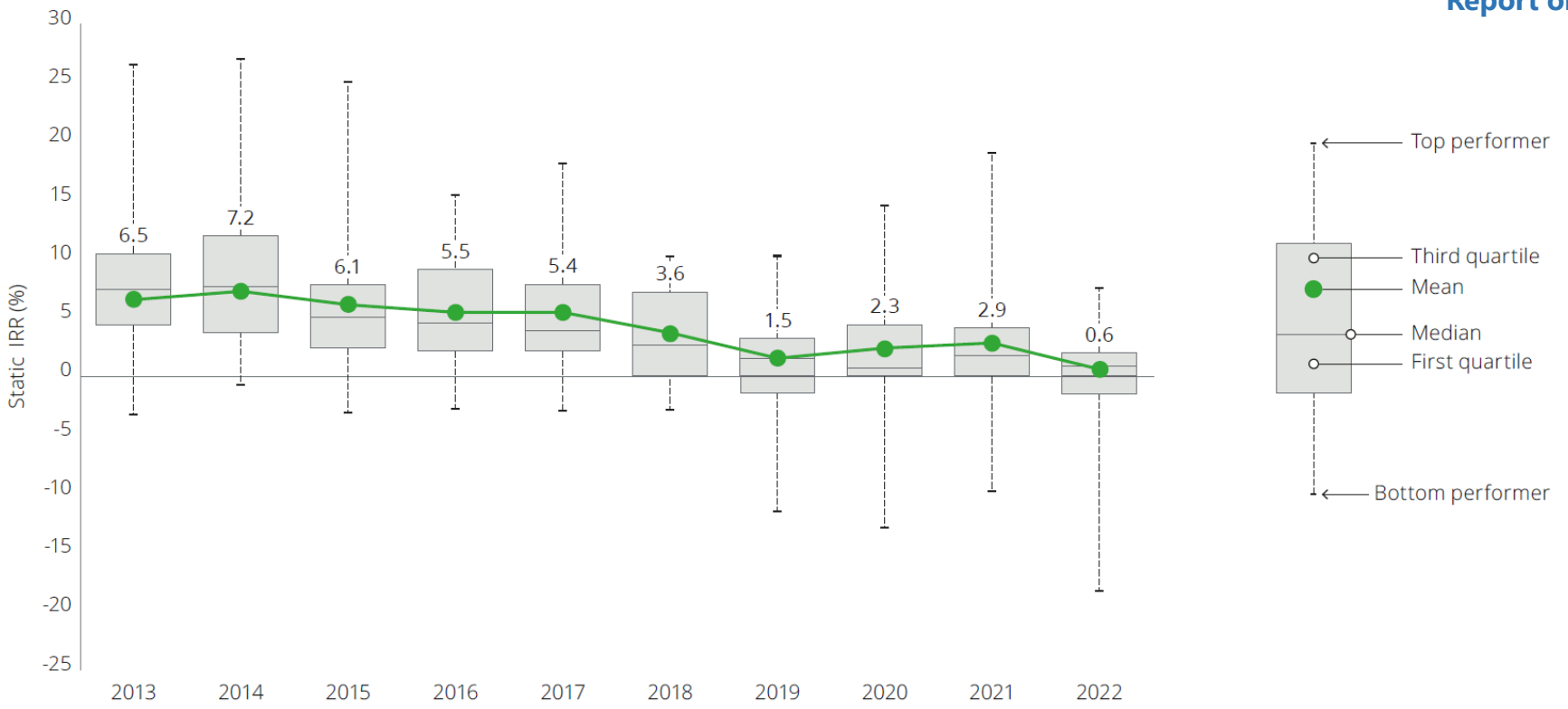
[1]See IQVIA Institute, *Lifetime Trends in Biopharmaceutical Innovation*, 2017. (link)
[2]See Standish Fleming, "Why Pharma Risk Is Inherently Unpredictable And Why It Matters," *Forbes* Nov 6, 2018. (link)

Pharma R&D Returns are Close to Zero

Deloitte.

Report on pharma innovation, Jan 2023

Figure 3. Return on late-stage pipeline, 2013-22, without EUA assets



Source: Deloitte analysis, 2022.

Please note: 2013-2019 data includes the 15 companies of the combined cohort; 2020-2022 data includes the results of the top 20 companies by 2019 R&D spend. See appendix 2 for the data of each cohort. Compared to last year's report 2020 and 2021 figures have been restated to include the top 20 companies by R&D spend as of 2020.

"Last year we witnessed a notable rise in IRR to 6.8%, driven by forecasted high-value COVID-19 assets (including vaccines and treatments) and one high-value late-stage neurological asset that has subsequently underperformed post-launch and is no longer seeking approval beyond the FDA. As some of these assets have moved into the commercial portfolio, the IRR has declined to 1.2%. This is driven by the successful approvals of high-value forecasted assets that have been commercialized and therefore left the scope of our analysis."

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

What Makes a Giant Market?

The key phrase that identifies large markets is “transformational treatments”. Almost universally, drugs developed by pharmaceutical companies are helpful but not transformational. Most drugs developed in the last two decades in immunology, oncology and psychiatry are not disease modifying but instead offer important symptomatic relief. If you take, Lipitor®, say, your risk of a heart attack goes down by 30%. That’s great. Incredibly helpful. But not transformational.

In contrast, if you take one of the modern GLP-1 drugs as directed - for enough time, you will get to a normal body weight – as long as you don’t park yourself inside a McDonalds restaurant. And, if you are overweight, this weight loss will have countless benefits. That’s transformational.

We’re tempted to say that the “grand game” is to develop transformational treatments for giant markets. Of course, to be able to do such a thing reliably would be amazing. But isn’t this just a tease? Sort of like saying, why don’t you just make yourself the world’s tallest person?

Disease Transformation is Key

The grand game in pharma is a simple one: find transformational treatments for human diseases that have giant commercial scale.

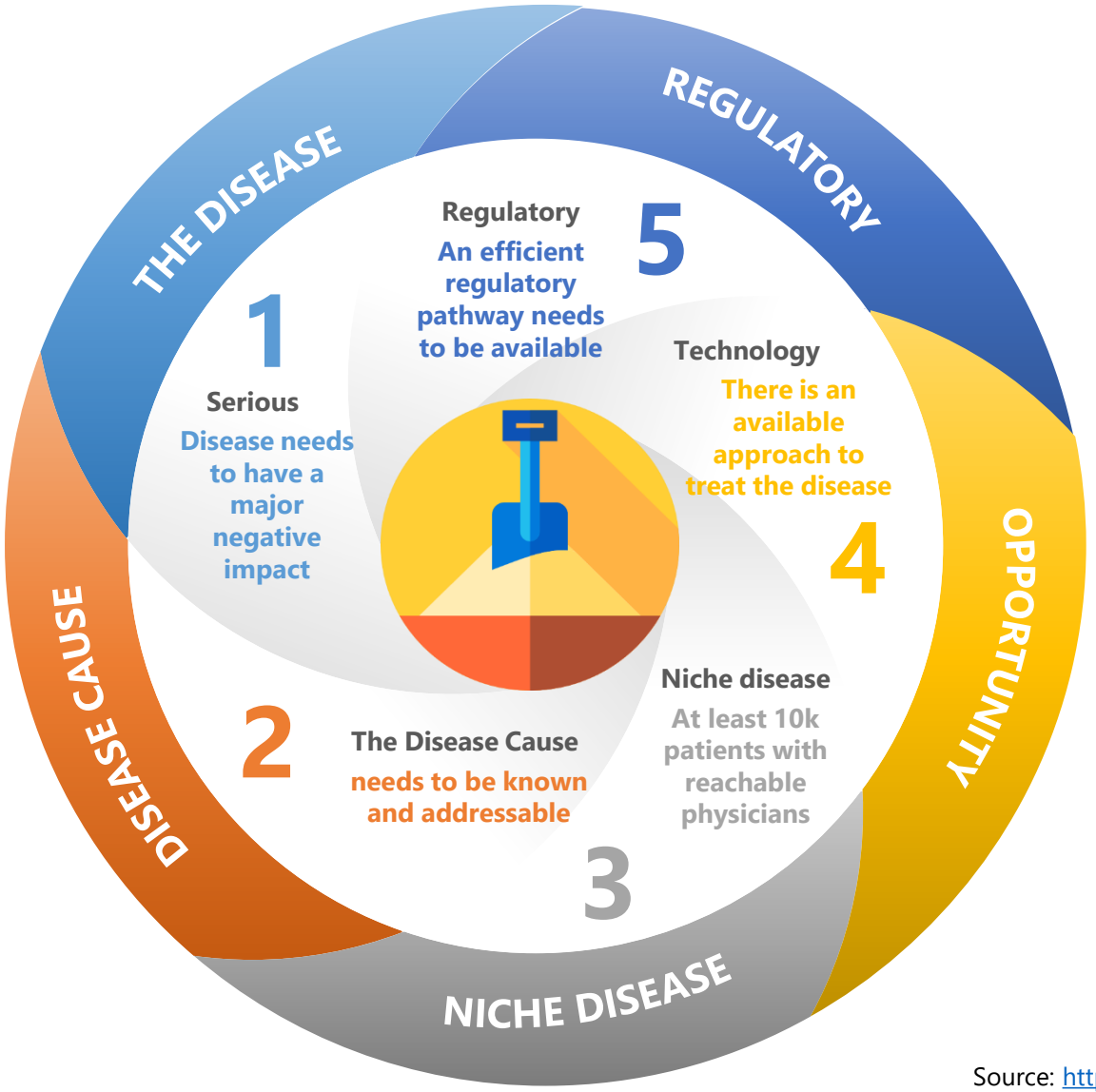
Vertex Pharma has pointed the way. Their main focus is to find treatments that will be transformational to patients. Their threshold number of patients is 10,000 or more. As noted on the two pages that follow, the Vertex model is to systematize the search for transformational drugs by focusing on diseases with major unmet needs and the potential to meet the need with an emerging transformational technology.

Their disease-first R&D strategy is unique in the pharma industry as most other players have a business model that is either channel dominant, platform-centric, science field centric or commercial area dominant.

This is not to say that other approaches cannot generate great success. Indeed, deep scientific knowledge is an essential prerequisite to coming up with innovative products.

Vertex Success Built on a Disease Centric Model

Look for Diseases in the "Sandbox". Be unafraid of novel modalities and new approaches.



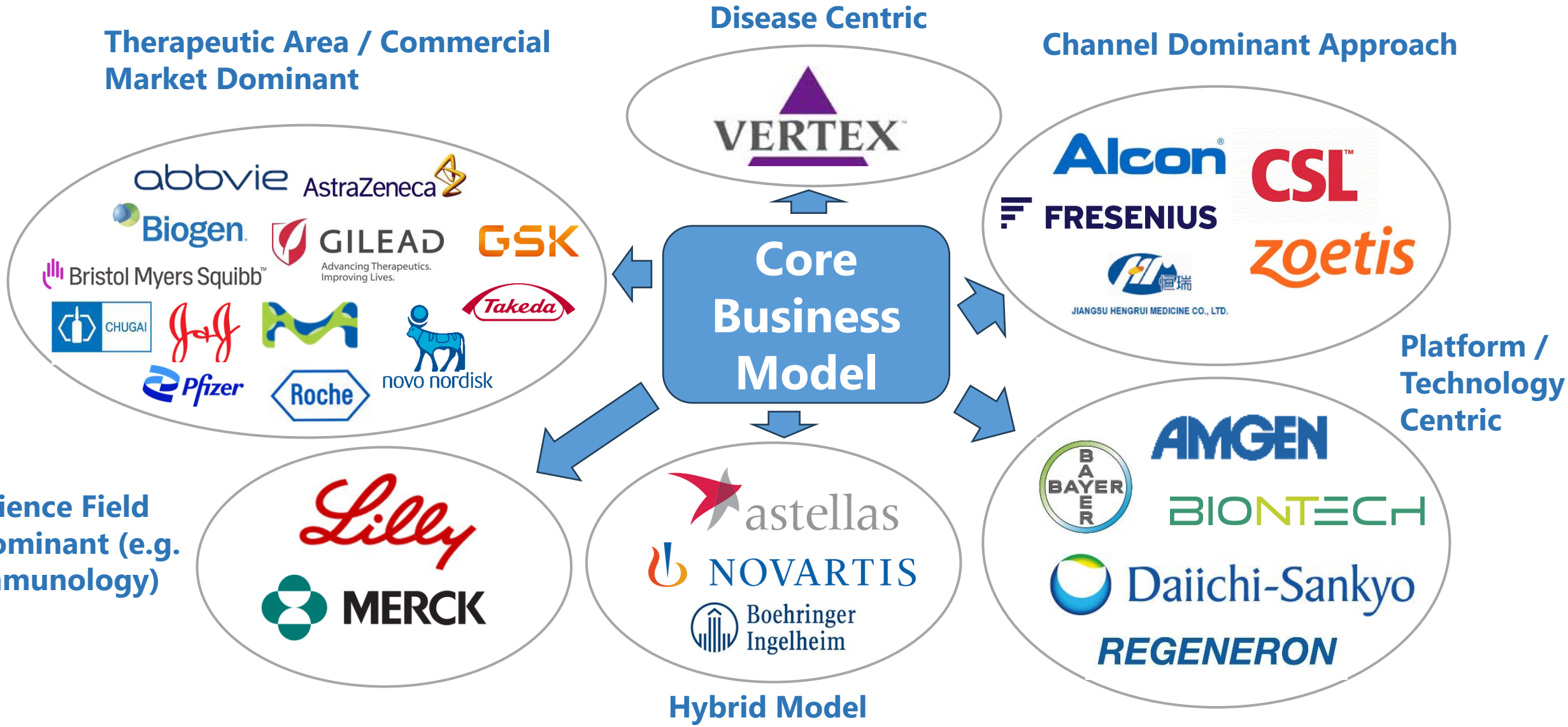
Andrew Dunn, *Business Insider*, Oct 4, 2023

"Rather than just maximize profits in CF, Vertex is plowing cash into its unique disease centric research strategy. While most drugmakers build a pipeline around a key technology or a related group of diseases, Vertex is picking certain diseases like sickle cell or diabetes and then going all in on attempts to transform how they're treated.

[CEO Reshma] Kewalramani calls it the "sandbox" approach. Scientists search for diseases that check five boxes, including an understanding of the illness' biology and an efficient regulatory pathway. If a disease fits those criteria, it's considered "in play," or in the sandbox. That has led to going after unrelated diseases like sickle cell, diabetes, muscular dystrophy, kidney disease, and pain. And instead of homing in on one technology the way Moderna focuses on messenger RNA, Vertex is agnostic, partnering with (and sometimes acquiring) other biotechs to gain access to a wide range of tools, including CRISPR-Cas9."

Source: https://www.businessinsider.com/vertex-ceo-interview-on-future-growth-crispr-cures-2022-9

Vertex Business Model Differentiated From Peers



Some Market Opportunities are Just Very Large

To be clear, we are not necessarily advocating that one copy the Vertex model *per se*. Rather, we are advocating a strategy to focus on big impactful opportunities even if the regulatory pathway might be costly and the requirement that a disease have a major negative impact could rule some large commercial opportunities. We are headed increasingly into a consumer centric market where willingness to pay will go beyond how life-threatening a disease might be.

When one asks consumers how much they are willing to pay for an obesity drug that delivers transformational results, it quickly becomes apparent that $100 billion revenue markets are not hyperbole. We think those that are limiting themselves to $100bn or less forecasts for the obesity forecast have probably not pulled out a spreadsheet and run the math. It's not difficult to convince oneself that obesity drug sales could hit $200 billion, particularly if one looks at the market on a global basis. Some market opportunities are just very large. There are a lot of obese people and almost all of them would prefer to be thin.

Big Impactful Opportunities are Key

Strategic Intent to Transform a Disease

We're starting to get a little closer to the punchline. If one reviews the success stories of companies that have hit on large products in recent years including Eisai, Lilly and others it becomes clear that there was a *long-term strategic intent* to attack specific diseases. Each company understood that a giant problem in medicine might be addressed with a scientific approach that remained not fully understood.

Those diseases were chosen because of the scale of the unmet medical need but also the conviction that it would be possible to achieve scientific breakthroughs in the respective areas approached by each company.

At various points along the way each company faced critics who thought they were tilting at windmills. Each company faced internal conversations about terminating programs that were costly, risky and had long timelines.

And each company avoided the fate of terminating an ultimately successful program because of long-term strategic intent embedded in their leadership team to design a drug that would transform a disease that matters.

Strategic Intent Typically Involves Focused Strategies That are R&D Driven and Come with CEO / Board Support: Lilly Example

Peter Loftus, *Wall Street Journal*, April 3, 2023

"The company also needed to move faster. One internal committee after another second-guessed every recommendation to advance a promising drug candidate. "The decisions got revisited every step of the way," recalled J. Anthony Ware, who led product development at Lilly before retiring in 2017. The committees were intended to ensure thorough vetting, but in practice became a limiting process that squeezed out bold ideas, according to Dr. Skovronsky.

Lilly's scientists, for instance, were among the first to see potential for a new type of breast cancer drug targeting proteins known as CDK4 and CDK6 that play a role in tumor growth. It took them too long to get internal funding for clinical trials, however, handing competitors Novartis AG and Pfizer Inc. the advantage of bringing their therapies to market first. Lilly's drug, Verzenio, was approved by the FDA in 2017, after Pfizer's Ibrance in 2015 and Novartis's Kisqali earlier in 2017. Lilly also missed out on cancer immunotherapies, ceding the treatments to rivals such as Merck & Co. and Bristol-Myers Squibb Co.

Dr. Skovronsky was frustrated with Lilly's slow pace. "Let me understand this," he recalled saying at a committee meeting setting timetables for getting experimental drugs to market. "Our goal is to be slower than average, and we're failing at that goal? This can't be the way to do things."

In 2015, Lilly's board of directors asked Dr. Skovronsky, then senior vice president of clinical and product development, to help analyze Lilly's research flops over the prior 10 years and figure out how to do R&D better.

A big reason for the failures, Dr. Skovronsky found, was that Lilly's business-unit heads, focusing on sales potential, were making decisions about which drugs to promote to late-stage studies. The result: The company advanced into the large, expensive studies candidates that had mixed results in earlier testing. Dr. Skovronsky found that drugs that had earlier mixed results often failed the later studies.

Dr. Skovronsky recommended Lilly pursue drug projects where it best understood the science, and lean less on commercial sales estimates. Lilly was not very good at predicting a drug's sales over time anyway, he concluded, but could better predict the scientific probability of a drug's success.

Lilly jettisoned research on diseases where it was tougher to deliver an advance, including osteoporosis and psychiatric conditions, and doubled down in areas where it had expertise: diabetes, oncology and Alzheimer's disease."

Strategies to transform diseases typically require long timelines, a willingness to fail, R&D insight, bold ideas, aligned leadership and a highly focused approach.

Companies that make major decisions in large committees may not be good at this.

Source: https://www.wsj.com/articles/ozempic-mounjaro-weight-loss-drug-wegovy-eli-lilly-66f2906

PHARMACEUTICALS

Eli Lilly shares tank after Alzheimer's drug fails in late-stage trial CNBC

PUBLISHED WED, NOV 23 2016•4:38 PM EST | UPDATED WED, NOV 23 2016•4:39 PM EST

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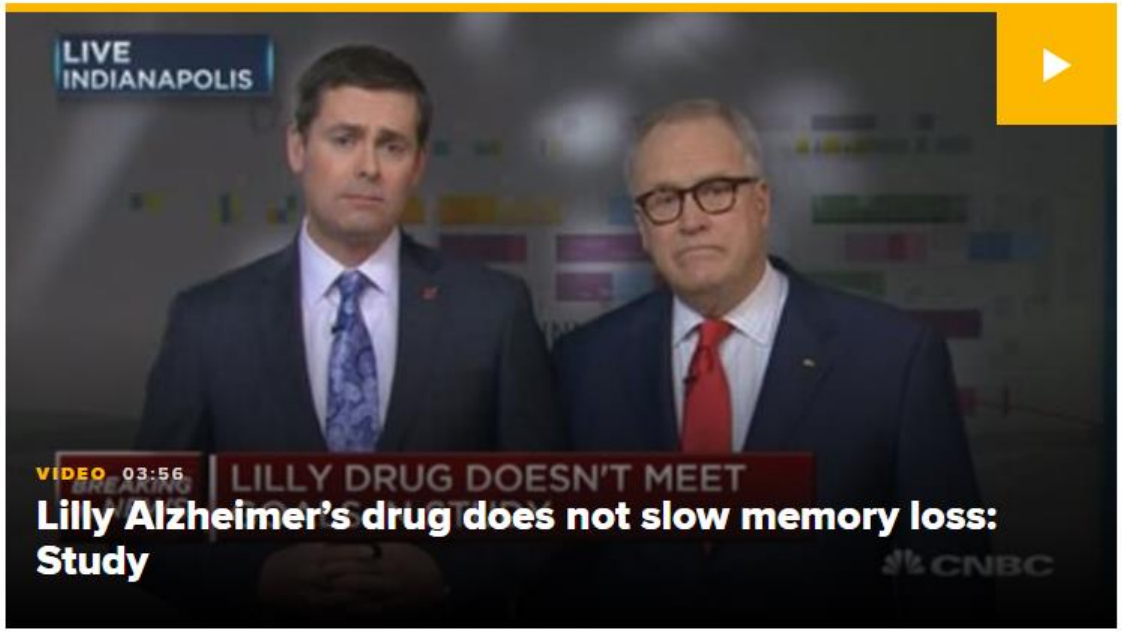


"An experimental drug from Eli Lilly failed to slow the loss of cognitive ability in patients with mild Alzheimer's disease, the company said Wednesday. Shares of Lilly shed 10.5 percent on Wednesday following the report. Based on the failure of the more than 2,100 patient study in Phase III clinical trials, Lilly said it won't seek U.S. approval of solanezumab, the infused drug for mild dementia."

Source: https://www.cnbc.com/2016/11/23/eli-lilly-shares-tank-after-alzheimers-drug-fails-in-late-stage-trial.html

Before succeeding with donanemab in 2023, Lilly faced numerous failures in Alzheimer's disease R&D including a particularly challenging late-stage failure of Solanezumab in 2016 highlighted at left.

One of the most remarkable things about the 2016 CNBC interview with outgoing CEO John Lechleiter and incoming CEO Dave Ricks, was that both indicated that Lilly would remain committed to finding drugs that work for Alzheimer's Disease despite yet another failure.

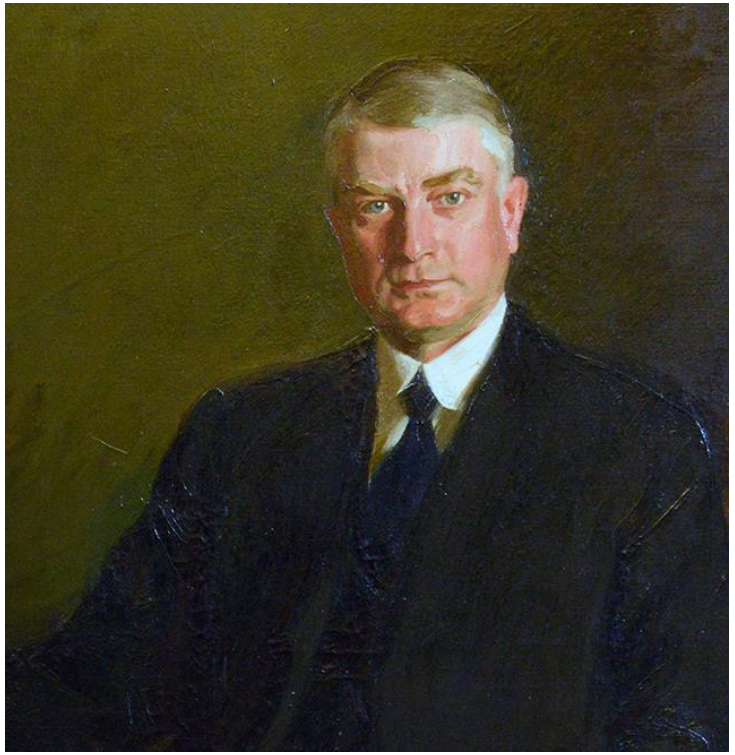
Lilly stuck with a long-term strategic commitment based on scientific understanding of the disease to develop transformative treatments for this disease and felt the pain along the way associated with that commitment.

The Importance of Imagination

We once had lunch we had once with a big pharma executive in 2002 who complained that all the good ideas had already been turned into drugs and that there wasn't that much left to do.

Obviously, one needs to have a little imagination to think about what might be possible. To quote Bill Mayo, an early ambassador of the medical profession, one needs to "look through a half-opened door into the future, full of interest, intriguing beyond my power to describe…"

Imagination, the ability to envision a yet unseen opportunity, again and again has been the critical success factor behind IP-intensive industries. This imagination typically emerges from a thorough understanding of current technologies and a sense of what is possible with novel technologies. We are reminded of Einstein's letter to FDR about the potential for an atom bomb. Einstein understood the emerging field of nuclear physics and could see its implications. Einstein himself said: "Imagination is more important than knowledge. For knowledge is limited whereas imagination embraces the entire world, stimulating progress, giving birth to evolution."



"I look through a half-opened door into the future, full of interest, intriguing beyond my power to describe, but with a full understanding that it is for each generation to solve its own problems and that no man has the wisdom to guide or control the next generation."

William J. Mayo, 1931

Translational Imagination and Vision

If one reviews the story of how Lilly came up with their latest generation obesity drugs, it was less about technology per se than knowing what to do with a technology. Lilly carried out a detailed search for solutions using a specific set of drug candidates applied to relevant disease models in an area that they already knew well. Lilly spent a tremendous amount of time working with different configurations of incretins to identify approaches that would be effective in treating obesity.*

We call this *translational imagination*. Obviously, it comes with more than it's share of perspiration and frustration. But, the key is to understand what drugs could be enabled by a specific technology or biological insight. Obviously, it helps if an R&D team already has great strength in a specific area of research.**

The history of both the pharmaceutical and technology industries is defined by visionaries who were able to see what could be done with new technologies.

A classic example is Robert Noyce, co-founder of Fairchild Semiconductor. Noyce understood the importance of William Shockley's 1956 invention of the semiconductor. He is credited with the invention of the microchip which enabled the personal computer and helped to found Intel. Mr. Noyce was able to imagine the unlimited upside using semiconductors to create integrated circuits and "chips" that had many such circuits.

* See, for example, https://www.wsj.com/articles/ozempic-mounjaro-weight-loss-drug-wegovy-eli-lilly-66f2906

** We very much enjoyed the recent write-up of AZ's Mene Pangalos' R&D approach including his mantra that AZ double down on its strengths.

The Importance of Perceptive Agility

How often do persons in business look for one thing and find another thing that is even bigger? And then, miss it?

Framing is an important human trait. Humans all frame what they see, exploring business opportunities with many preconceptions. Humans interpret observations based on those preconceptions. The ability to react appropriately to surprises, what Donald Rumsfeld called "unknown unknowns", is a critical success trait in drug discovery. The case of Henry Hudson illustrated at right is a classic example of failure to react to new information.

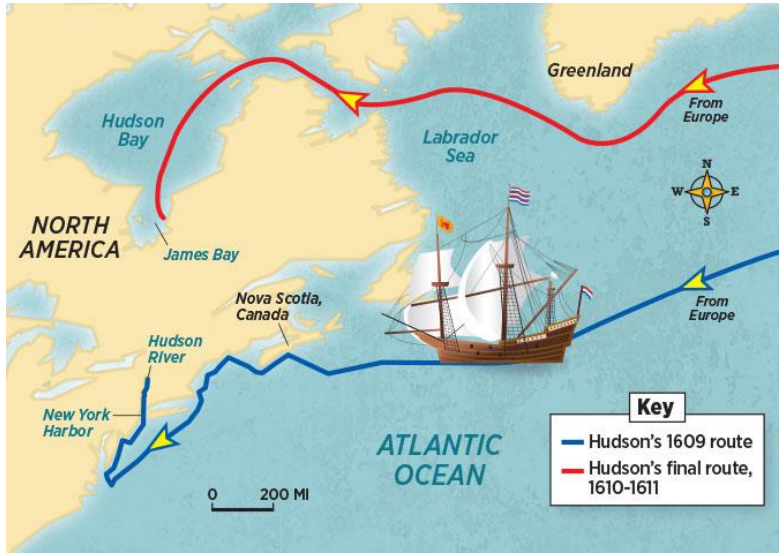
"Perceptive Agility" refers to the ability to recognize an unexpected discovery and react to it appropriately. There are countless examples of serendipitous discoveries in medicine where a scientist had the perceptive agility to recognize the implications of an incidental finding from a trial or experimental result.*

The Case of Henry Hudson

Henry Hudson was an entrepreneur of his day. He went on three voyages searching for the "Northwest Passage" – a short cut from Europe to Cathay.

He never found it, but he did discover New York Harbor, Manhattan and the Hudson River in 1609.

Hudson did not understand the importance of his discovery. The New York area (and Northeast) was *far more* important than the route to Cathay. Hudson died in a mutiny in James Bay not knowing how important his voyages were.



* See, for example: https://www.theguardian.com/lifeandstyle/2017/jul/11/from-viagra-to-valium-the-drugs-that-were-discovered-by-accident

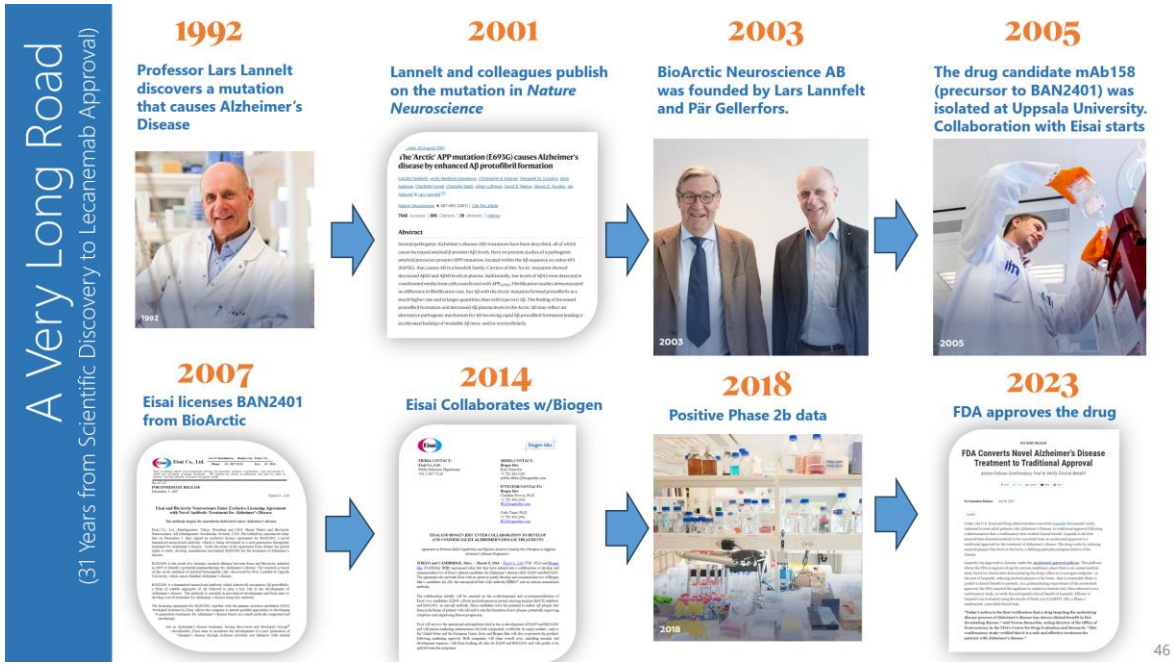
R&D Insight and Early-Stage Business Development

We have previously highlighted the importance of Eisai's license deal with BioArctic in 2005 (chart at right).

By 2005 Eisai was well invested in understanding Alzheimer's disease and had a long-term corporate approach that allowed it to recognize the importance of Professor Lannelt's discovery of an arctic mutation that led to Alzheimer's disease and BioArctic's commitment to leverage the discovery with an antibody.

There are numerous examples of where an R&D department's insight into a disease led it to carry out an early-stage licensing transaction that later looked brilliant. A strong R&D group should, in general, be accompanied by aggressive efforts to acquire relevant technologies and drug candidates early in their life cycle.

A classic example was J&J's 2012 deal with Genmab to license a Phase 1b CD38 antibody, daratumumab, for $55 million upfront. J&J had a well-developed immunology team that recognized



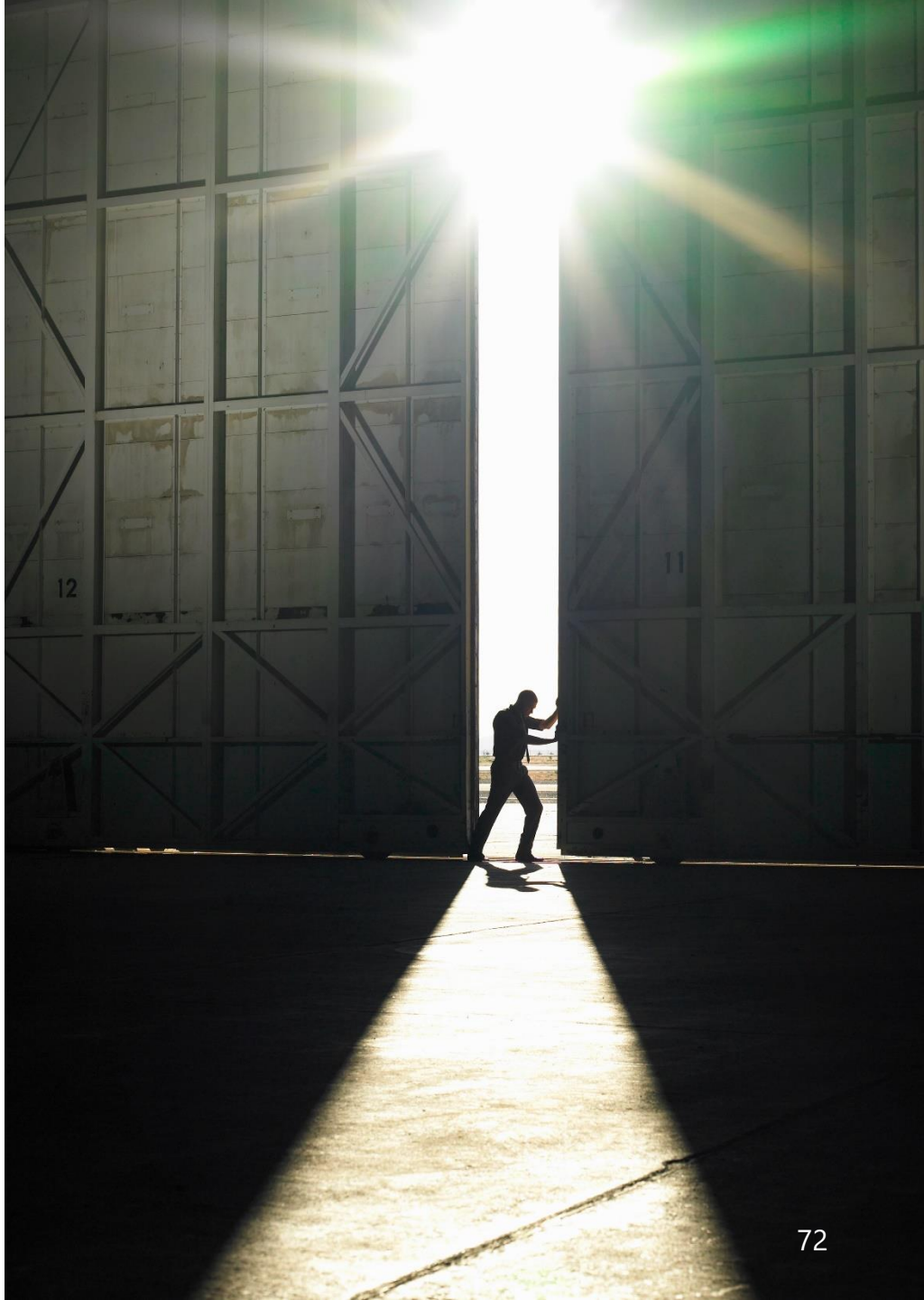
the relevance of the target given the historical success of Rituxan® and the expression levels of CD38 seen on B cells. A similar story can be told about AbbVie's deal with BI for Skyrizi®. It is very difficult to generate value from late-stage M&A deals. Value can be more easily created by having an R&D team that recognizes the importance of a specific external asset due to its own internal work and then catalyzes a transaction to get the asset.

So Where Are the Next Big Opportunities?

One might bucket the search for the next generation of transformational treatments into two major categories:

Payor Centric Solutions: Opportunities to deliver solutions to payors. If payors face very high costs from dealing with a disease, they should be willing to pay handsomely for a solution to such disease. This is not to discount the patient's role in any way, but someone must be willing to pay for a new drug and introducing a product with high cost-saving potential or brilliant life saving properties is essential in today's brutal pricing environment.

Consumer Centric Solutions: The excitement for obesity drugs to date is more patient driven than payor driven. Many people are willing to spend a lot of money to get thin. There are obviously many things that consumers want other than to lose weight. One need not look far into our society's many travails to identify what opportunities might exist. Historically, almost all large drugs have been payor-driven rather than consumer-driven but this can change. It's a critical point in a post-IRA world where payor behavior is shifting.



Illustrative Payor Centric Needs

Relevant areas where patients are suffering, and payors need solutions are abundant. Illustrative areas are:

Cancer: The largest market in cancer is in front-line treatments for the big five tumor types. A giant opportunity is to develop a pan-cancer treatment approach with efficacy that extends beyond today's chemotherapies and checkpoint inhibitors. Illustrative companies and targets are shown at right (from our June 5 report). We don't think this is a "windmill tilting" area given where the science is. A good pan-cancer drug would likely dwarf the obesity category economically.

COPD: Current treatments treat the inflammatory aspects of COPD but do not impact the underlying causes of lung disease which involve cellular damage and fibrosis. The literature suggest that this disease is a highly heterogenous phenotype that could be treated with a range of targeted approaches.* With an economic cost in the U.S. alone of at least $50bn per annum, there is obviously large commercial potential for a transformative drug.**

Pan Tumor Biotech Stories On the Radar

bicatla	Developing BA3182 which is an EPCAM t-cell engager that is tumor specific. EPCAM expressed on almost all solid tumors. Starting in clinic.
inatherys smart treatments for complex diseases	CD71 preferentially expressed on surface of solid/liquid tumor cells as its part of tumor cell's heavy use of iron. Developing first CD71 ADC.
Kojin Tx	Exploiting iron addiction of tumors to induce iron-dependent cell death (ferroptosis) using novel biology. Preclinical but very interesting.
LOKNA	LAE002 is an AKT inhibitor that is showing efficacy in a broad range of tumors as is a similar molecule from AstraZeneca.
ONCHILLES PHARMA	Human neutrophils release ELANE to selectively kill cancer cells (but not normal cells), but in cancer ELANE function is silenced. Onchilles' neutrophil elastase fixes this problem.
PEPTOMYC	Directly going after MYC gene with a cell-penetrant peptide. In Phase 1. Highly differentiated from CDK9 approach being pursued by AZ, Kronos, Prelude, Vincerx and others.
REVOLUTION MEDICINES	Developing a family of RAS inhibitors and pan-KRAS drugs that collectively have potential to make a major dent in most solid tumors. Very promising pan-KRAS approach at Boehringer-Ingelheim.

*See, for example: https://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201303-055AW
**See, for example: https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-burden

Illustrative Payor Centric Needs (continued)

Heart Failure: Despite several approved pharmaceutical agents, heart failure remains one the largest costs in Medicare as patients experience frequent and expensive visits to hospitals as their heart muscle weakens. A number of researchers are working on novel, promising approaches to this disease.

Insulin Insensitivity: Type 2 diabetes accounts for roughly 25% of all healthcare expense in the United States. Over two thirds of Type 2 diabetics suffer from insulin insensitivity which is a well-defined biological failure to transport glucose into a cell. The societal and patient consequences are extreme. Current insulin sensitizers such as pioglitazone are far from ideal. We note a number of promising approaches to this problem in the literature. A good drug in this area would easily cross $50bn in sales.

Kidney Failure: Chronic kidney disease remains a fatal and costly disease. Today's RAS inhibitors and SGLT2 inhibitors help but do not reverse the disease in any way. There is an acute need for new treatments in this area and a number of promising scientific developments involving the underlying fibrotic process. A good drug here could easily hit $50bn in sales.

Illustrative Patient Centric Pharma Opportunities

Lifestyle Oriented Patient Needs

Patients are interested in drugs that:

1. Would cause them to be less fatigued
2. Enable them to age more slowly
3. Enable them to look better
4. Avoid allergies
5. Improve their recall and cognition
6. Improve their mood
7. Avoid the common cold
8. Reduce their anxiety
9. Avoid hair loss
10. Require them to sleep less
11. Reduce skin problems such as acne

Serious Symptomatic Diseases of High Concern

Patients are interested in drugs that address:

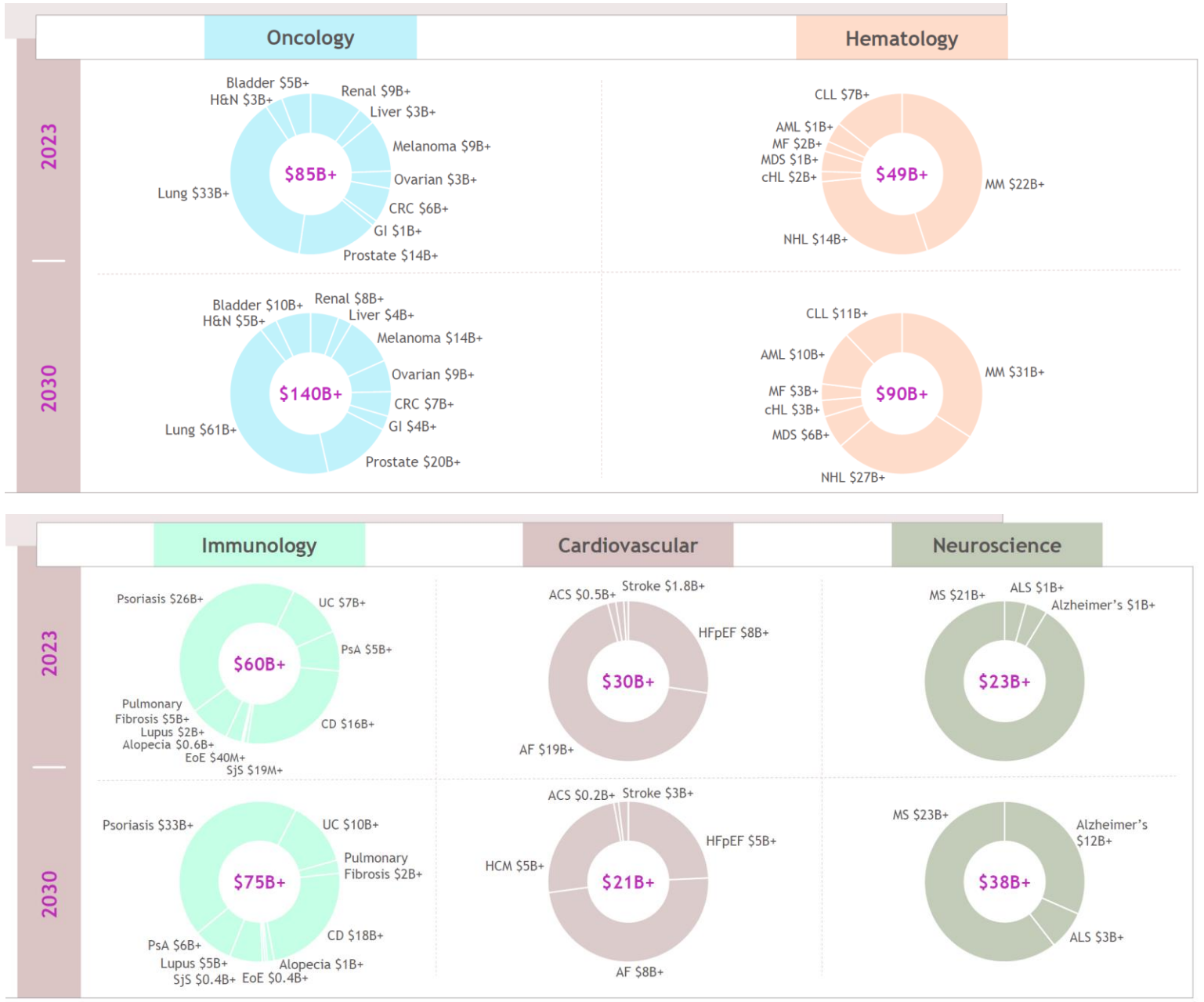
1. Addiction to cigarettes and drugs
2. Asthma
3. Autism spectrum disorder
4. Chronic fatigue syndrome
5. Dementia and Alzheimer's
6. Dry eye
7. Endometriosis
8. Fibromyalgia
9. Hashimoto's disease
10. Lower back pain
11. Osteoarthritis

BMS TAM Sizing Exercise Last Week

In its R&D day presentation last week BMS published the charts at right showing the estimated total addressable markets for various disease categories.

We would note that this is an admirable move for BMS to convey the opportunities for successful drugs in the various categories.

It's also worth noting that these data were obtained from Evaluate Pharma which aggregates analyst forecasts. Analysts essentially look at the drugs in the pipeline and indicate how big they might get as opposed to how big they could get with a transformative treatment. For example, before semaglutide and tirzepatide hit, analysts forecast that the total addressable market size of the global obesity market was less than $5 billion.



Source: https://www.bms.com/assets/bms/us/en-us/pdf/r-and-d-day/2023/bmy-r-and-day-presentation.pdf

Huge Upside in Future

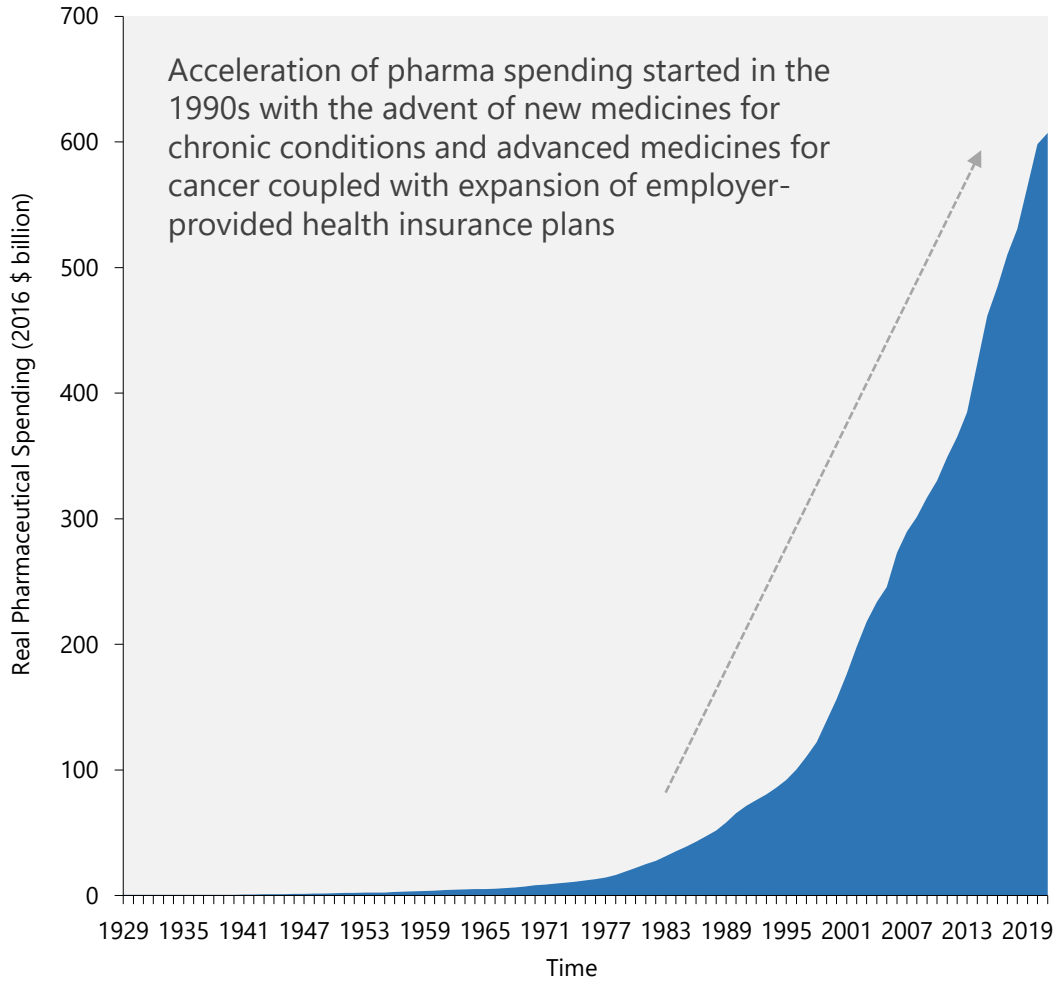
We are now navigating the Post-Pandemic era of pharmaceutical industry growth. This growth is fueled by growing incomes and innovation built on biological knowledge accumulated over centuries.

While many are focused on sector risks such as those associated with the Inflation Reduction Act, we wish to note that the pharma industry has seen hypergrowth for decades and that this high rate of growth is unlikely to slow anytime soon.

The reason is that emerging technologies have the promise to radically transform the treatment of burdensome diseases.

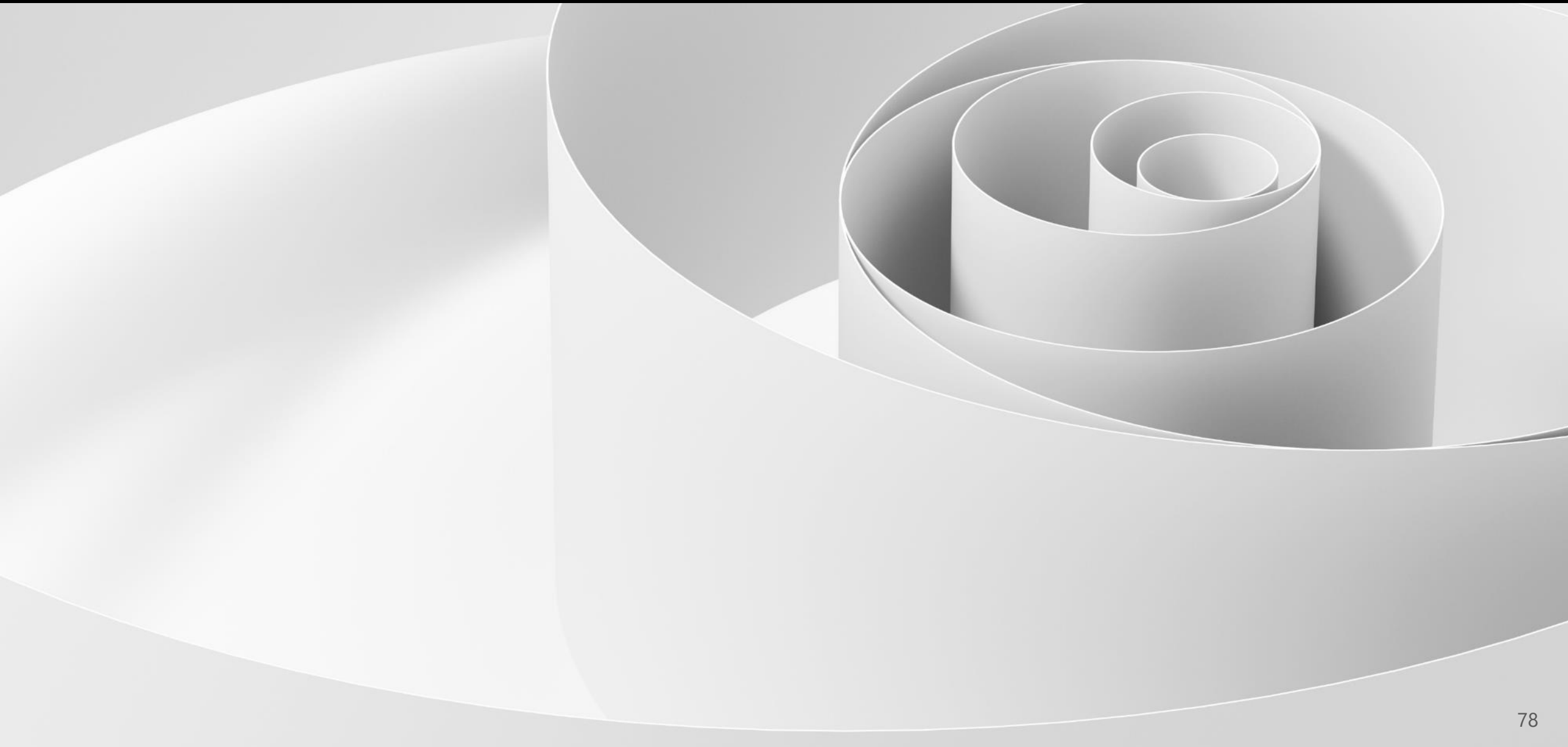
As the pharma industry recognizes and reacts to these opportunities, we expect to see unprecedented industry scale and success as incumbent players and new entrants pursue the grand game of new drug innovation. It's for this reason that we continue to believe that the pharma industry remains in its early days.

Total U.S. Pharmaceutical Spending in 2016 Dollars (Billions)



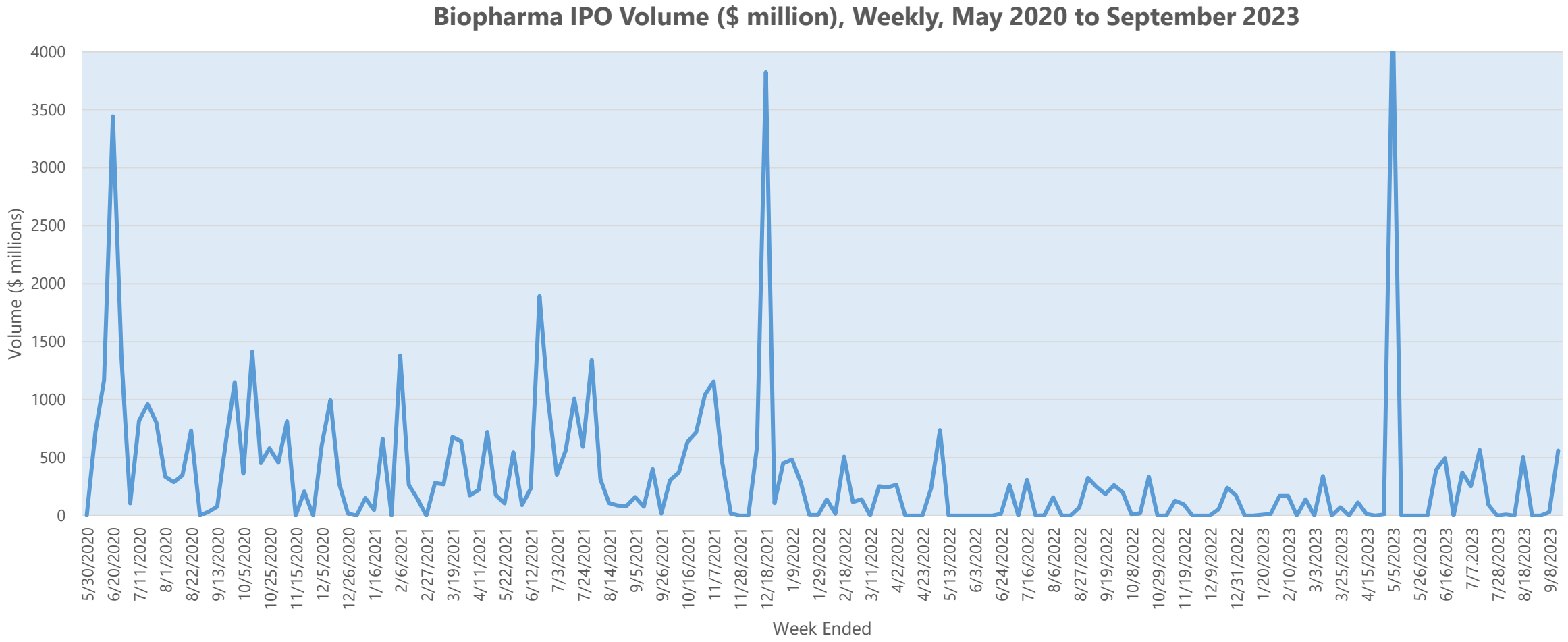
Source: U.S. Bureau of Economic Analysis, National Income and Product Accounts.

Capital Markets Environment and Deals



IPO Market Wakes Up

Last week saw both Neumora and Rayze price highly oversubscribed IPOs.



Source: Data from CapitalIQ and Stifel research.

Rayze Bio Prices IPO

Sep 14, 2023. SAN DIEGO--(BUSINESS WIRE) -- RayzeBio, Inc. (Nasdaq: RYZB), a targeted radiopharmaceutical company developing an innovative pipeline against validated solid tumor targets, today announced the pricing of its upsized $311 million initial public offering of 17,277,600 shares of common stock at a price to the public of $18.00 per share.

RayzeBio is offering 16,114,600 shares of common stock and the selling stockholder named in the prospectus is offering 1,163,000 shares of common stock. RayzeBio will not receive any proceeds from the sale of shares by the selling stockholder.

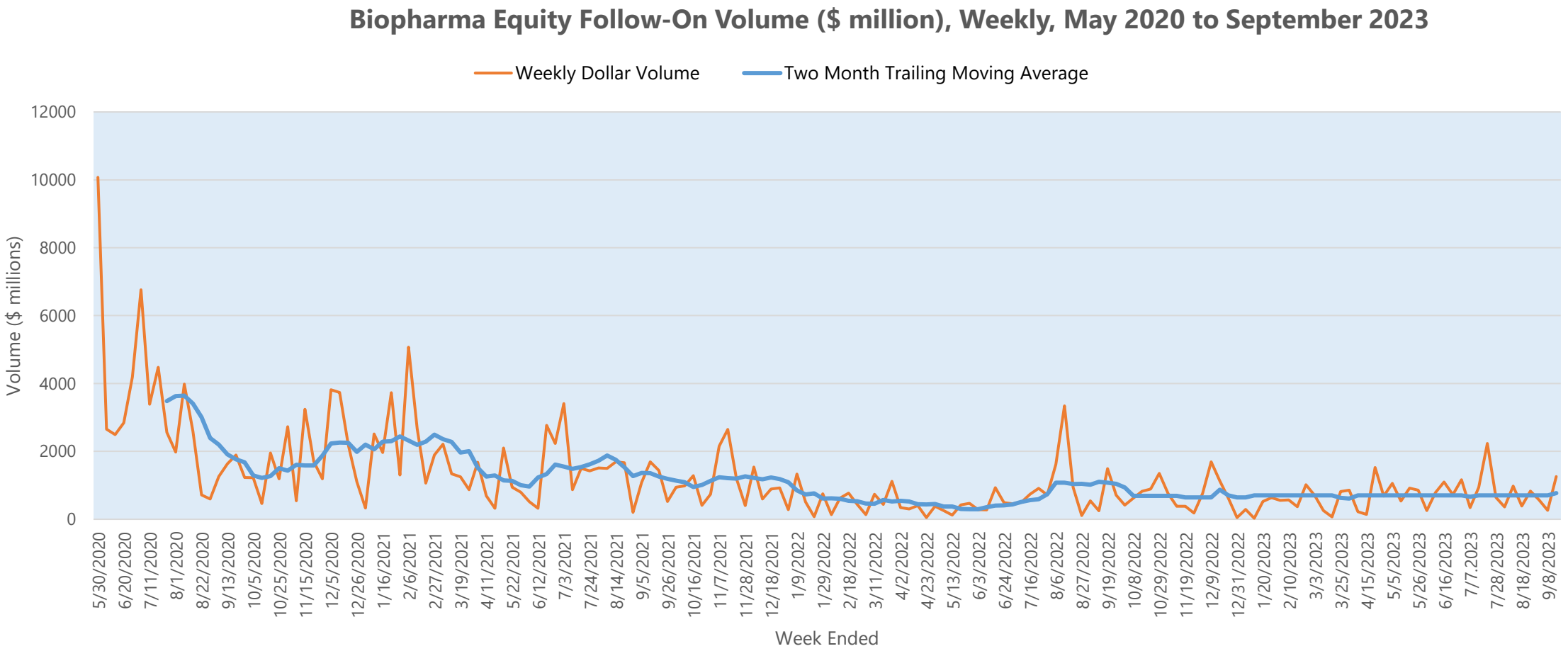
The gross proceeds to RayzeBio from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by RayzeBio, are expected to be approximately $290.1 million. In addition, RayzeBio has granted the underwriters a 30-day option to purchase up to an additional 2,591,640 shares of common stock at the initial public offering price, less underwriting discounts and commissions.

RayzeBio is building a vertically integrated radiopharmaceutical therapeutics (RPT) company to treat various cancers, with its lead program in a Phase 3 clinical trial. RayzeBio has created a pipeline of multiple drug candidates in therapeutic areas with significant market opportunities.

Source: https://investors.rayzebio.com/news-releases/news-release-details/rayzebio-inc-announces-pricing-upsized-311-million-initial

Last Week Was Brisk for Follow-On Offerings

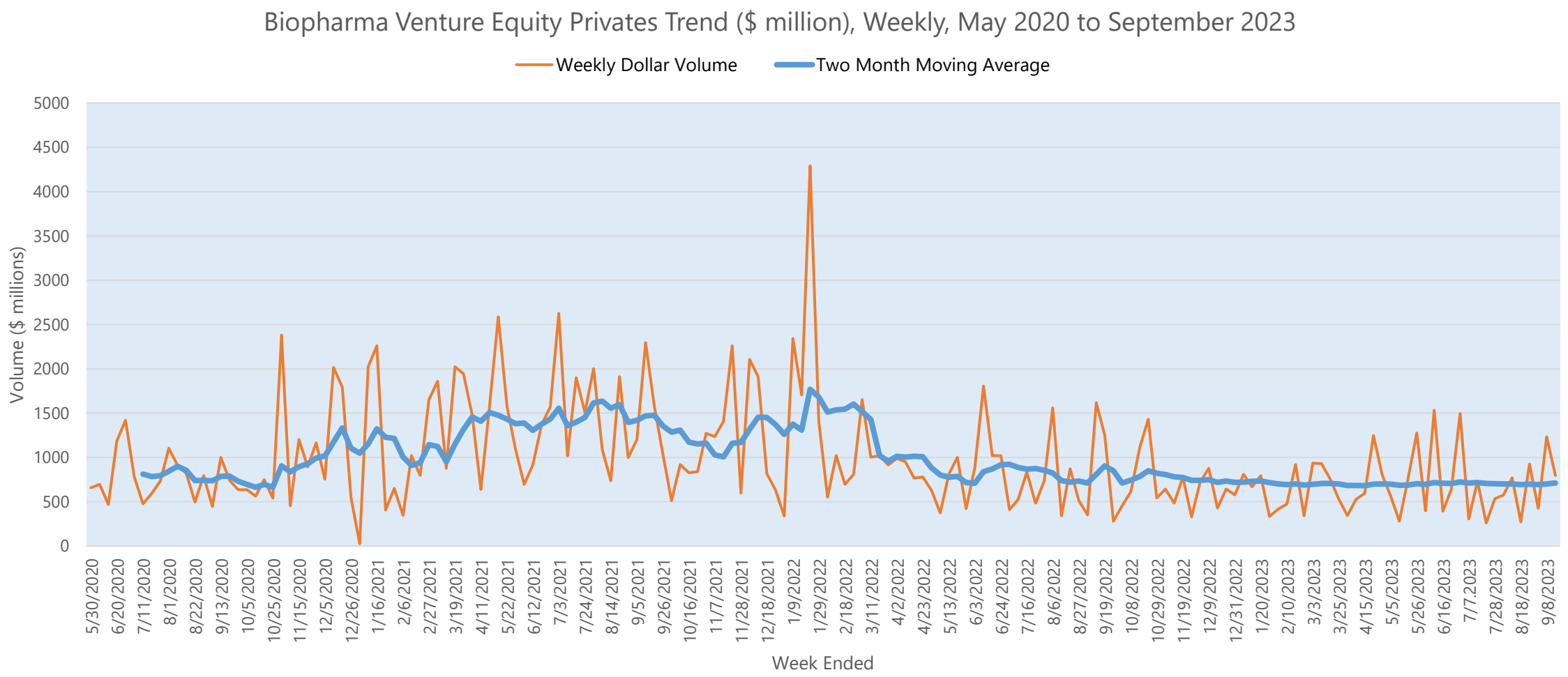
Last week saw issuers raise $1.25 billion in the follow-on equity offering market across 19 deals. This was the third highest volume week of the year. The largest transactions were follow-ons from Innovent and Crinetics. CymaBay and Rocket also did large deals on the back of positive catalysts.



Source: Data from CapitalIQ and Stifel research.

Venture Equity Market Strong Last Week

Last week saw 39 companies raise $800 million in the venture equity market.



Source: Data from CapitalIQ, Crunchbase.

Generate:Biomedicines Raises $273 Million in Largest Biotech Series C of 2023

Jonathan Grinstein, *Genetic Engineering and Biotech News*, Sep 14, 2023

When Molly Gibson, PhD, left her position as Kaleido Biosciences' leader of computational biology and joined Flagship Pioneering in 2017, she had been mulling over the question of what the main drivers of biology were for rethinking the drug development process.

"If you could look at the millions of protein sequences to learn nature's rules for conferring functionality and then generate novel proteins for specific functions, you could almost reimagine the entire drug discovery process and change the economies of scale, the number of programs any individual company could go after, and ultimately the outcome and the success rate of those medicines, which the field and the industry as a whole are in desperate need of," said Gibson, who is chief strategy and innovation officer at Generate:Biomedicines and senior principal at Flagship Pioneering, in an interview with *GEN Edge* last December.

At the time, biophysics dominated the field of protein sciences. It was the only way to understand and design new proteins. However, Gibson, whose doctoral training was in computational and systems biology, said that this approach has a lot of problems with scalability and brittleness.

There are two core components to Generate:Biomedicines' technology. One is based on de novo protein generation, in which a computer suggests sequences with binding specificity without previous knowledge of binding on a target of interest instead of being limited to what the immune system produces. The second piece is around optimizing. Computationally thinking up a protein is one thing, but making it a viable therapeutic, which requires mastery of affinity, immunogenicity, and manufacturability, is another. To address this, Generate:Biomedicines has created an optimization suite that allows them to take raw native proteins and make them into viable therapeutics for desired targets.

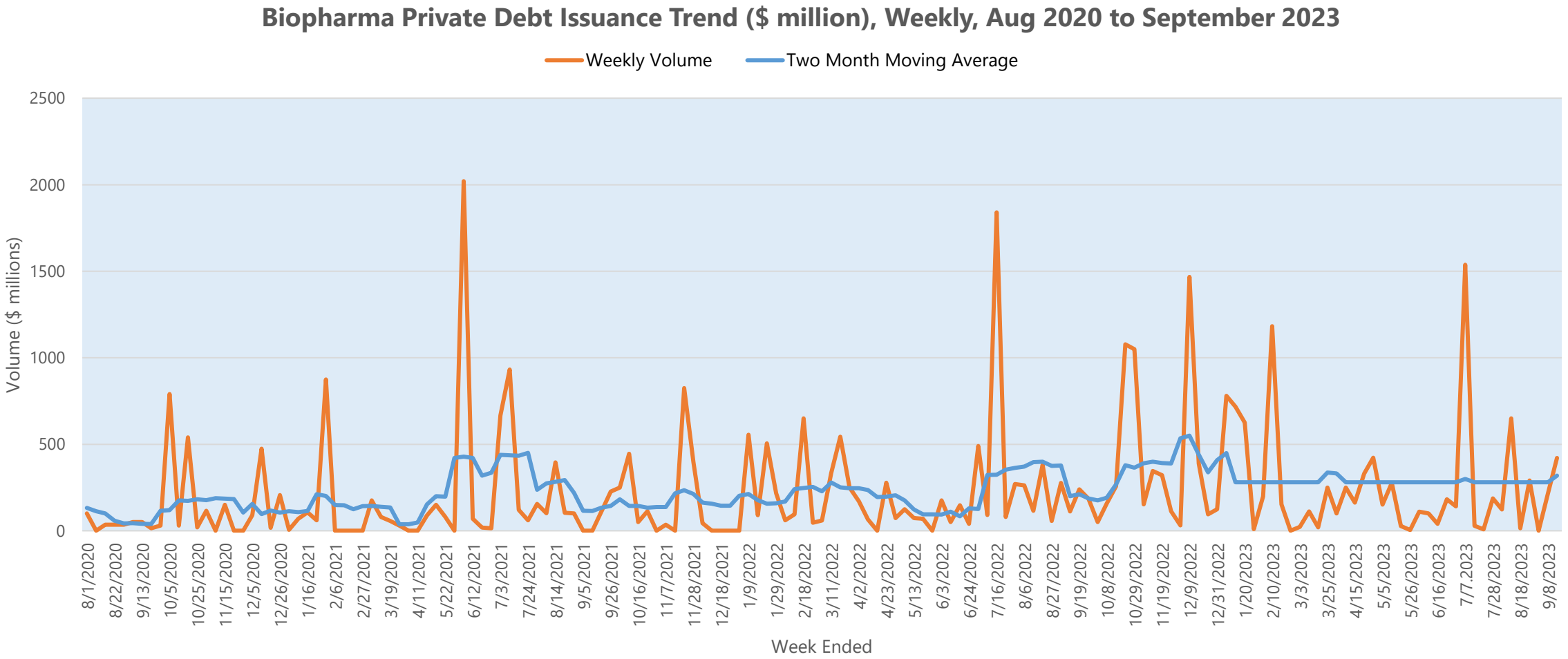
Fast forward to today, and Generate:Biomedicines has announced the largest Series C for a biotech company in 2023 at $273 million, bringing their total equity financing since 2020 to nearly $700 million and eclipsing the $226.5 million raised by Apollo Therapeutics just weeks earlier.

In addition to company founder Flagship Pioneering, all of Generate:Biomedicine's existing series B investors participated in this round, including a wholly owned subsidiary of the Abu Dhabi Investment Authority (ADIA); Fidelity Management & Research Company; funds and accounts advised by T. Rowe Price Associates; ARCH Venture Partners; and March Capital. Additionally, This financing round attracted many new investors, including Amgen; NVentures, NVIDIA's venture capital arm; MAPS Capital (Mirae Asset Group); and Pictet Alternative Advisors.

Source: https://www.genengnews.com/topics/artificial-intelligence/generatebiomedicines-raises-largest-biotech-series-c-of-2023/

Weekly Global Biopharma Venture Debt Placements

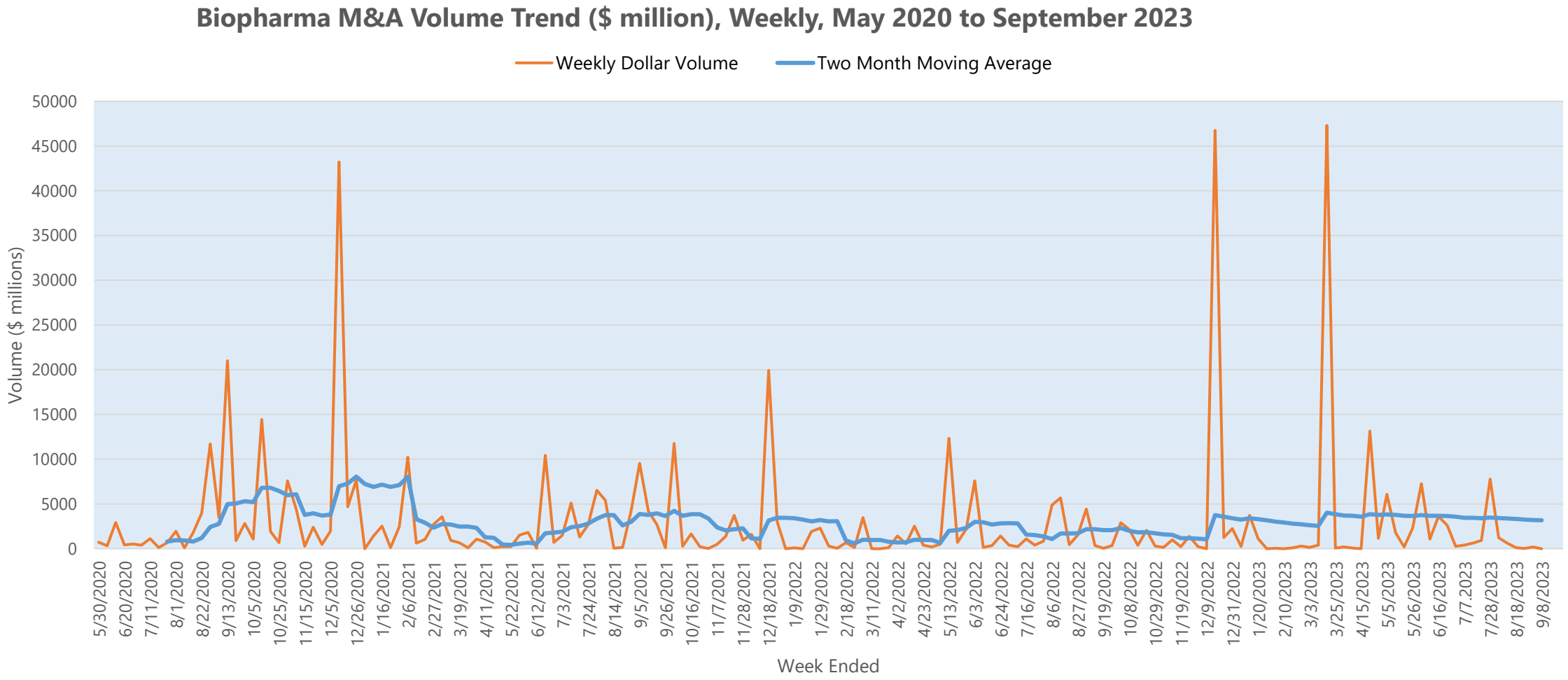
We saw four deals in the private debt market last week with $421mm raised. The largest deal was a $350 raise by Nephron Pharma from Blackrock and PNC.



Source: Data from CapitalIQ, Crunchbase.

Last Week Saw Zero Dollars in Announced M&A Volume

Last week saw three M&A deals announce that did not provide dollar values. These included Pierre Fabre's acquisition of Vertical Bio, Zoetis' acquisition of adivo, and PharmaS' acquisition of Mabo Farma. Mabo Farma, a generics manufacturer, has trailing revenue of $35 million.



Source: S&P, CapitalIQ

CDMO's, Specialty Pharma Among Verticals Driving European M&A in Healthcare

Alvarez & Marsal, Sep 15, 2023

Last year saw pharma M&A settle down into a slower pace as a result of macroeconomic uncertainty, rising interest rates and volatile capital markets, a trend that has continued into 2023. PE-led activity has struggled even more given the higher cost of debt, with PE investments in the European healthcare sector declining 27% in 2022, according to S&P Ratings. One of the main reasons behind the slowdown has been the mismatch in pricing expectations between sellers and buyers, leading to several failed processes over the last two years.

We observe that appetite from both trade and financial buyers remains strong in certain sub-sectors within the healthcare & life science space, which could provide the backdrop for more dealmaking towards the rest of the year.

In particular, Contract Development & Manufacturing Organisations (CDMOs), biologics and specialty pharma are three verticals that we believe are well-suited to lead the way to more M&A activity. Against this background, CDMOs M&A continued apace in 2023 with PE buyers looking to buy their way into the buoyant sub-sector and incumbent players seeking to consolidate or broaden their capabilities. Industry-specific growth and competitive dynamics mean many deals are bucking the trend and commanding a premium in today's tougher M&A market.

Historically, deal activity has been fuelled by decades-long trends in outsourcing, with big pharma continuously divesting assets to rationalise their manufacturing footprint and become asset-light businesses. More recently, the emergence of novel modalities, such as cell therapies and biologics, has become a major driving force.

Specialty pharmaceuticals have undergone a fundamental change in the past few years, moving away from small molecules and a business model that relied on aggressive price hikes. Instead, today's growth agenda has largely shifted towards specific therapeutic areas, meaning low-volume drugs that treat complex and chronic conditions.

Several strategic players are increasingly looking for assets to build their niche platforms as well to develop the specialist capabilities needed to produce these drugs. Conversely, smaller specialty firms are ripe for investments as they often do not have the resources to bring their innovative drugs to the market. Examples of recent deals in this space include HIG Capital's acquisition of Aspire Pharma, a provider of niche generic and branded specialty pharmaceuticals that offer innovative formulations and supply arrangements in underserved markets. This was followed by an add-on acquisition of Morningside Healthcare and Morningside Pharmaceuticals in 2022.

Another trend in specialty pharmaceuticals is the use of public-to-private transactions. A recent example is the acquisition of Dechra Pharmaceutics, a global specialist in veterinary pharmaceuticals and related products including Vetoryl, a medicine for Cushing's disease in dogs, and Felimazole, a medication for treating feline hyperthyroidism. The business was acquired by EQT for £4.5 billion, one of the biggest buyouts in the UK this year.

Source: https://www.alvarezandmarsal.com/insights/cdmos-specialty-pharma-among-verticals-driving-ma-activity-healthcare

Pharma Deal Making: A Bright Spot Amid the Gloom

Melanie Senior, *Nature Biotechnology*, Sep 15, 2023 (excerpt)

Big pharma's deal-making splurge came later than many hoped, but it's here. After a dismal 2022, biopharma mergers and acquisitions (M&A) value reached over $95 billion by mid-2023, according to BioCentury, putting this year on track to be the strongest since 2019. Pfizer's $43 billion Seagen acquisition accounts for the lion's share of M&A dollars so far, but a dozen of 2023's deals are worth $1 billion or more.

Most deals focus on late-stage or marketed assets, as pharma buyers attempt to fill gaps left by blockbusters set to lose patent exclusivity. There's resurgent interest in treatments for chronic, widespread conditions across immunology and cardio-metabolic diseases, although rare diseases remain popular among some buyers. Initial public offerings (IPOs) and follow-on public financings are also reappearing, as investors take confidence from pharma's renewed M&A activity.

Yet this revival is selective and fragile. It offers little comfort for biotechs without late-stage assets or those lacking strong mid-stage clinical data. Biotech stocks are recovering far more slowly from the 2021–2022 downturn than they did from previous troughs in 2016 and 2002, according to investment bank Stifel; blame the flurry of premature listings and outsized valuations during the pandemic-induced biotech bubble, continued macroeconomic gloom and generalist investors' current craze for artificial intelligence stocks. At almost a quarter of publicly traded US biotechs, their cash on hand is worth more than their market capitalization (the combined value of their shares), and that cash will last barely more than 18 months on average. With exits hard to come by for all but the chosen few, and muted pharma licensing activity, some venture capitalists are also holding back.

Biotech's slow rebound is set against still-rising interest rates, which curb investors' risk appetite by setting a higher bar for risk-free returns. Dealmakers also have two other sources of uncertainty to contend with: the US Inflation Reduction Act (IRA), which reduces the value of some small-molecule drugs, and a more aggressive Federal Trade Commission (FTC) scrutinizing biopharma acquisitions. The FTC's most prominent target so far: Amgen's proposed $84 billion acquisition of Horizon, announced late 2022. (As Nature Biotechnology went to press, Amgen agreed to a settlement with the FTC, and the deal is expected to close in the fourth quarter of 2023.)

Acquisitions of companies with just one or two assets — so-called 'bolt-on' deals — may remain popular as they are less likely to attract FTC attention. And as phase 3 and later programs are picked off, deals will start to move upstream — though they will still be constrained by buyers' more rigorous data requirements. In June 2023, Eli Lilly paid $2.4 billion for Dice Therapeutics, whose lead oral interleukin (IL)-17 inhibitor is in phase 2; the target is well known.

Big diseases are back

Among bigger buyers, drugs treating widespread, chronic immunology and cardiometabolic diseases are more popular. It's hard to fill the multi-billion-dollar-sized shoes of genericizing blockbusters such as AbbVie's autoimmunity disease drug Humira (adalimumab) or Johnson & Johnson's Stelara (ustekinumab) with niche products.

Three of 2023's top ten acquisitions are in immunology. The revolution in obesity treatment, spearheaded by Novo Nordisk's GLP-1 agonist Wegovy (semaglutide, also sold as Ozempic for diabetes) has whet buyers' appetites across cardiometabolic diseases. In July 2023, Lilly boosted its obesity pipeline further by acquiring Versanis Bio for up to $1.9 billion (the size of the up-front payment was not disclosed).

Source: https://www.nature.com/articles/s41587-023-01958-7

Disclosure

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