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US Biotechnology

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See Disclosure Appendix of this report for important Disclosures and Analyst Certifications

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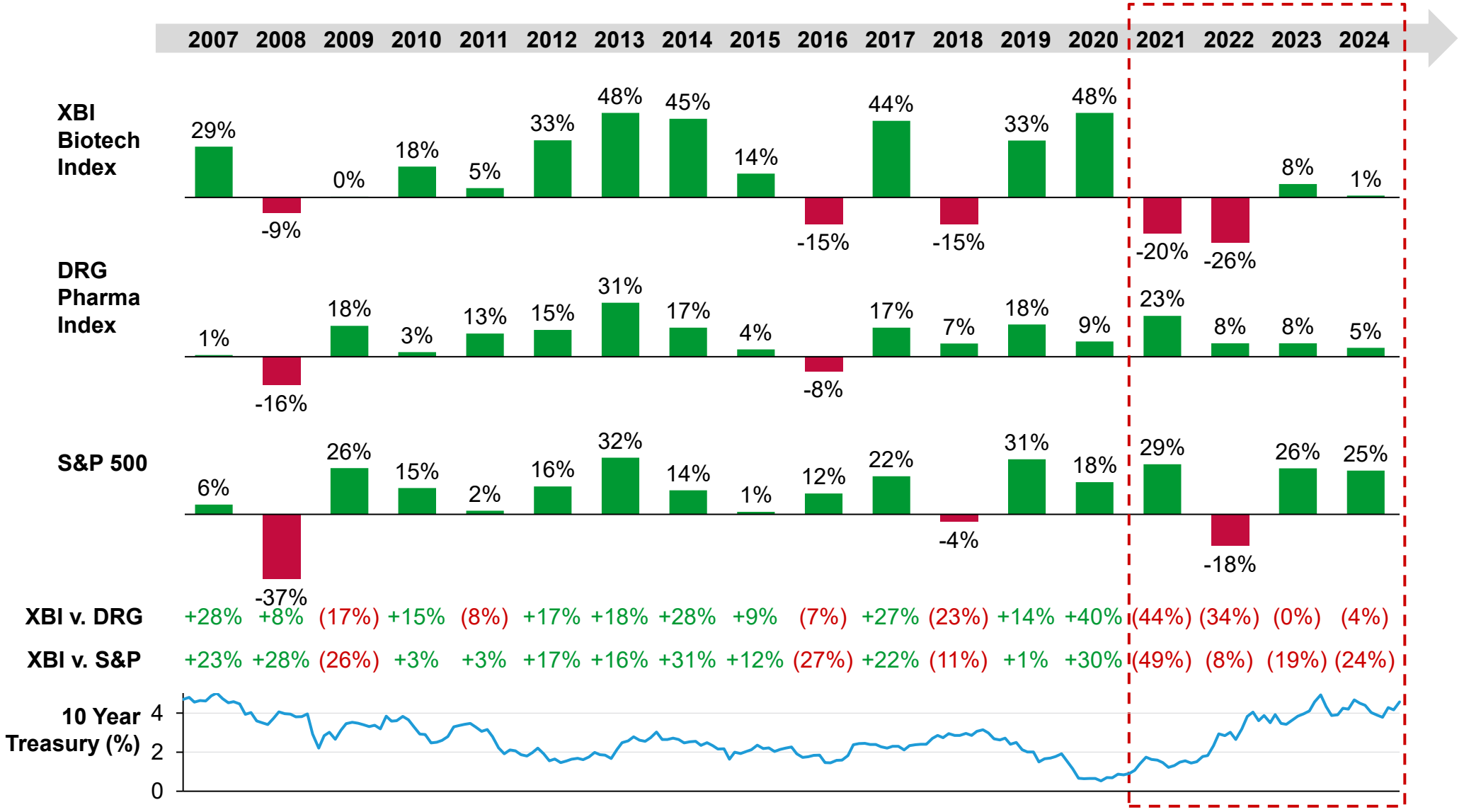
What we'll cover today

1. Biotech fundamentals: Sector performance, segmentation, POS valuation framework, segmentation

2. Recent trends
   - Funding and M&A
   - FDA
   - Innovation
   - AI

Annual total return | Biotech has underperformed pharma and the S&P for 4 years running, with prolonged high rates a key driver



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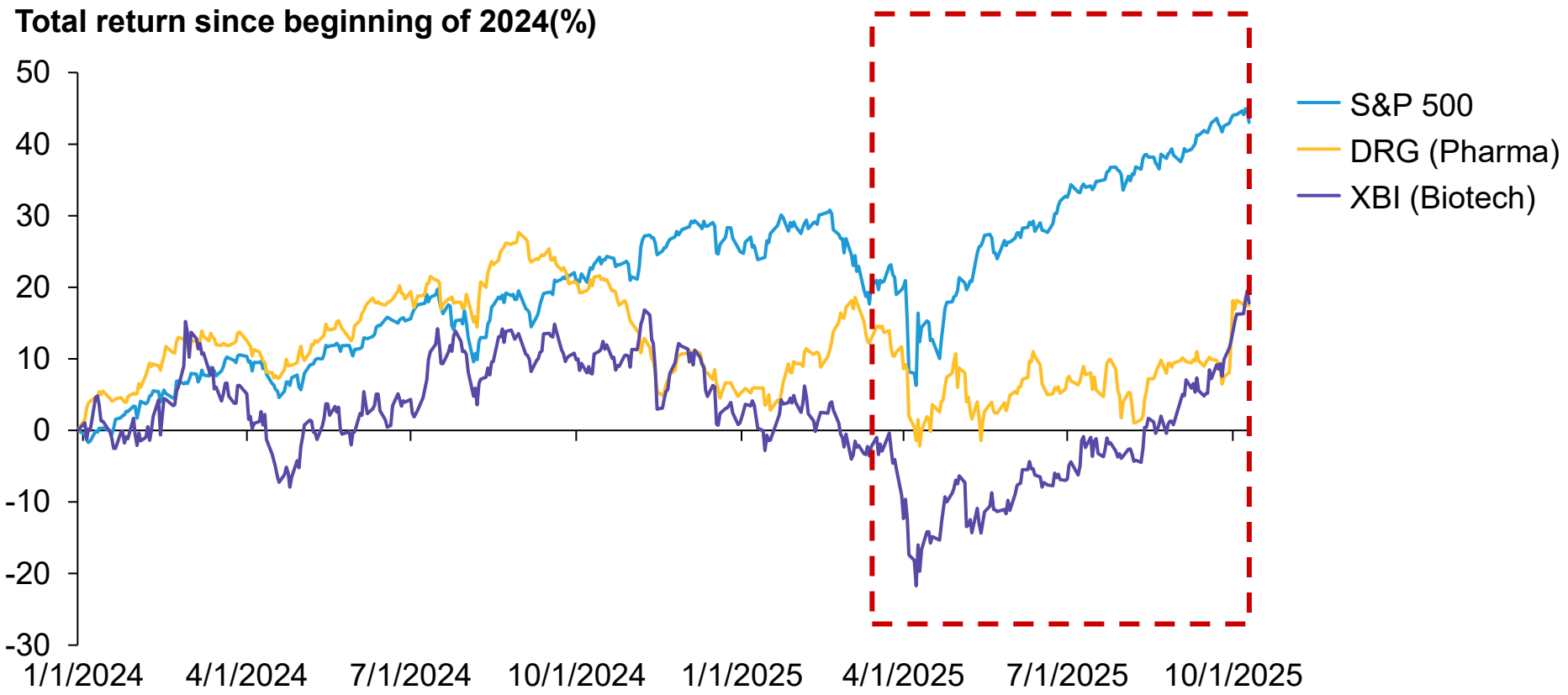
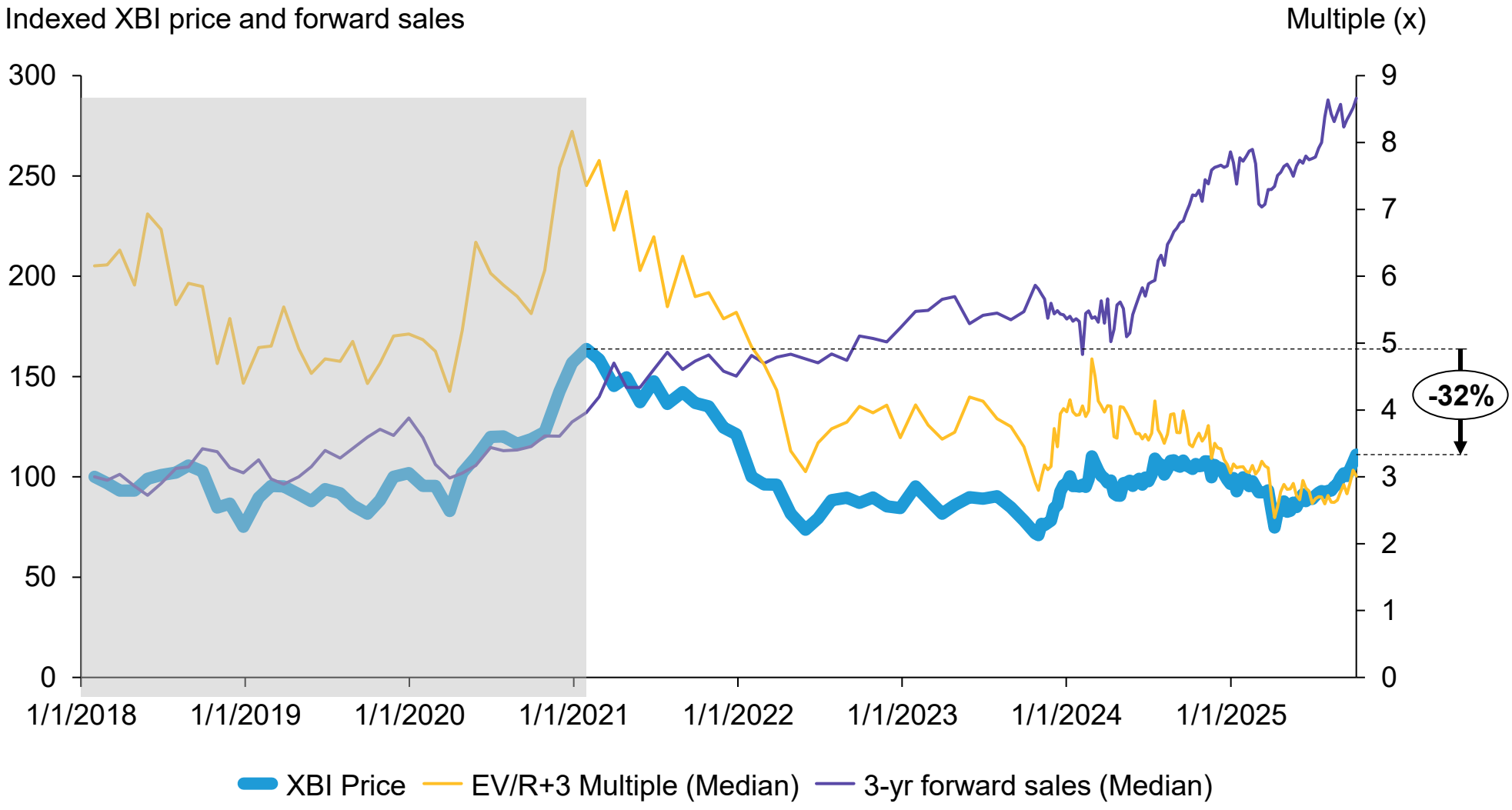
Note: Includes gross dividends
Source: Bloomberg, Bernstein analysis

In 2025 biotech is finally starting to rebound, up 18% YTD



Source: Bloomberg, Bernstein analysis; priced as of market close on October 9, 2025

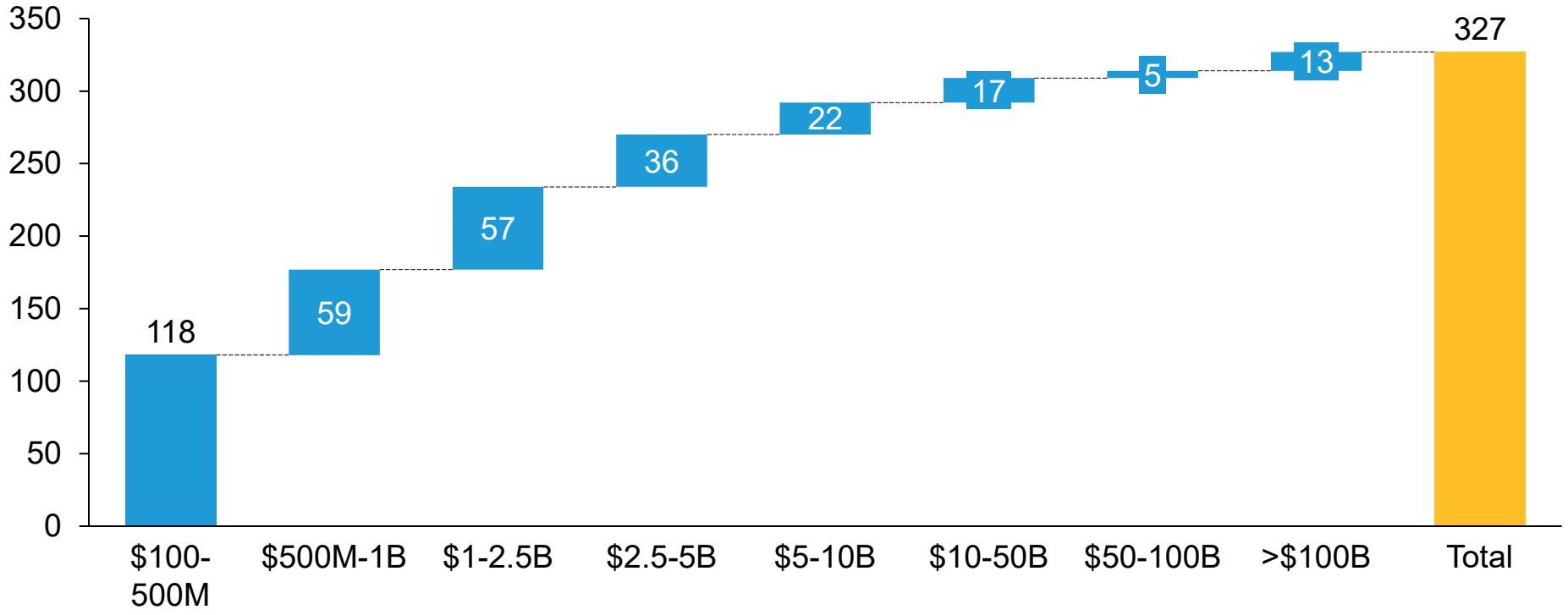
Biotech is still ~30% off its early 2021 peak; multiples are depressed even as sales expectations continue to climb



Source: Bloomberg, Bernstein analysis; priced as of market close on October 9, 2025

The investible universe is large… ~330 publicly traded biotechs >$100M market cap in Western countries, of which ~150 have market cap >$1B

Number of public biotech/biopharma[1] by market cap



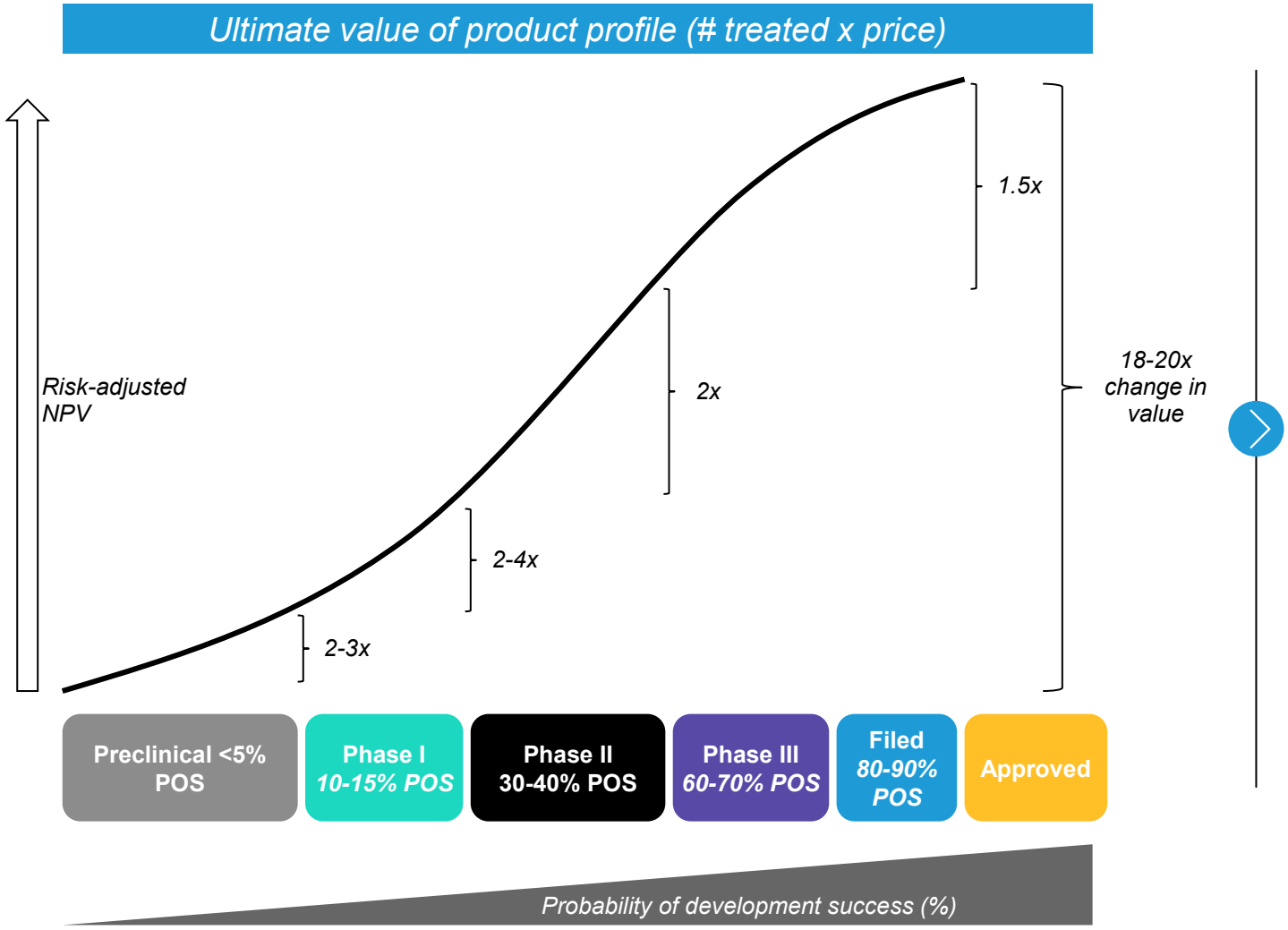
Example BIOAGE TYRA Intellia THERAPEUTICS IMMUNOVANT AVIDITY BIOSCIENCES Biogen Alnylam VERTEX

1. Large-cap companies are included as long as they have meaningful internal R&D; Exclusion criteria: Market cap <$100M; HQ outside North America, Western Europe, or ANZ; MedTech and orthobiologics
Source: Bloomberg, Bernstein analysis

Many different strategies have been applied in biotech but most strategies work best in certain subsectors of the bioverse

Source: Bloomberg, Bernstein analysis

Value creation in biotech comes from clinical trial success that increases the *risk-adjusted* NPV of the pipeline



Implications

Companies trade on trial success and incremental changes in the perceived riskiness of assets

The catalyst path is critical

Forecasts and valuations need to be adjusted for risk

 Source: Discussions with market participants, Bernstein analysis

Making sense of the madness | How to conceptualize SMID-cap biotech

Therapeutic area

- Oncology
- Neurology
- Infectious Disease
- Immunology
- Endocrine
- Ophthalmology
- Metabolic
- Cardiovascular
- Other

Technology

- Small molecule
- Traditional biologics
- Cell therapies / CAR-T
- Gene therapy and gene editing
- mRNA
- RNAi and Antisense
- Other

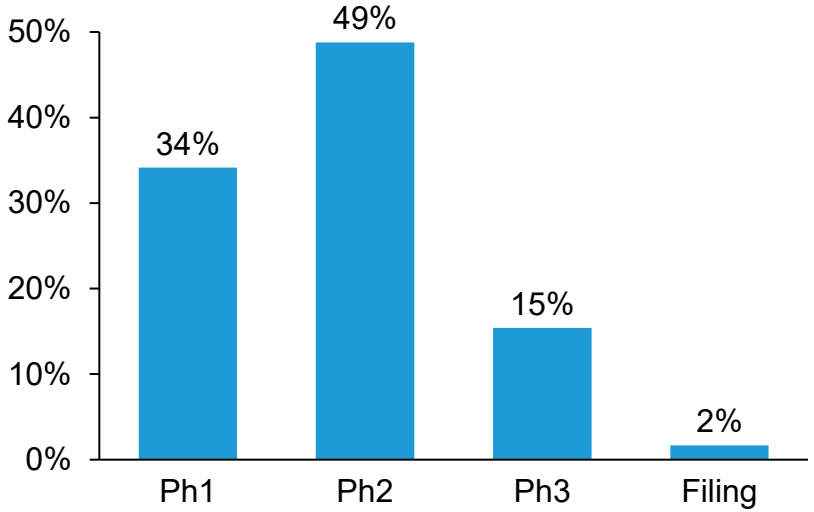
Development stage

- Pre-clinical
- Phase 1
- Phase 2
- Phase 3
- Regulatory filing
- Commercial

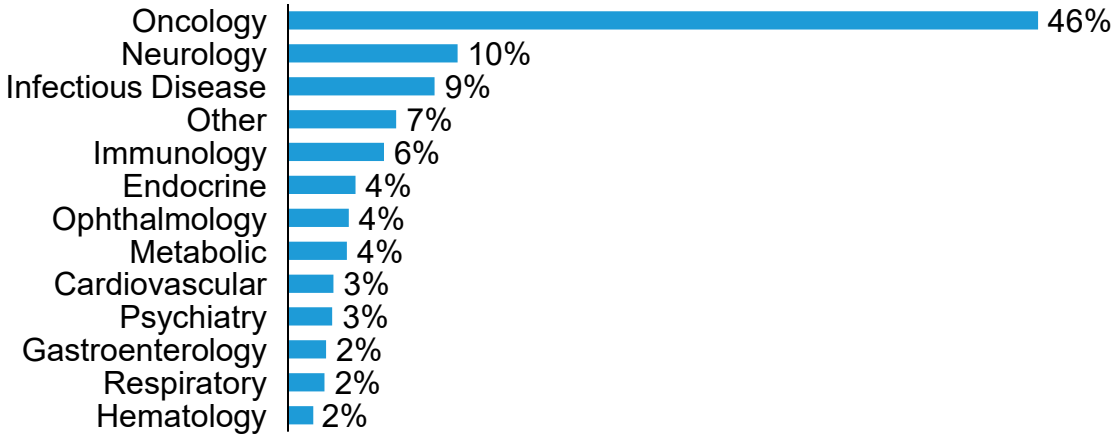
Source: Discussions with market participants, Bernstein analysis

Current drug pipeline | Development phase, TA, modality, and other candidate attributes

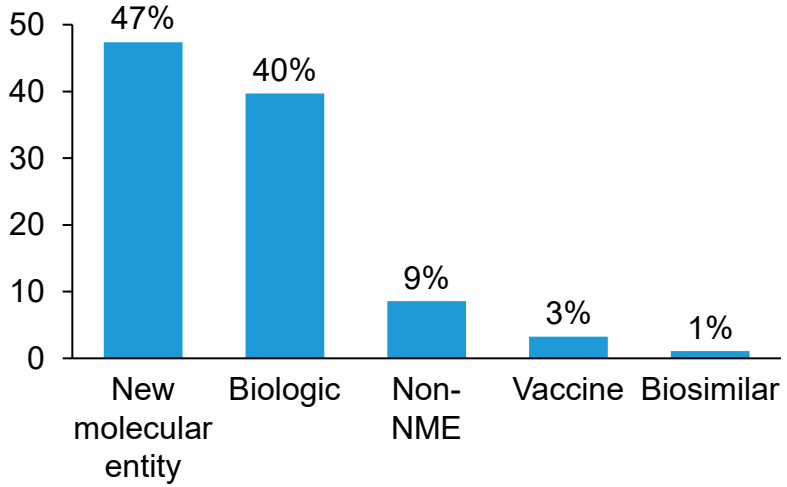
Pipeline assets by development phase



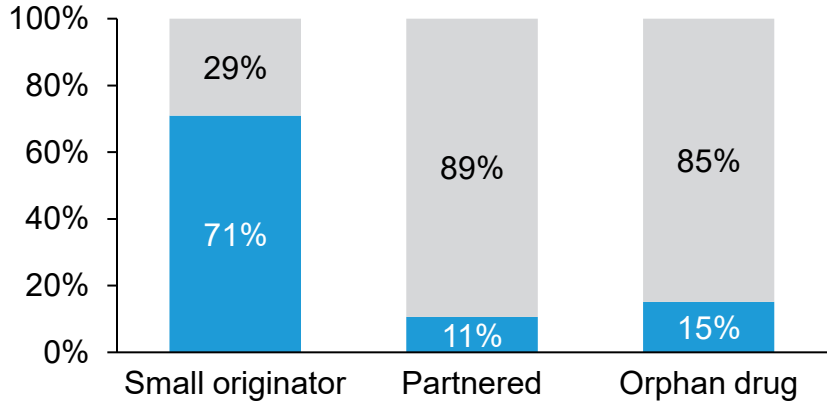
Pipeline assets by TA



Pipeline assets by modality



Pipeline attributes by misc. characteristics



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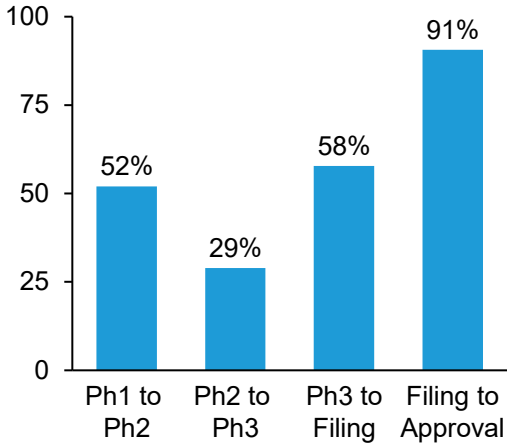
Source: BIO, Bernstein analysis

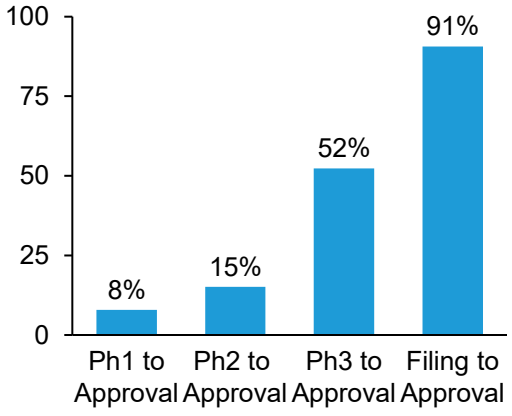
Probability of success | First you need to know the benchmarks

Cross-industry averages

Phase transition POS (%)

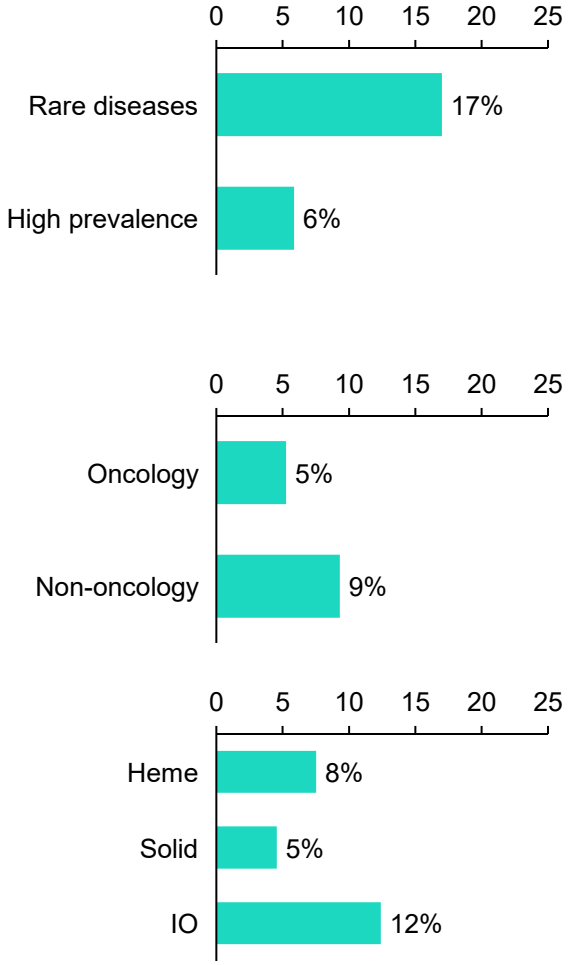


Cumulative likelihood of approval POS (%)

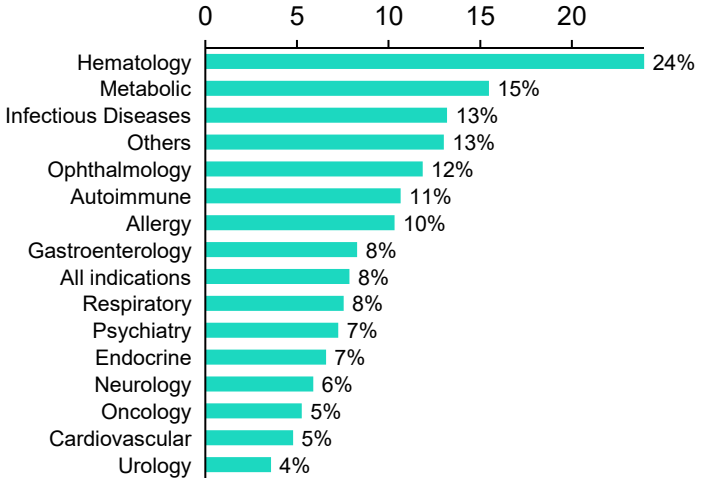


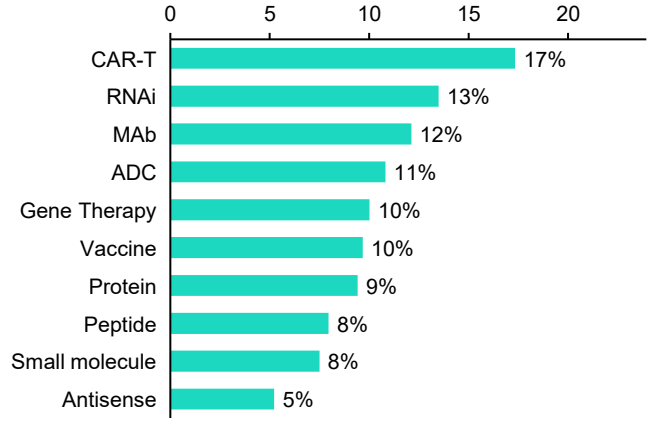
Subcategory averages (TA, modality, etc.)

Cumulative POS, Ph1 to Approval (%)



Cumulative POS, Ph1 to Approval (%)





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Note: Some averages have changed since data was collected, e.g., antisense POS today is higher
Source: BIO report for 2011-2020, Bernstein analysis

Probability of success | …Next step is to analyze the drug, disease, and trial design to identify and assess specific risks of trial failure

Key questions to help refine probability of success

- **Biology risk:** Does the target and mechanism actually address the disease pathology?
- **Safety:** Is the risk-benefit profile expected to be favorable in the context of the disease and at the dose levels being tested?
- **Endpoints:** Are the primary and key secondary endpoints generally accepted as meaningful? Are they objective or subjective? Is the placebo effect typically large or small?
- **Patient selection:** Is the study being run in patients that are particularly well suited for the study drug?
- **Biostatistics:** Is the study adequately powered? Is there uncertainty about expected event rates? For interim analysis, how much alpha is being "spent"?
- **"The bar":** What does good look like given currently available therapies?

Specific examples

- **Biology risk:** Recent failure of Roche's anti-TIGIT candidate (tiragolumab) vs. MRK's Keytruda in NSCLC.
- **Safety:** NaV inhibitors for pain… VRTX achieved where others failed based on more selective, potent drug with favorable side effect profile allowing higher dosing
- **Endpoints:** MADRS in depression… large placebo effect size
- **Patient selection:** REGN/SNY development of itepekimab in former smoker subpopulation of COPD given results of earlier trials.
- **Biostatistics:** ALNY HELIOS-B trial… High level of uncertainty about study powering and background event rates given that 40% of patient also on another drug
- **"The bar":** Ascendis fell 16% in Nov '22 after sharing achondroplasia data that showed benefit but unclear if differentiated vs. BioMarin

Source: Company reports, KOL interviews, investor discussions, Bernstein analysis

Key FDA regulatory concepts you are likely to come across

Term	Definition
Accelerated Approval	Regulatory pathway that allows the FDA to approve drugs based on surrogate endpoints that are likely to predict clinical benefit, particularly for serious conditions where there is an unmet needs.
Advisory Committee (AdCom)	A panel of independent experts convened by the FDA to provide recommendations on the approval of new drugs or medical devices. The FDA isn't required to follow the AdCom's recommendations, but they often do.
Breakthrough Therapy Designation	Expedites development and review of drugs intended to treat a serious condition based on preliminary clinical showing potential for substantial improvement over available drugs. Eligible for everything fast track designation gets you + "intensive guidance" from the FDA.
Center for Biologics Evaluation and Research (CBER)	The part of the FDA that regulates biologic products for human use, including allergenics, blood and tissue-based products, cell and gene therapies, and vaccines.
Center for Drug Evaluation and Research (CDER)	The part of the FDA that regulates over-the-counter and prescription drugs, as well as other products (e.g., sunscreen). CDER is responsible for all NDAs and some BLAs, including monoclonal antibodies.
Clinical Hold	When the FDA delays/suspends a clinical trial due to either significant risk to study participants or a clinical protocol that doesn't meet requirements. The hold lasts until the FDA is satisfied the issues have been resolved.
Complete Response Letter (CRL)	FDA communication indicating that the review of an NDA or BLA is complete, but the application is not ready for approval. A CRL outlines deficiencies and, in some cases, offers guidance on how to address them.
Emergency Use Authorization (EUA)	FDA authorization during public health emergencies to allow the use of unapproved medical products or unapproved uses of approved medical products when there are no adequate, approved, and available alternatives.
Fast Track Designation	Expedites development and review of drugs for serious conditions that fill an unmet medical need. Allows for more frequent FDA interactions and eligibility for accelerated approval and priority review.
Investigational New Drug (IND) Application	Application that a sponsor submits to the FDA before starting in-human studies. The IND contains preclinical data, proposed protocols, and information about the drug's composition and manufacturing.
New Drug Application (NDA)	The request for the FDA to approve a new drug for sale in the U.S. The NDA includes data from preclinical and clinical trials, and information about the drug's manufacturing, labeling, and safety.

Term	Definition
Orphan Drug Designation	Status given to rare disease drugs for conditions affecting <200,000 people in the U.S. Provides benefits such as tax credits, user fee waivers, and market exclusivity for seven years post-approval.
Post-Marketing Requirement / Commitment (PMR, PMC)	Studies that the FDA requires (PMR) or requests (PMC) a sponsor to conduct after a drug is approved, to gather additional information about the drug's safety, efficacy, or optimal use.
Priority Review	Shortens the FDA's review period for an NDA or BLA from the standard 10 months to 6 months. Granted to drugs that offer significant improvements in the treatment, diagnosis, or prevention of serious conditions.
Priority Review Voucher (PRV)	Awarded by the FDA to sponsors of approved treatments for certain neglected diseases and rare pediatric diseases. PRVs can be used to expedite the review of another drug or sold to another company.
Refuse to File (RTF)	FDA action when an NDA or BLA is deemed incomplete or not organized, leading to a rejection of the submission without a full review.
Regenerative Medicine Advanced Therapy Designation (RMAT)	Benefits include those given for fast track and breakthrough therapy designations but is only available for certain regenerative medicine therapies that intend to treat serious conditions with a large unmet need.
Risk Evaluation and Mitigation Strategy (REMS)	Plan required by the FDA for certain drugs to ensure that their benefits outweigh their risks. REMS can include measures such as medication guides, communication plans, or restricted distribution programs.
Rolling Review	A process where the FDA reviews portions of a drug's NDA or BLA as they are completed, rather than waiting until the entire application is submitted. Often used in conjunction with Fast Track designation.
Surrogate Endpoint	A biomarker or other measurement used in clinical trials as a substitute for a direct measure of clinical benefit (e.g., survival or symptom improvement). Surrogate endpoints can be used in Accelerated Approval pathways.
Type A, B, and C Meetings	Different types of meetings that sponsors can request with the FDA: Type A: Typically to discuss a stalled development program or clinical hold. Type B: Held at pivotal stages in development, such as before submission of an IND, NDA, or BLA. Type C: Anything that doesn't fall into Type A or B.

Source: FDA, Bernstein analysis

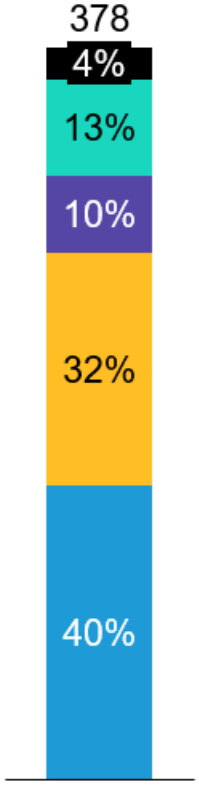
Sales forecasting | Much less foreign than POS for investors coming from other sectors, but still some nuances to keep in mind

- Starting point is epidemiology: Prevalence rate, diagnosis rate, and treatment rate
  - Many companies, especially European, have epi appendices in their presentations
  - Rare diseases with limited treatment options often have poorly characterized epi with non-static dx and tx rates
- Standard approach is TAM x market penetration x share x price…
  - But for markets in which share and penetration changing a lot simultaneously, double check that your y/y revenue growth rates look smooth
- Bottom-up model for US is essential, while for ex-US may be sufficient to just index it to US based e.g., 50% price x 125% volume
- The same drug may be in development for multiple indications… need to probability adjust each indication separately
- Assets do not have terminal value…
  - Check the 10-K for exclusivity periods (e.g., patents, and regulatory exclusivity) or, for those of you with access, just use IPD analytics

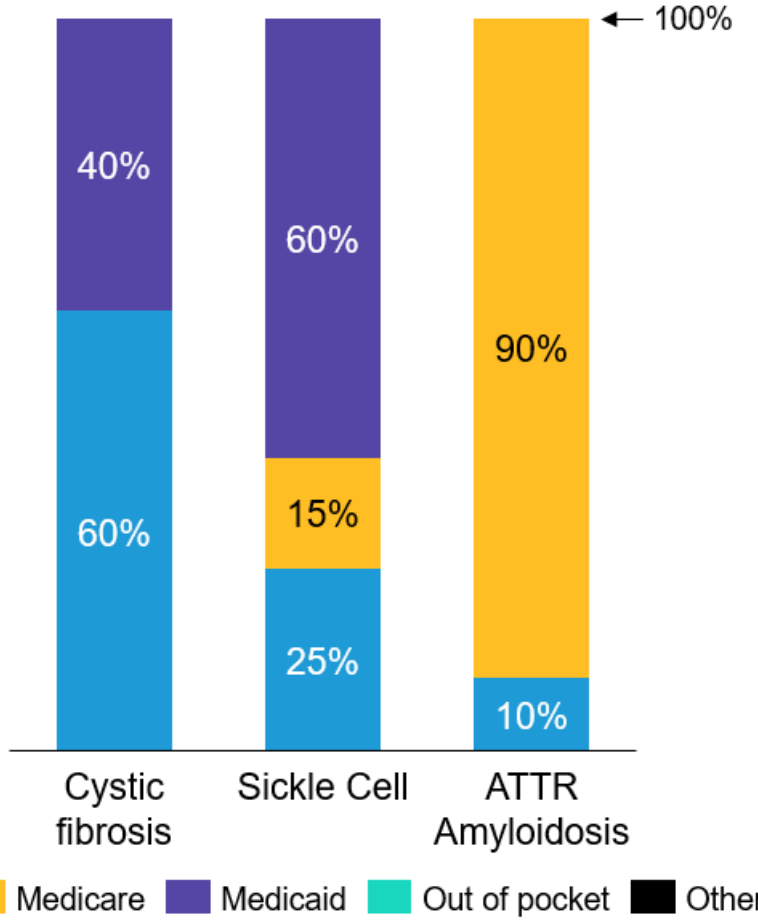
Source: KOL interviews, Investor discussions, Bernstein analysis

Addressable market | Prescription drug spend in the US is ~$400B; investors need to understand the payer mix of the drugs they are analyzing

US prescription drug expenditures ($B)



Example of 3 diseases with very different payer mixes



Why it matters

- **Private (commercial) insurance pays the most**
- **Medicare is subject to price negotiations under the Inflation Reduction Act**
- **Medicaid pays least, is managed at the state level, and is slowest to enact coverage policies**

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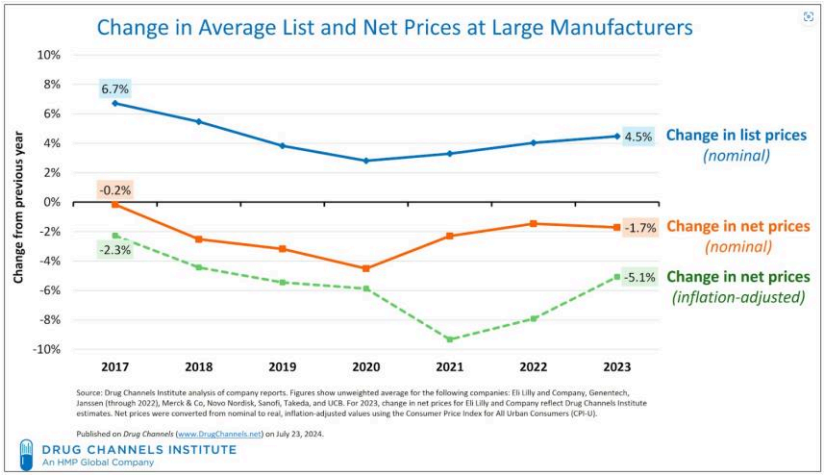
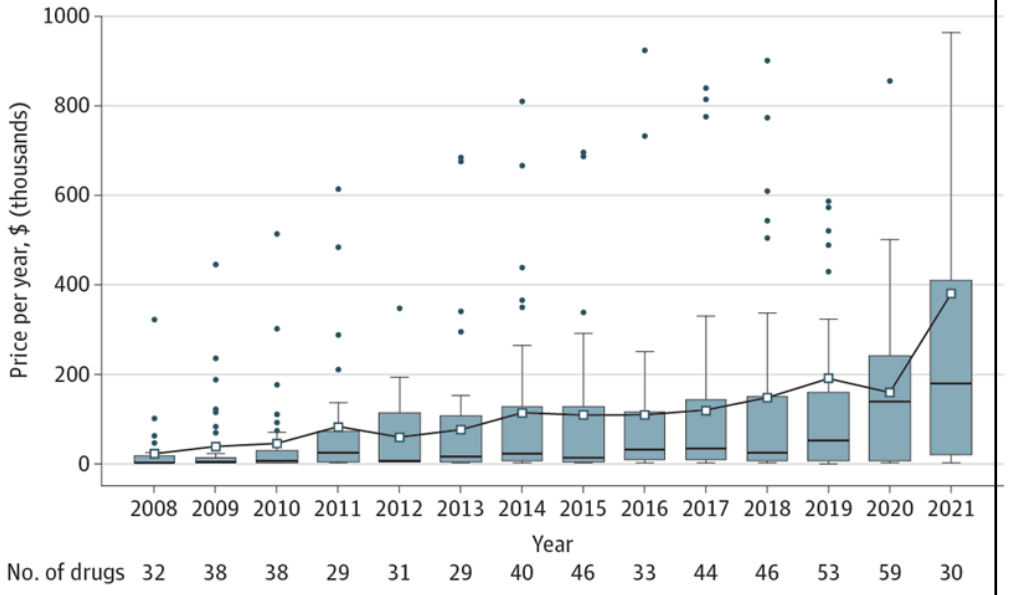
Drug pricing | Industry using higher launch pricing to counteract downward post-launch pressure, expect Inflation Reduction Act (IRA) to amplify this effect

List price growth post-launch has slowed and net price growth is now slightly negative

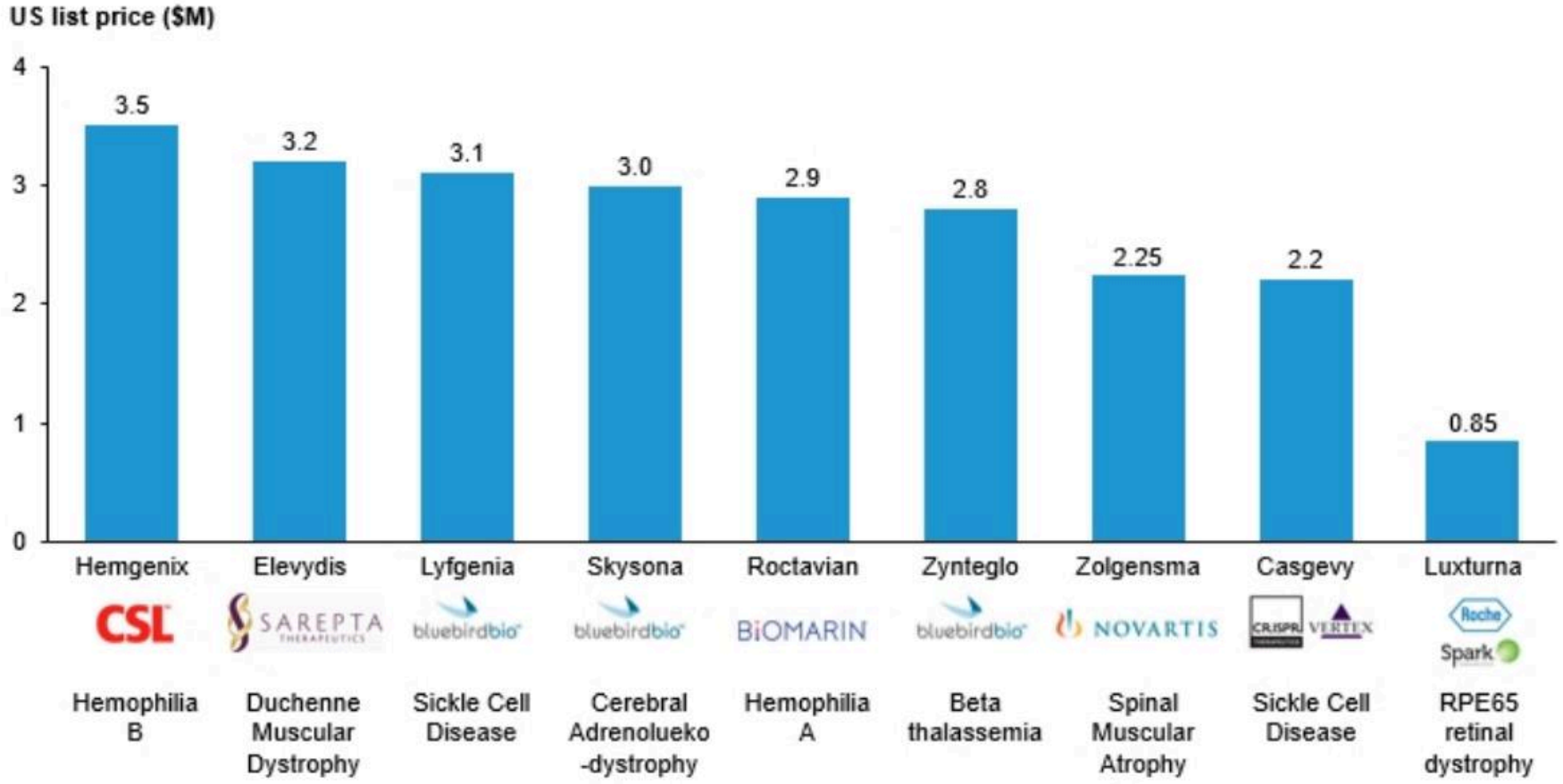


However, pharma has responded to this downward pressure by raising launch prices significantly - $200-400k/year not uncommon



Source: Drug Channels Institute, JAMA, Bernstein analysis

Drug pricing | Gene therapy drugs often carry multi-million dollar price tags, but investors prefer chronically dosed meds rather than 1-and-done



Source: Company reports, Bernstein analysis

Drug pricing | IRA cut list prices by ~60-70%, but only 22% impact on net price

Key provisions of the IRA

- Price negotiation for drugs with highest Medicare spend, with certain exemptions including
  - Small molecules for 9 years post-approval
  - Biologics for 13 years post-approval
  - Drugs with orphan drug designation
  - Drugs with biosimilar or generic competitor
- Maximum fair price varies by time since approval
  - 9-12 years: 75% of non-federal AMP
  - 12-16 years: 65% of non-federal AMP
  - >16 years: 40% of non-federal AMP
- Part D prices first take effect in 2026
- Part B negotiations start in 2026, first take effect in 2028
- Drug companies pay rebates if prices rise faster than inflation for Medicare beneficiaries, beginning in 2023
- Lower out-of-pocket cap in Medicare Part D, beginning 2024
- Drug companies pay 20% discount on drug spend above the out of pocket cap in Part D, beginning 2025
- Insulin monthly cost sharing capped at $35, beginning in 2023

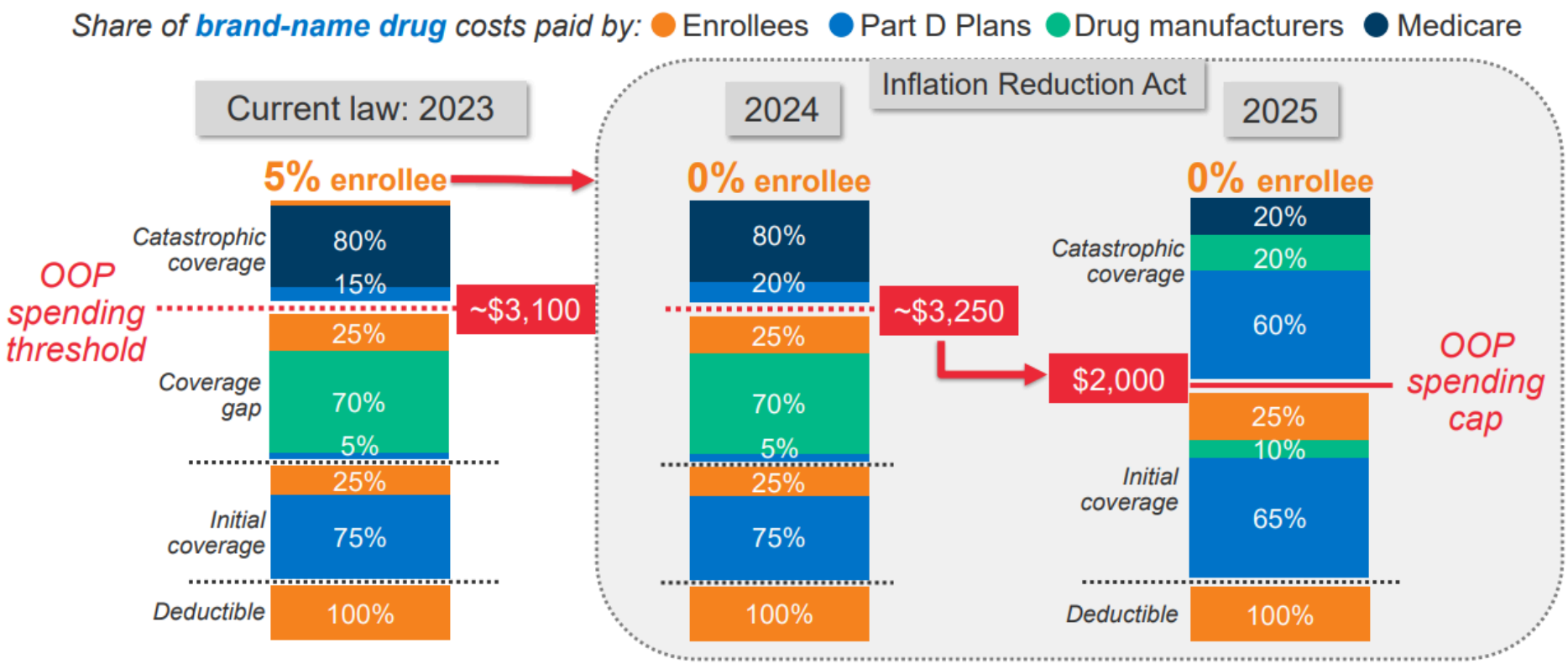
Drug selected for first round of negotiations

Drug	Company	IRA discount to list price	Gross Part D Spend ($B)	Medicare patients
Eliquis	BMS/Pfizer	56%	16.5	3,706,000
Jardiance	Boehringer Ingelheim	66%	7.1	1,573,000
Xarelto	Bayer	62%	6.0	1,337,000
Januvia	Merck	79%	4.1	869,000
Farxiga	AstraZeneca	68%	3.3	799,000
Entresto	Novartis	53%	2.9	587,000
Enbrel	Amgen	67%	2.8	48,000
Imbruvica	AbbVie/J&J	38%	2.7	20,000
Stelara	J&J	66%	2.6	22,000
Fiasp/Novolog	Novo Nordisk	76%	2.6	777,000

But average discount to net price only 22%

 Source: CMS, Company reports, Bernstein analysis

Drug pricing | Changes to Part D cost sharing are favorable to members and unfavorable to Part D plans



For indications with competing Part B and Part D drugs, these changes are incrementally positive for the Part B drug, though Medicare Advantage plans continue to be responsible for 100% of Part B drug costs

 Source: Visualization from KFF; CMS; Bernstein analysis

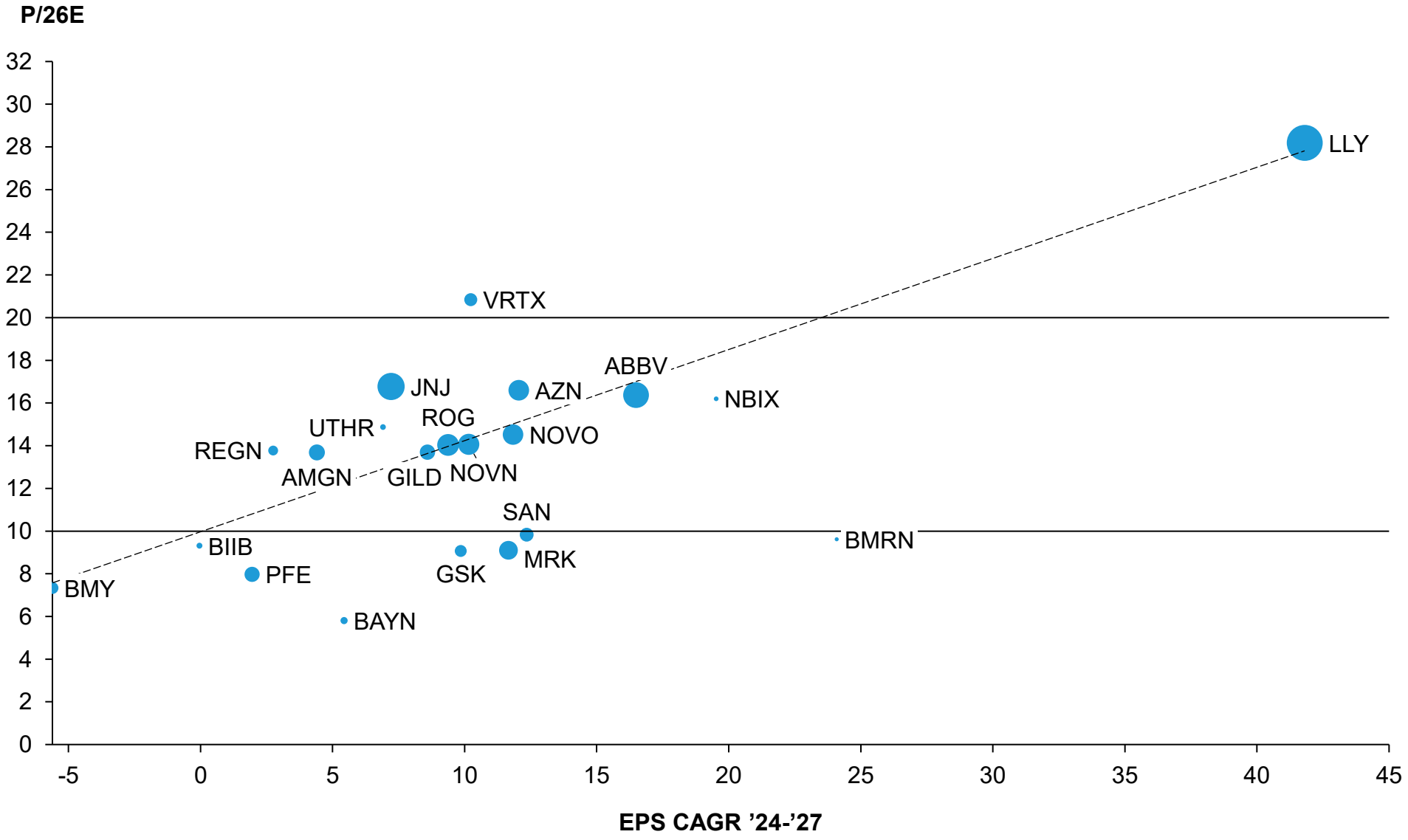
Valuation | 3 primary approaches to valuation – DCF is most important

1. Risk-adjusted DCF: Whole-company or sum of the parts
2. Price to sales or EV to sales
3. Price to earnings

Source: Bloomberg, Bernstein analysis

Valuation | Profitable biotech and biopharma typically trades at 10-20x P/E

Earnings growth matters, but long-term revenue durability also very important



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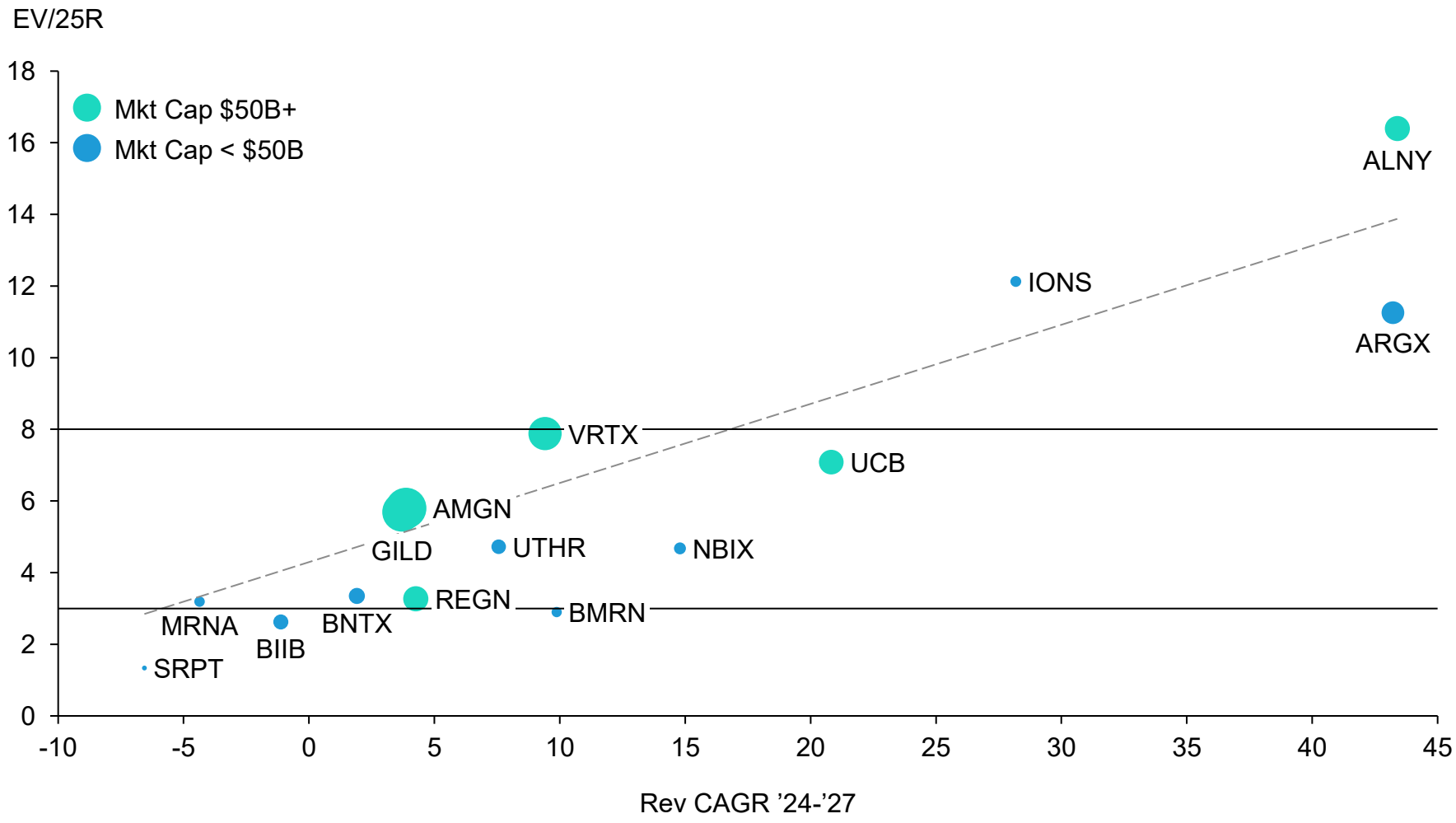
Note: The following companies use 2023 EPS because '24 numbers impacted by one-time expenses: VRTX, GILD, BMY
Source: Bloomberg consensus, Bernstein analysis

Valuation | Commercial-stage biotech typically trades at 3-8x sales

Growth off a larger base is often rewarded more



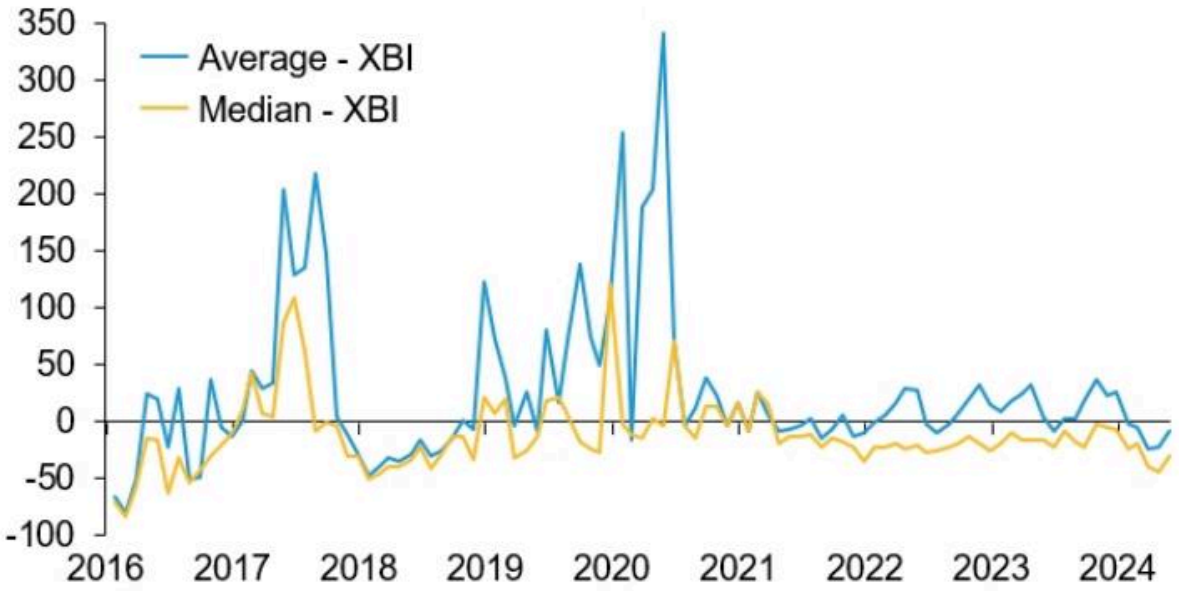
 Source: Bloomberg consensus, Bernstein analysis

The number of biotechs trading below cash has spiked since YE24 and reached an all-time high of 133 in March 2025

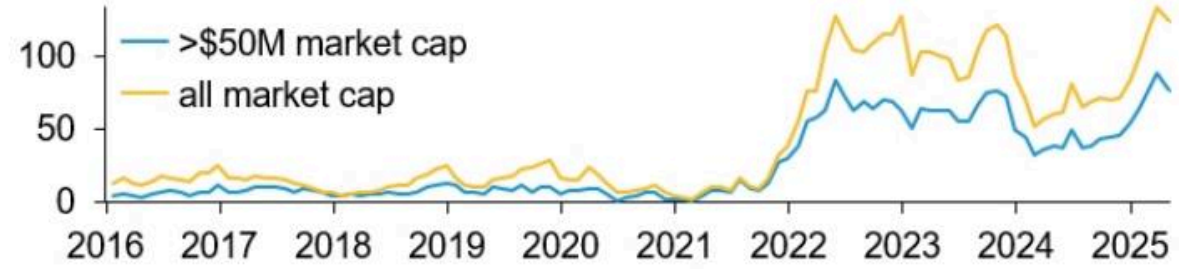
Source: Bloomberg, Bernstein analysis

Just blindly buying sub-cash biotechs appears to be a viable strategy, but it depends on a few "big wins"

1-year forward return vs. XBI: sub-cash companies with market cap >$50M



 # sub-cash companies



Observations

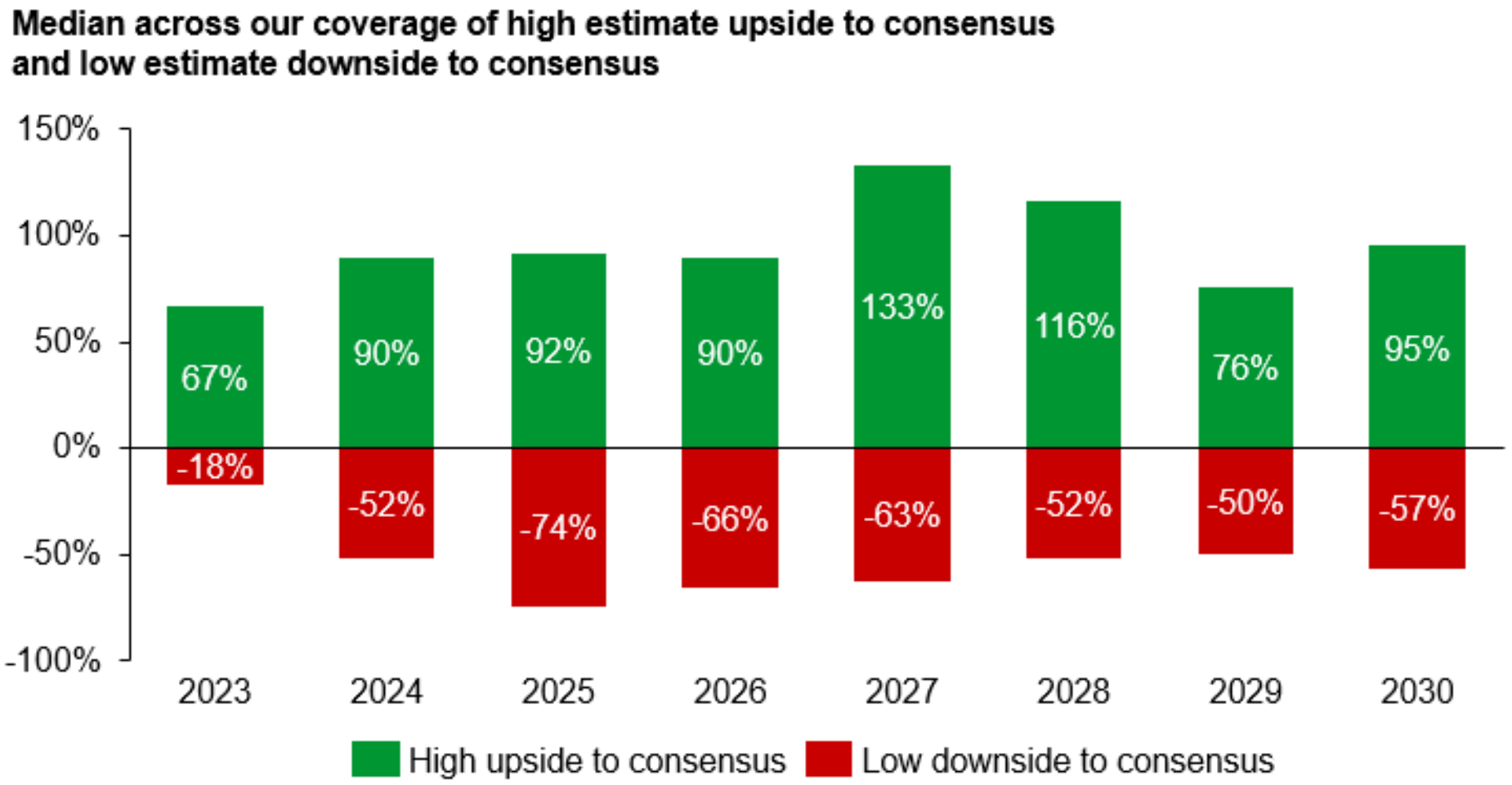
- Average beats XBI in 57% of periods (58/101)
- Median beats XBI in 21% of periods (21/101)
- Individual stocks beat XBI in 36% of cases (815/2,254)

Conclusion and implications

- Relative returns are positively skewed
- Strategy tends to work better during periods when there are more sub-cash companies

Source: Bloomberg, Bernstein analysis

What consensus? Sell-side consensus is less informative/important in biotech because the range of estimates is so wide



Source: Bloomberg, Bernstein analysis

What we'll cover today

1

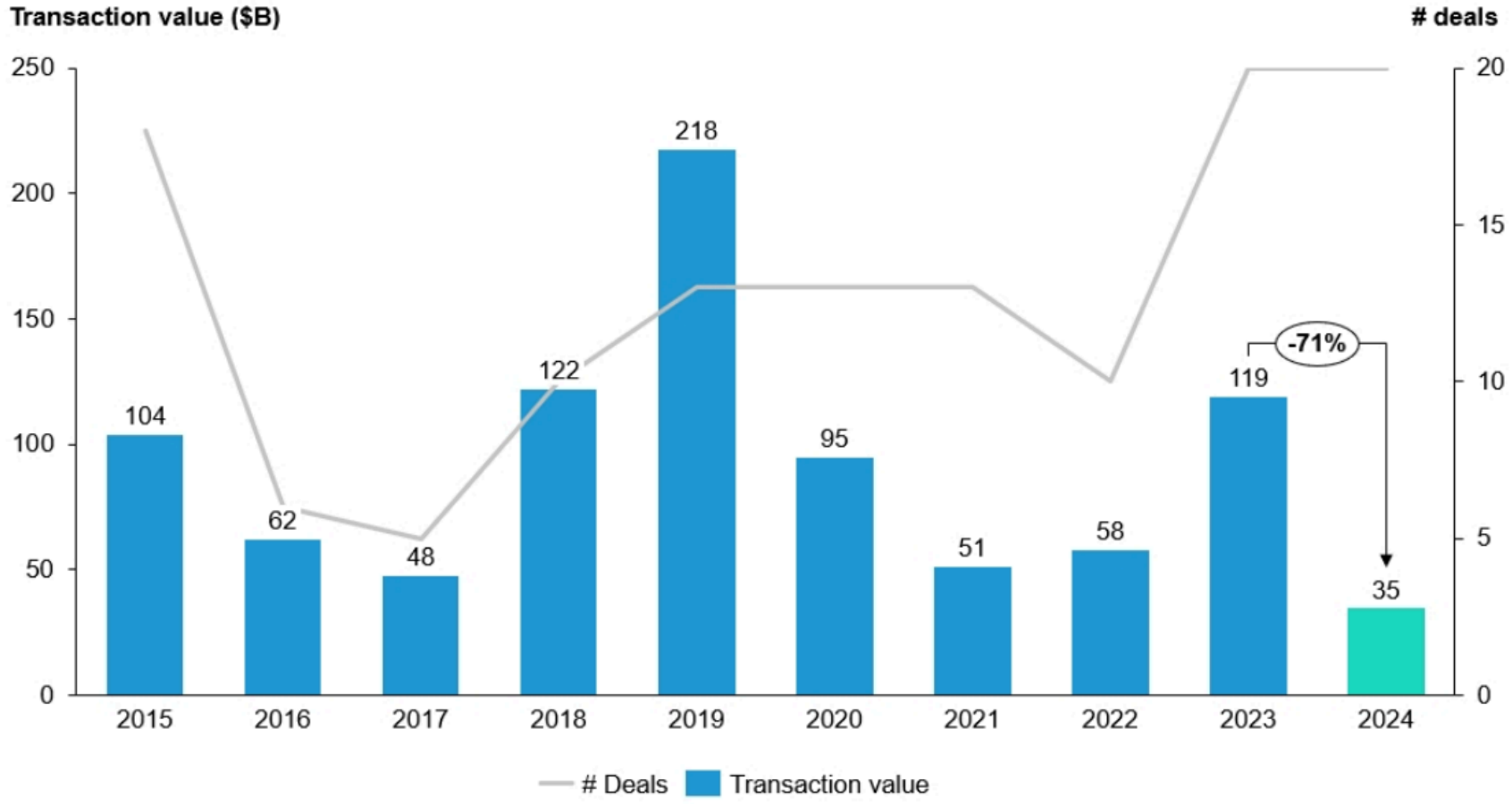
Biotech fundamentals: Sector performance, segmentation, valuation framework

2

Recent trends

- Funding and M&A
- FDA
- Innovation
- AI

M&A | Cumulative transaction value down 70% in 2024 even as deal volume flat



Source: Bloomberg, Company reports, Bernstein analysis

M&A | In 2024 we saw a large number of small deals, while in 2025 it's been the opposite

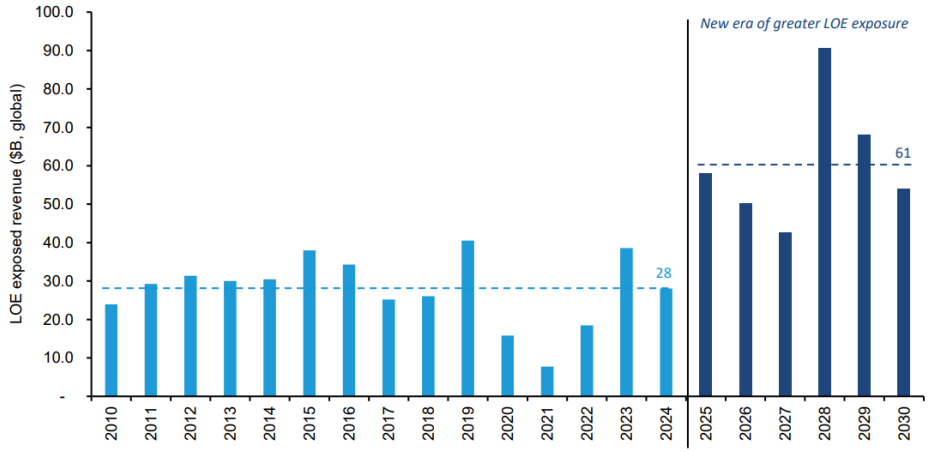
Target	Acquirer	Announcement date	TA	Lead asset phase	Transaction value
Intra-Cellular Therapies Inc	Johnson & Johnson	2025 Jan 13	CNS	Approved	14,279
Blueprint Medicines Corp	Sanofi	2025 Jun 02	Inflammation & Immunology	Approved	9,100
SpringWorks Therapeutics Ir	Merck KGaA	2025 Apr 28	Oncology	Approved	3,900
Scorpion Therapeutics Inc	Eli Lilly & Co	2025 Jan 13	Oncology	Ph1/2	2,500
Capstan Therapeutics Inc	AbbVie Inc	2025 Jun 30	Inflammation & Immunology	Ph1	2,100
Vicebio Ltd	Sanofi	2025 Jul 22	Other/Multiple	Ph1	1,150
Tourmaline Bio Inc	Novartis AG	2025 Sep 09	Cardiovascular & Renal	Ph2	1,039
IDRx Inc	GSK PLC	2025 Jan 13	Oncology	Ph1	1,000
Alpine Immune Sciences Inc	Vertex Pharmaceutica	2024 Apr 10	Inflammation & Immunology	Ph2	4,600
Cymabay Therapeutics Inc	Gilead Sciences Inc	2024 Feb 12	Rare Disease	Filed	3,515
Longboard Pharmaceuticals	H Lundbeck A/S	2024 Oct 14	CNS	Ph3	2,475
MorphoSys AG	Novartis AG	2024 Feb 05	Oncology	Ph3	2,369
Morphic Holding Inc	Eli Lilly & Co	2024 Jul 08	Inflammation & Immunology	Ph2	2,334
Profoundbio US Co	Genmab A/S	2024 Apr 03	Oncology	Ph2	1,800
Deciphera Pharmaceuticals I	Ono Pharmaceutical C	2024 Apr 29	Oncology	Approved	1,781
Ambryx Biopharma Inc	Johnson & Johnson	2024 Jan 08	Oncology	Ph1/2	1,544
Fusion Pharmaceuticals Inc	AstraZeneca PLC	2024 Mar 19	Oncology	Ph2	1,481
Aliada Therapeutics Inc	AbbVie Inc	2024 Oct 28	CNS	Ph1	1,400
Inhibrx Inc	Sanofi	2024 Jan 23	Rare Disease	Ph2	1,304
Nerio Therapeutics Inc	Boehringer Ingelheim	2024 Aug 29	Oncology	Preclinical	1,300
Eyebiotech Ltd	Merck & Co Inc	2024 May 29	Other/Multiple	Ph1/2	1,300
Yellow Jersey PR Ltd	Johnson & Johnson	2024 May 28	Inflammation & Immunology	Ph1	1,250
Human Immunology Bioscie	Biogen Inc	2024 May 22	Inflammation & Immunology	Ph2	1,150
Cardior Pharmaceuticals Gm	Novo Nordisk A/S	2024 Mar 25	Cardiovascular & Renal	Ph2	1,111
Calliditas Therapeutics AB	Asahi Kasei Corp	2024 May 28	Inflammation & Immunology	Approved	1,101
Kate Therapeutics Inc	Novartis AG	2024 Nov 21	Rare Disease	Preclinical	1,100
Mariana Oncology	Novartis AG	2024 May 02	Oncology	Preclinical	1,000
Aiolos Bio Inc	GSK PLC	2024 Jan 09	Inflammation & Immunology	Ph1	1,000

Source: Bloomberg, Company reports, Bernstein Analysis

M&A | Patent pressures are looming over the industry, putting pressure on large pharmas to do more deals

Patent cliffs double in 2025-2030 vs. prior years

EXHIBIT 4: **LOE exposure in 2025 rises to more than double the prior decades**



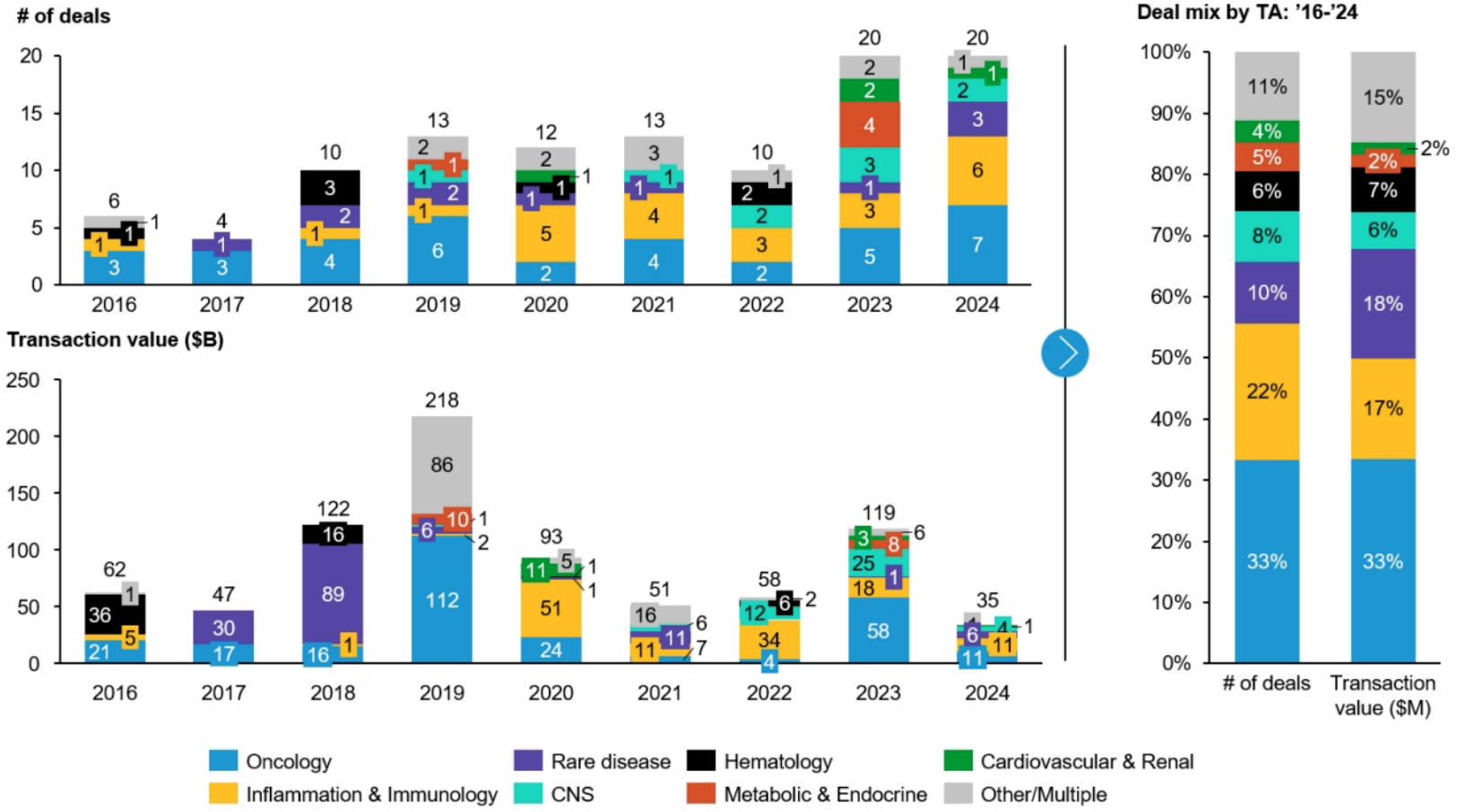
Year	LOE exposed revenue ($B, global)
2024	$28B
2025	$58B
2026	$50B
2027	$43B
2028	$91B
2029	$68B
2030	$54B

Top 5	Drug	Company	Revenue in LOE year ($B, global)
1	Eylea	Regeneron / Bayer	8.2
2	Nucala	GSK	2.3
3	Cimzia	UCB	2.2
4	Simponi	Johnson & Johnson	2.1
5	Ilaris	Novartis	1.5
1	Farxiga	AstraZeneca	7.7
2	Entresto	Novartis	7.4
3	Perjeta	Roche	4.3
4	Prolia	Amgen	4.1
5	Ofev	Boehringer Ingelheim	3.5
1	Eliquis	Bristol Myers Squibb	12.0
2	Prevnar 13	Pfizer	6.3
3	Vyndaqel	Pfizer	6.1
4	Imbruvica	Abbvie / Johnson & Johnson	3.1
5	Cabenuva	GSK	2.1
1	Trelegy Ellip	GSK	4.5
2	Comirnaty	Pfizer	4.1
3	Lynparza	AstraZeneca / Merck	3.7
4	Xtandi	Astellas / Pfizer	3.7
5	Ibrance	Pfizer	3.3
1	Keytruda	Merck	27.0
2	Gardasil 9	Merck	10.8
3	Jardiance	Boehringer Ingelheim / Eli Lilly	10.0
4	Opdivo	Bristol Myers Squibb	9.9
5	Dovato	GSK	4.0
1	Darzalex	Johnson & Johnson	17.4
2	Ocrevus	Roche	8.4
3	Cosentyx	Novartis	7.1
4	Shingrix	GSK	6.1
5	Vraylar	Abbvie	4.5
1	Vabysmo	Roche	9.4
2	Erleada	Johnson & Johnson	4.1
3	Taltz	Eli Lilly	3.4
4	Arexvy	GSK	3.4
5	Repatha	Amgen	2.7

Source: Evaluate, Bernstein Pharma

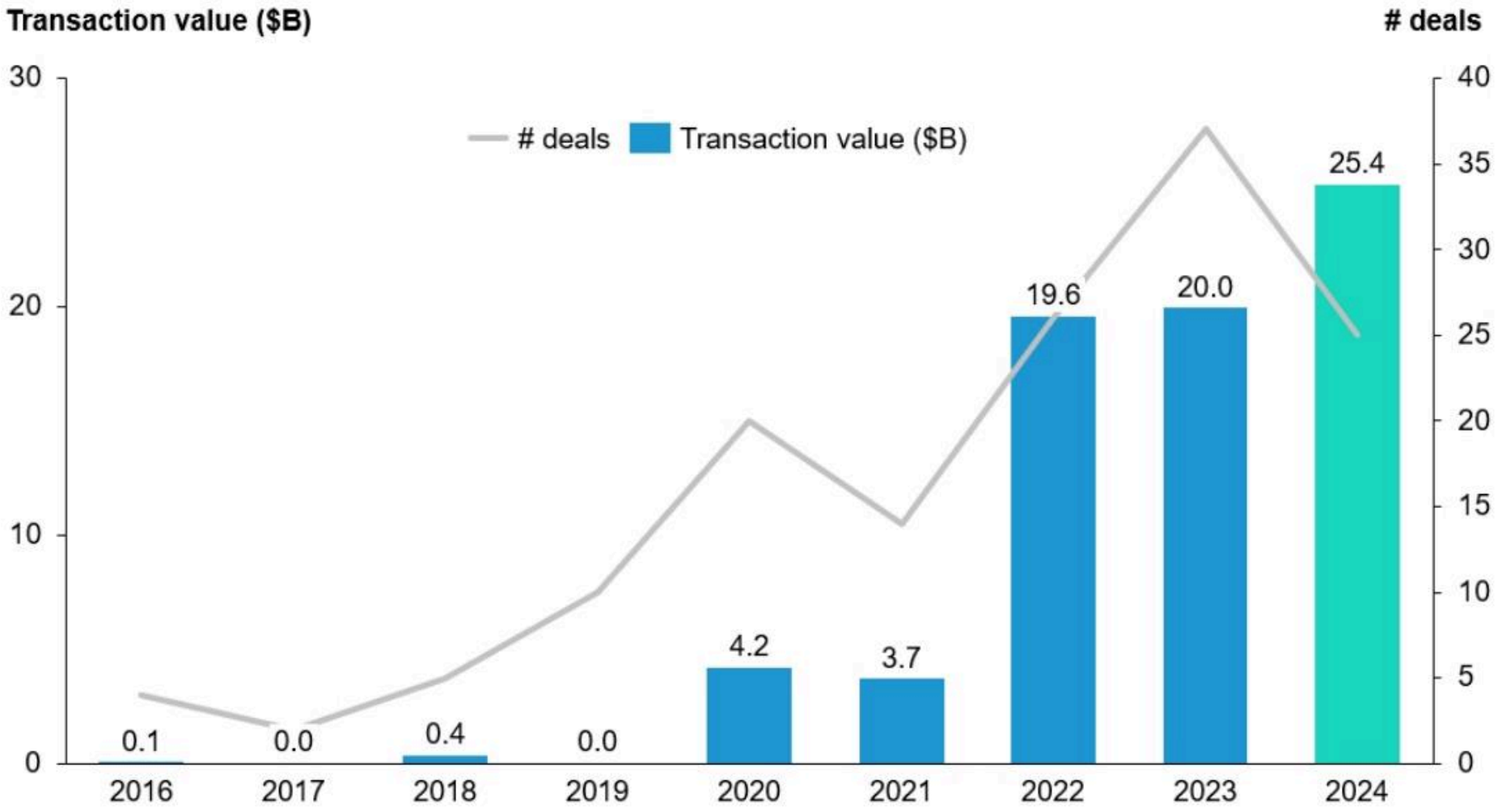
Source: Bloomberg, Bernstein analysis from Large Cap Pharma analyst Courtney Breen

M&A | Oncology, immunology, and rare disease are the most common TA's for deals, though CNS and metabolic are emerging areas of focus



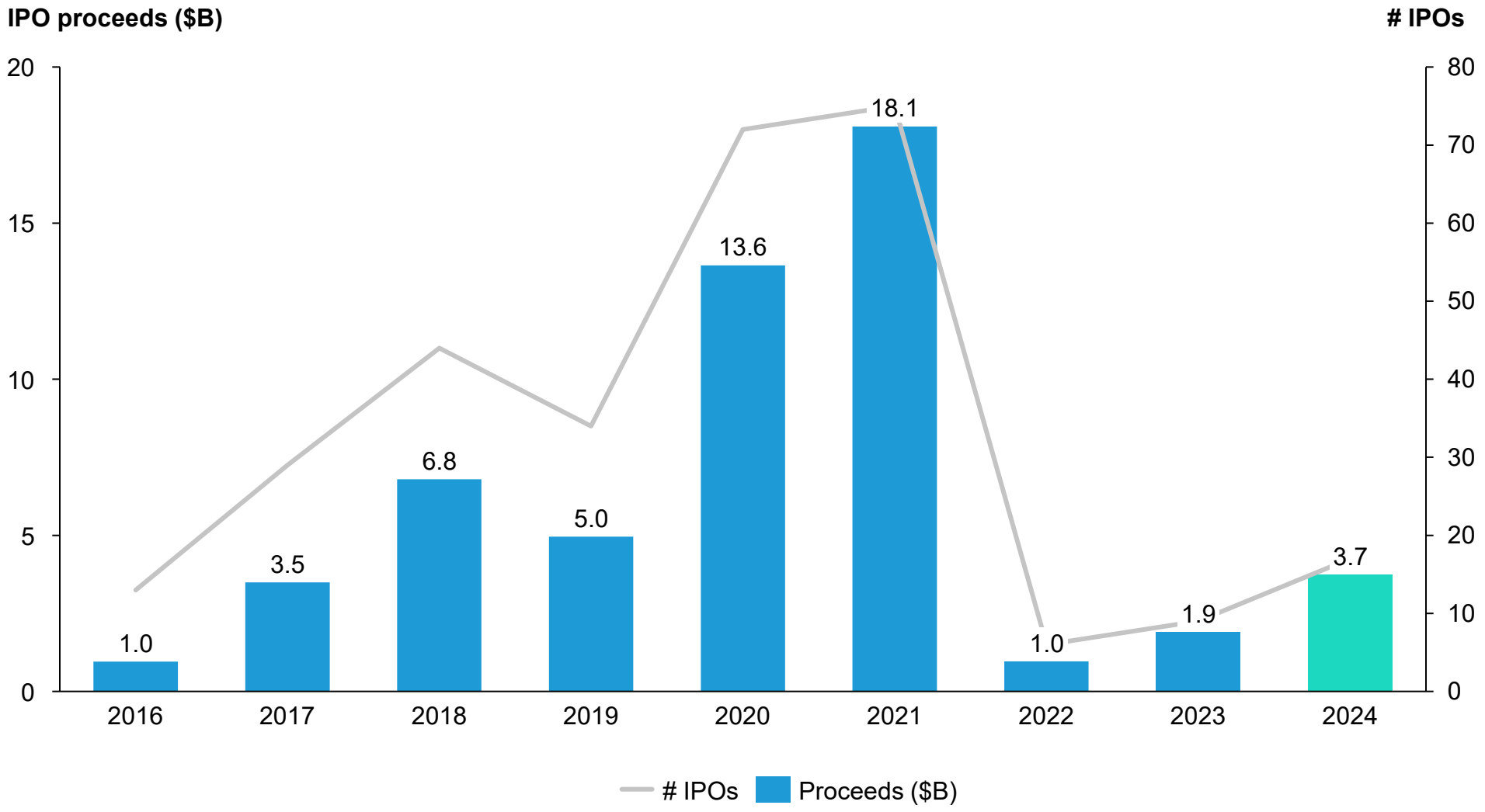
Source: Bloomberg, Company reports, Bernstein analysis

M&A | Pharma licensing deals for Chinese assets: Major spike in last 3 years



Source: Bloomberg, Bernstein analysis

IPO | Recovery continuing at a slow pace



Source: Bloomberg, Bernstein analysis

IPO | We have seen less activity in 2025 than 2024 (which was already not great), but the post-IPO performance for this year's class has been better

7 IPO's YTD and performance has been decent

Almost every IPO from 2023-2024 is underwater

Ticker	Company	TA/Tech	Size ($M)	Total return	IPO date
LBRX	LB Pharma	CNS	285	12%	9/11/2025
AARD	Aardvark	Obesity	98	-46%	2/13/2025
SION	Sionna	Cystic Fibrosis	248	27%	2/7/2025
BIOV	BioVersys	Anti-infective	85	-14%	2/7/2025
MAZE	Maze	Renal	140	46%	1/31/2025
MTSR	Metsera	Obesity	316	98%	1/31/2025
AAPG	Ascentage	Oncology	126	135%	1/24/2025
SEPN	Septerna Inc	GPCR	331	-21%	10/25/2024
CAMP	CAMP4 Therapeutics Corp	Regulatory RNA	75	-70%	10/11/2024
UPB	Upstream Bio Inc	Inflammatory	293	3%	10/11/2024
BIOA	BioAge Labs Inc	Obesity	228	-73%	9/26/2024
MBX	MBX Biosciences Inc	Endocrine/obesity	188	-32%	9/13/2024
BCAX	Bicara Therapeutics Inc	Oncology	362	-35%	9/13/2024
ZBIO	Zenas Biopharma Inc	Immunology	259	19%	9/13/2024
ARTV	Artiva Biotherapeutics	Immunology	167	-79%	7/19/2024
ALMS	Alumis	Immunology	210	-73%	6/28/2024
RAPP	Rapport Therapeutics	CNS	156	40%	6/7/2024
CTNM	Contineum Therapeutics	Immunology	119	-23%	4/4/2024
BOLD	Boundless Bio	Oncology	100	-93%	3/27/2024
MGX	Metagenomi	Gene editing	94	-88%	2/9/2024
KYTX	Kyverna Therapeutics	Immunology	367	-82%	2/8/2024
ANRO	Alto Neuroscience	CNS	148	-76%	2/2/2024
AVBP	ArriVent Biopharma	Oncology	201	9%	1/26/2024
CGON	CG Oncology	Oncology	437	75%	1/25/2024
CRGX	Cargo Therapeutics	Oncology	281		11/10/2023
LXEO	Lexeo Therapeutics	Cardio, CNS	100	-53%	11/3/2023
RYZB	RayzeBio	Radiopharma	358		9/15/2023
NMRA	Neumora Therapeutics	CNS	250	-90%	9/15/2023
TSBX	Turnstone Biologics	Oncology	88		7/21/2023
APGE	Apogee Therapeutics	Immunology	345	117%	7/14/2023
MLYS	Mineralys Therapeutics	Cardiorenal	221	132%	2/10/2023
GPCR	Structure Therapeutics (ADR)	Obesity	185	39%	2/3/2023

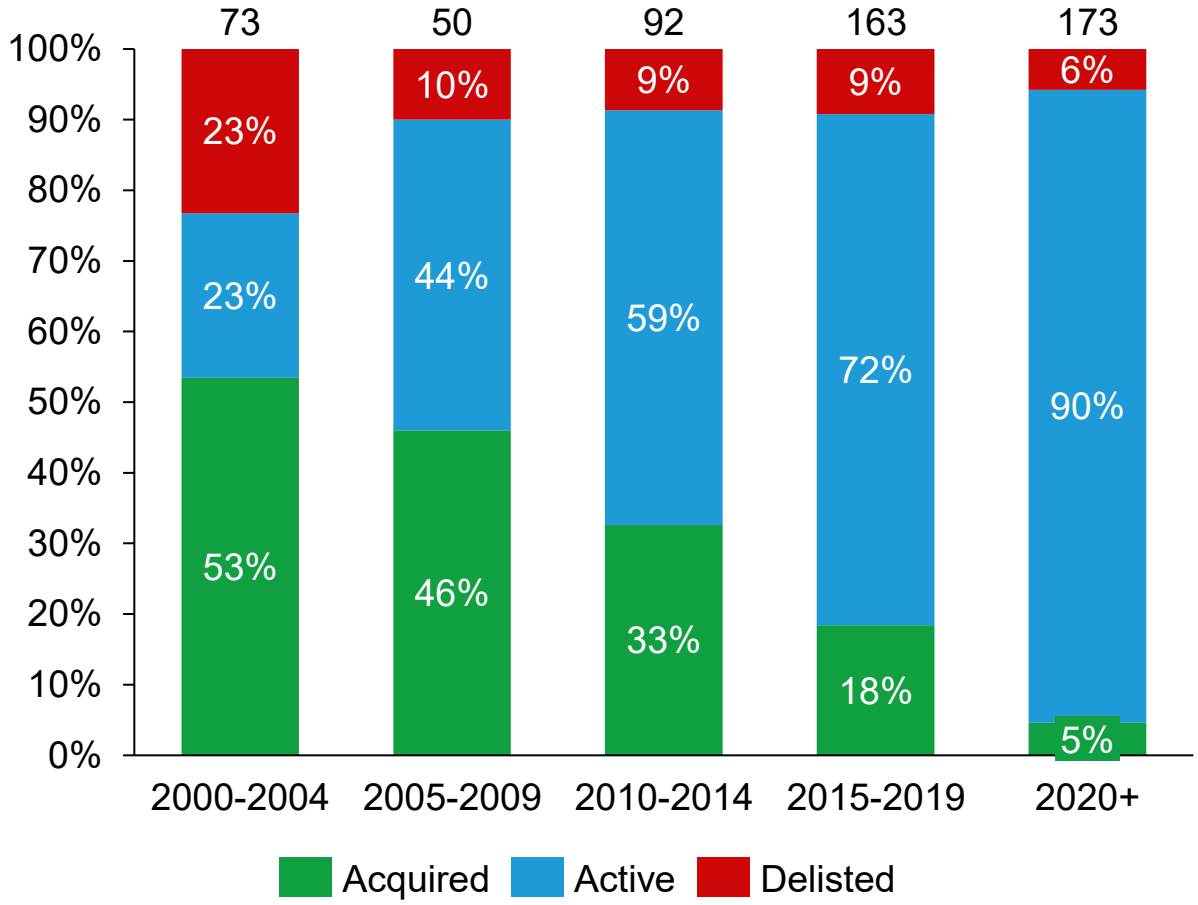
Source: Bloomberg, Bernstein Analysis; 2025 IPOs are as of September 15, 2025

IPOs | Biotechs rarely die and are often acquired… but relatively few generate positive positive lifetime returns

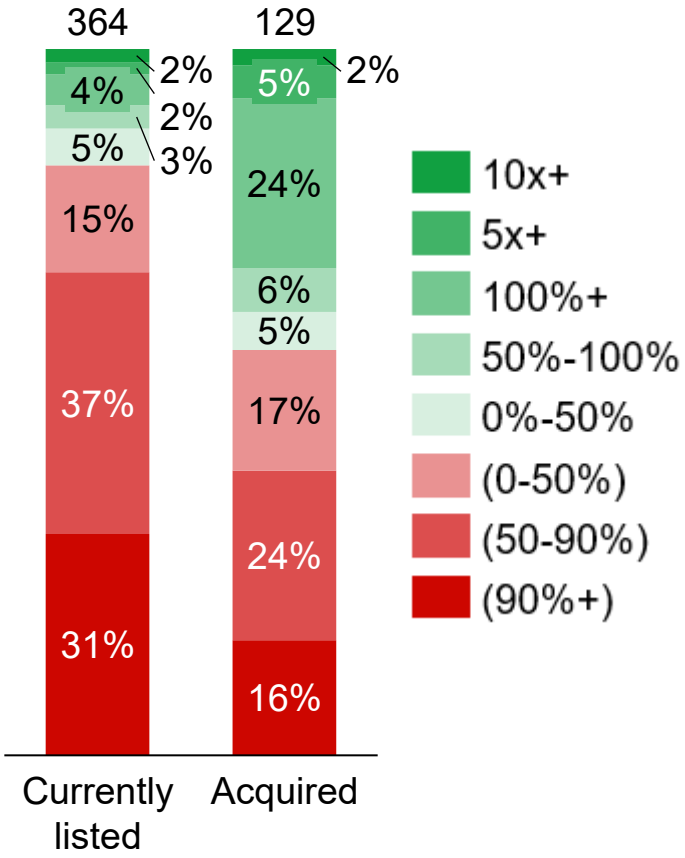
Cumulative total shareholder return (TSR) from IPO date to present, segmented by IPO year

Where are they now?

% of companies, grouped by IPO class year

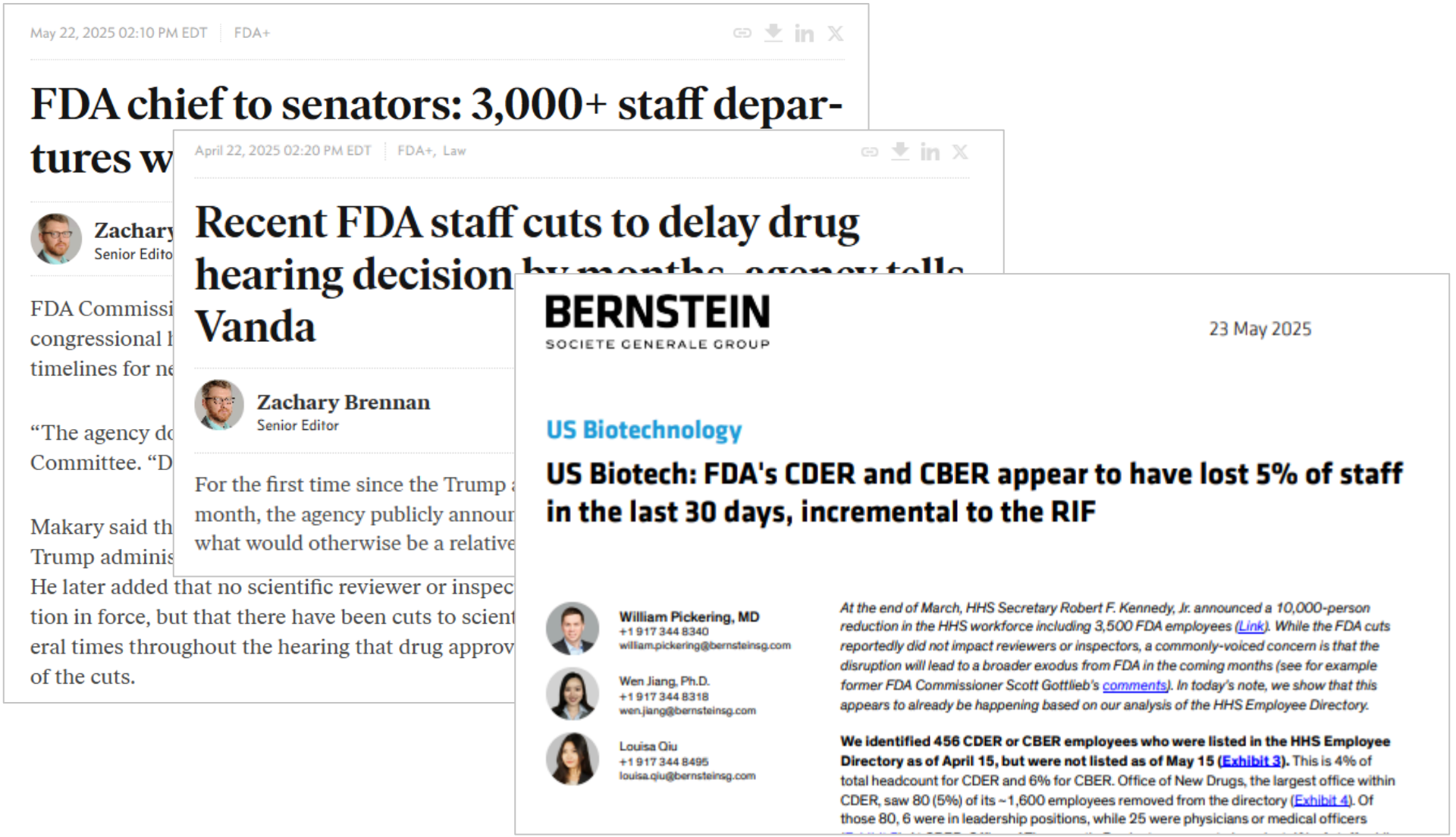


Lifetime TSR



Source: Bloomberg, Bernstein analysis

FDA FTEs are down ~20% vs. YE24… is it possible this can be absorbed without consequence?



May 22, 2025 02:10 PM EDT | FDA+

FDA chief to senators: 3,000+ staff depar-
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"The agency do
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Makary said th
Trump adminis
He later added that no scientific reviewer or inspec
tion in force, but that there have been cuts to scient
eral times throughout the hearing that drug approv
of the cuts.

April 22, 2025 02:20 PM EDT | FDA+, Law

Recent FDA staff cuts to delay drug
hearing decision
Vanda

Zachary Brennan
Senior Editor

For the first time since the Trump
month, the agency publicly annour
what would otherwise be a relative

BERNSTEIN
SOCIETE GENERALE GROUP

23 May 2025

US Biotechnology

US Biotech: FDA's CDER and CBER appear to have lost 5% of staff in the last 30 days, incremental to the RIF

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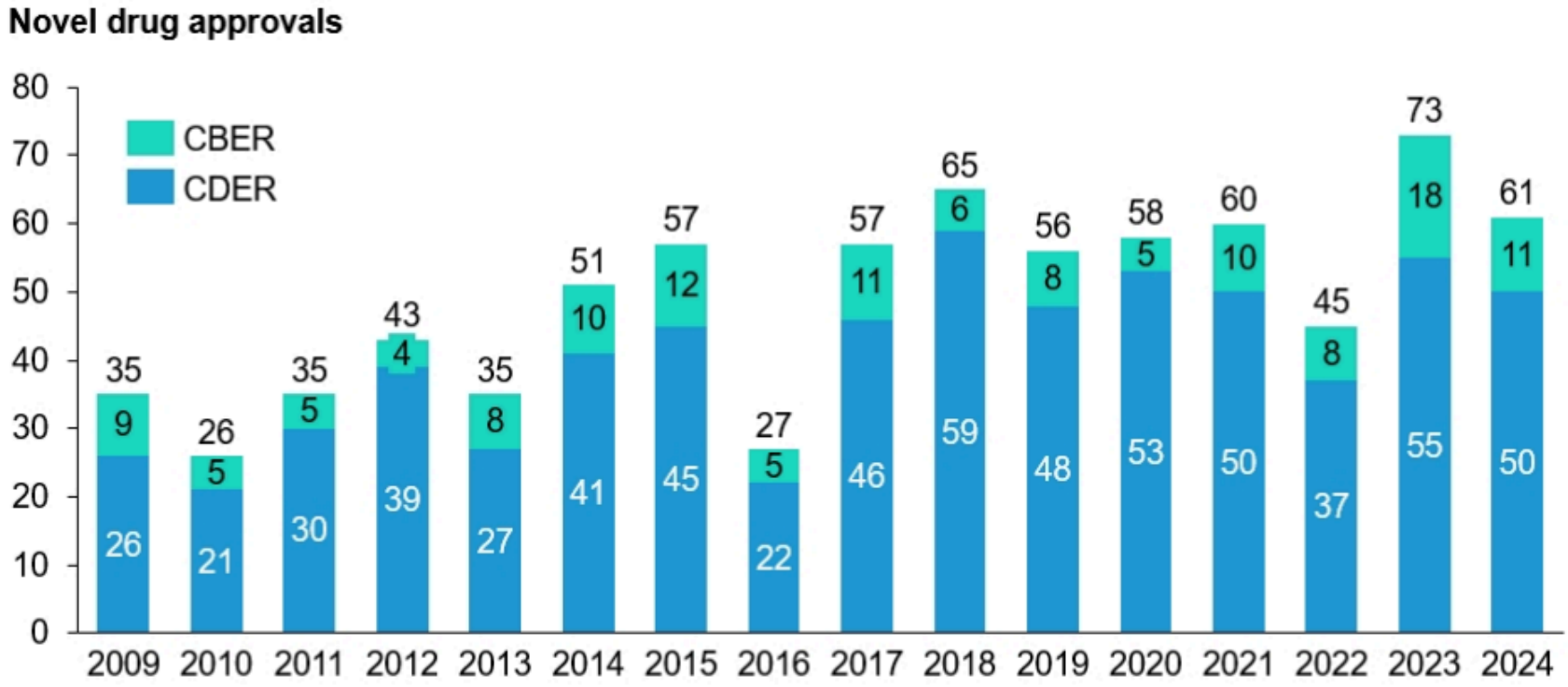
At the end of March, HHS Secretary Robert F. Kennedy, Jr. announced a 10,000-person reduction in the HHS workforce including 3,500 FDA employees (Link). While the FDA cuts reportedly did not impact reviewers or inspectors, a commonly-voiced concern is that the disruption will lead to a broader exodus from FDA in the coming months (see for example former FDA Commissioner Scott Gottlieb's comments). In today's note, we show that this appears to already be happening based on our analysis of the HHS Employee Directory.

We identified 456 CDER or CBER employees who were listed in the HHS Employee Directory as of April 15, but were not listed as of May 15 (Exhibit 3). This is 4% of total headcount for CDER and 6% for CBER. Office of New Drugs, the largest office within CDER, saw 80 (5%) of its ~1,600 employees removed from the directory (Exhibit 4). Of those 80, 6 were in leadership positions, while 25 were physicians or medical officers

Source: Endpoints, Bernstein analysis

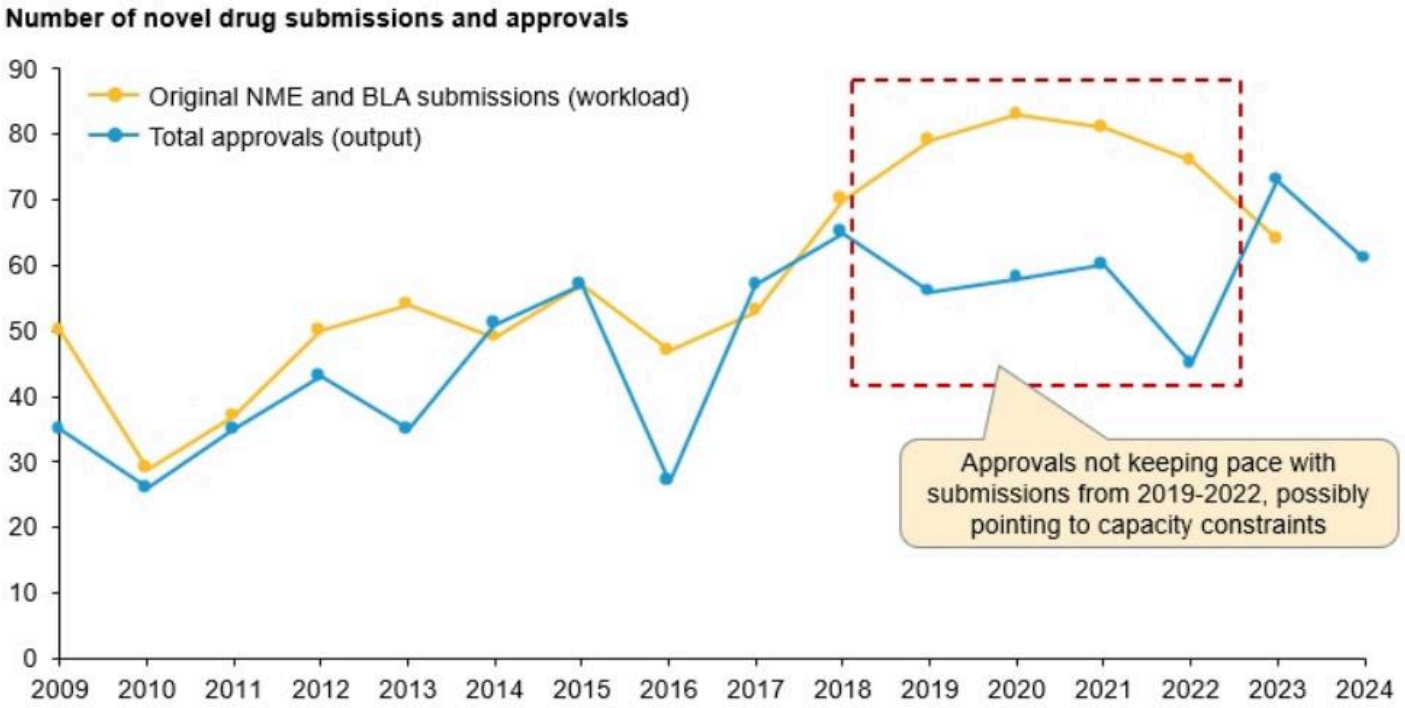
FDA | Novel drug approvals averaged ~60 per year under both Trump and Biden vs. only ~40 during the Obama years. Will recent job cuts at FDA take us back down to those lower levels?



Annual average	Obama ('09-'16)	Trump ('17-'20)	Biden ('21-'24)
CBER	7	8	12
CDER	31	52	48
Total	39	59	60

Source: FDA, Bernstein analysis

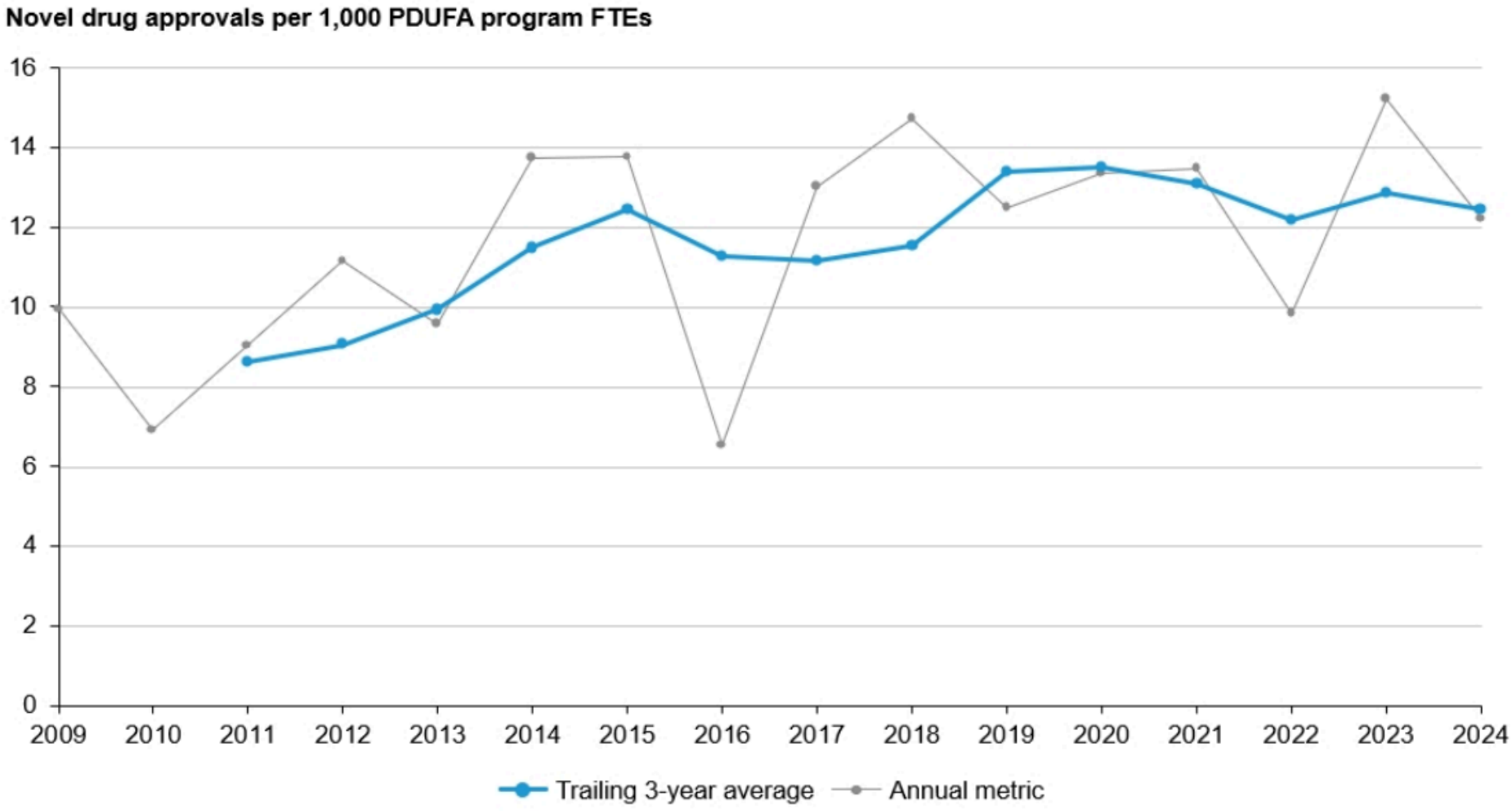
Approvals did not keep pace with submissions during period of heightened workload (2019-2022), potentially illustrating capacity constraints



Ratio of approvals to submissions, 3 year rolling average	83%	90%	80%	84%	89%	88%	90%	88%	88%	77%	72%	68%	81%

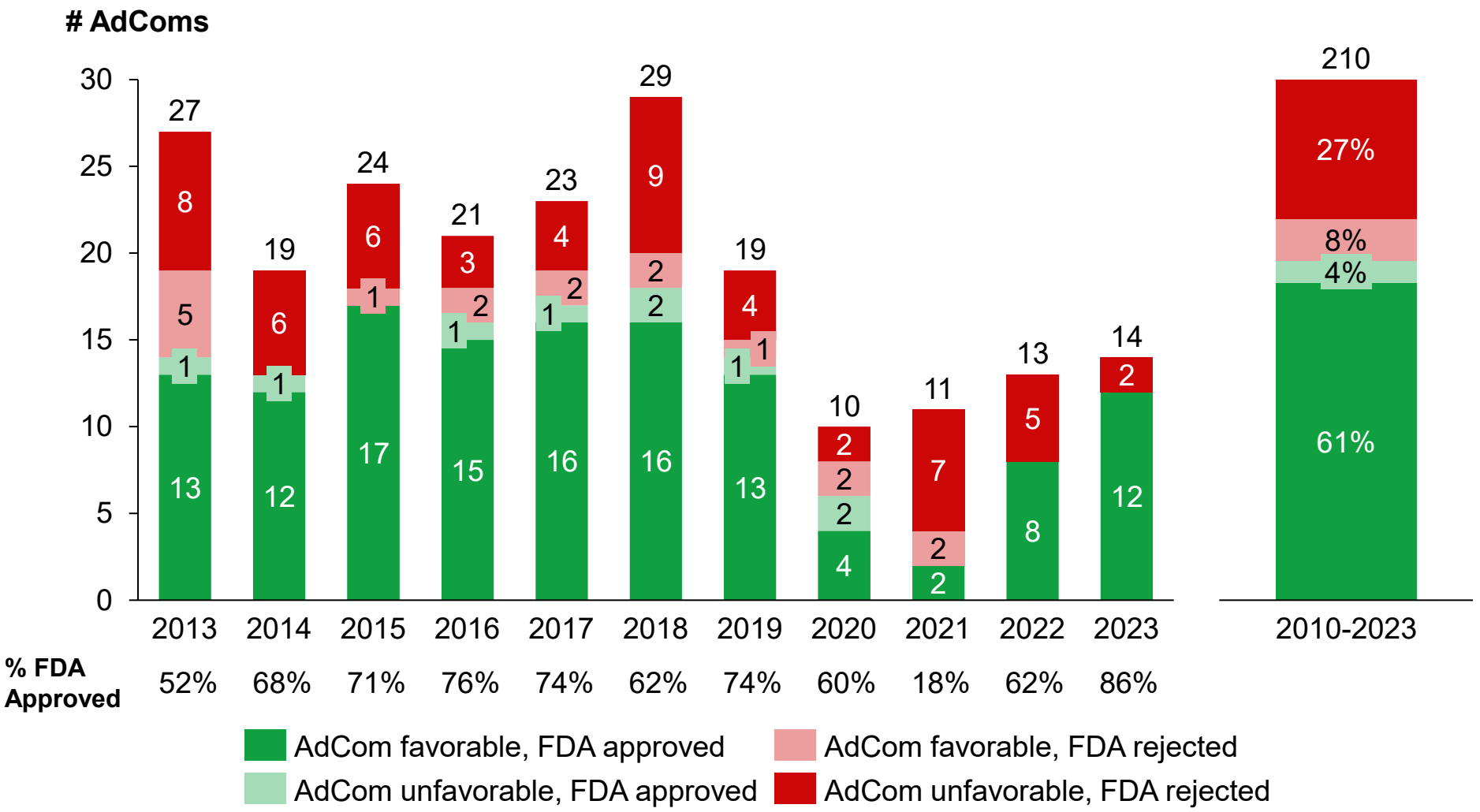
Source: FDA, Bernstein analysis

Historically, FDA annual approvals have not exceeded 15 drugs per 1,000 PDUFA program FTEs



Source: FDA, Bernstein analysis

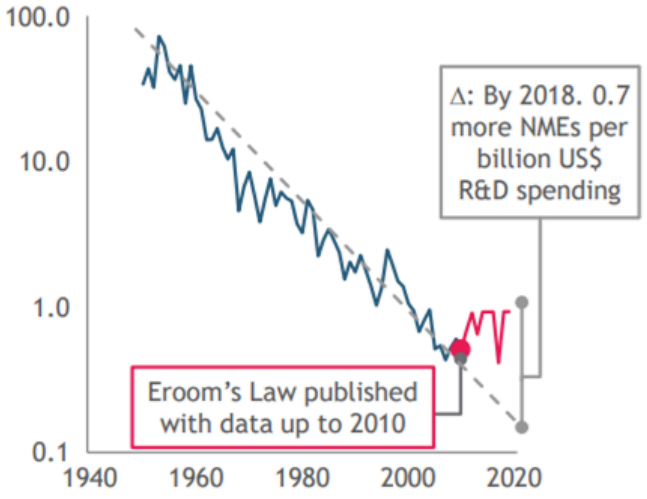
FDA | ~65% of drugs going before AdComs in the last 10 years were approved, seeing fewer AdComs post-COVID drop-off



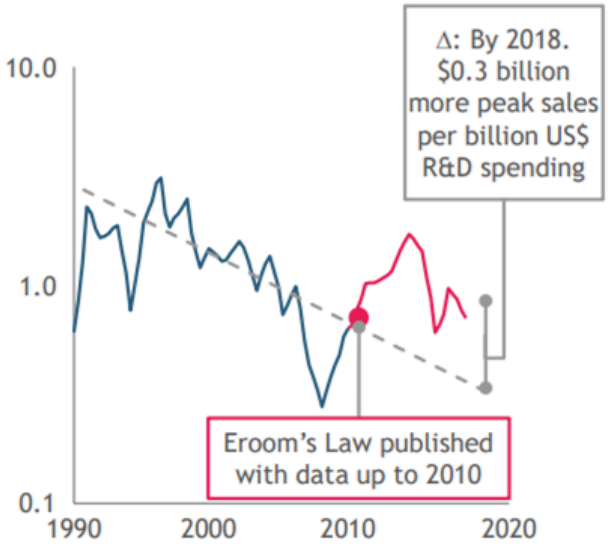
BERNSTEIN | SOCIETE GENERALE GROUP Source: FDA, Bernstein analysis

Innovation | Declining R&D productivity historically a real concern, but have seen some reversal in recent years

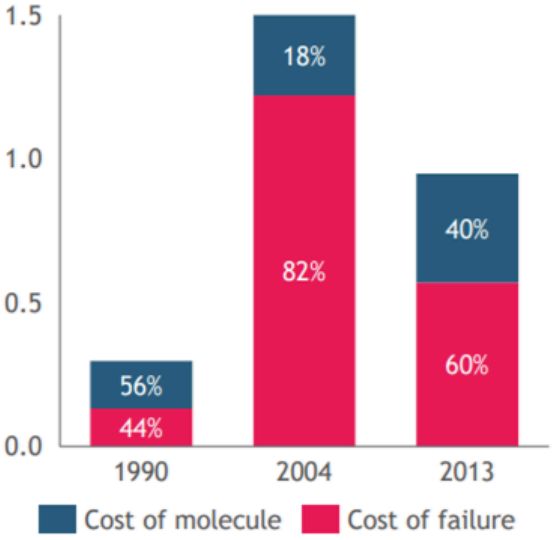
A **Number of NMEs per billion US$ R&D spending**



B **Peak sales of NME per billion $ of R&D spending**



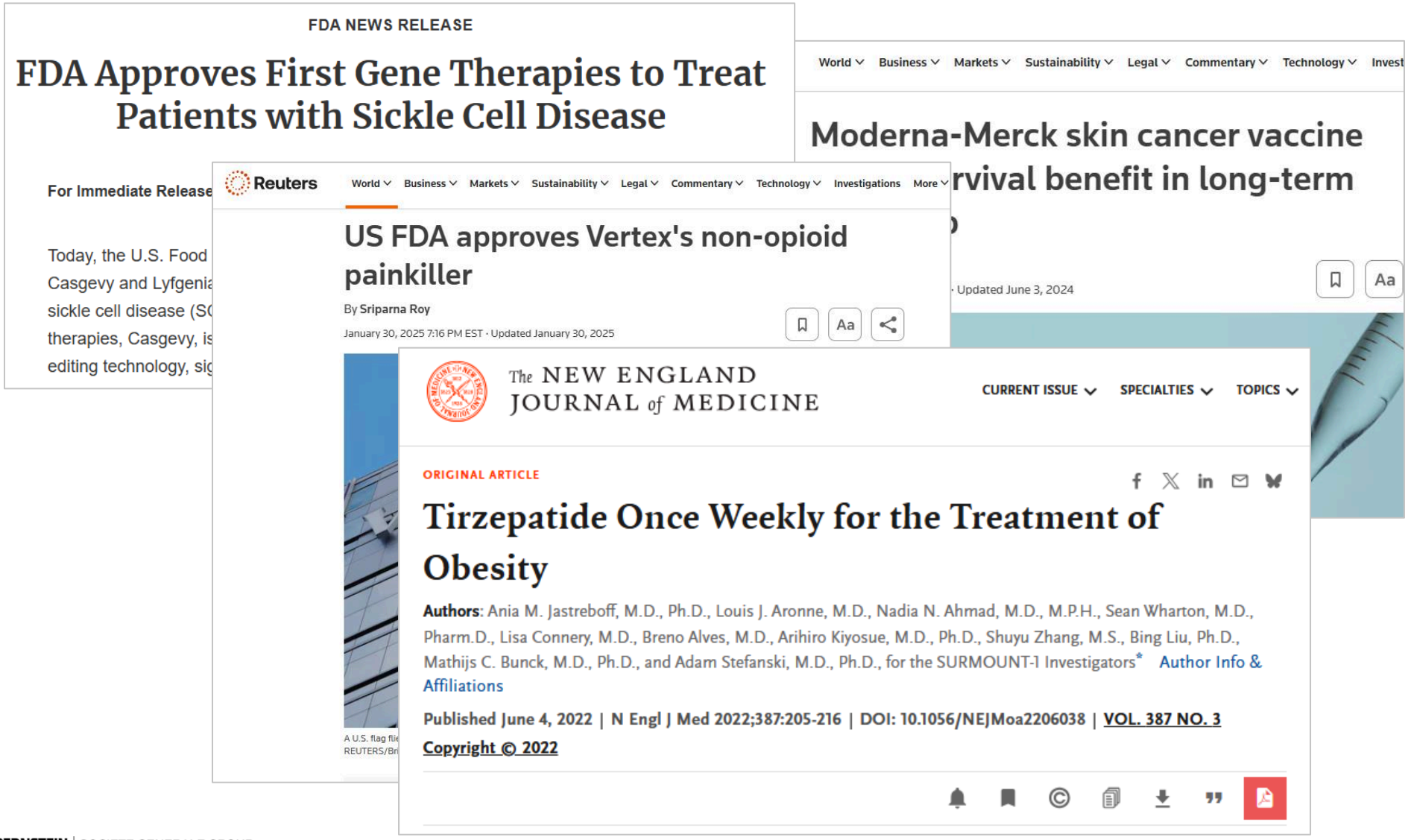
A **All-in cost of development per NME ($B)**



What changed? More information, making better use of that information, and changes in the risk/benefit profile of drugs seeking approval

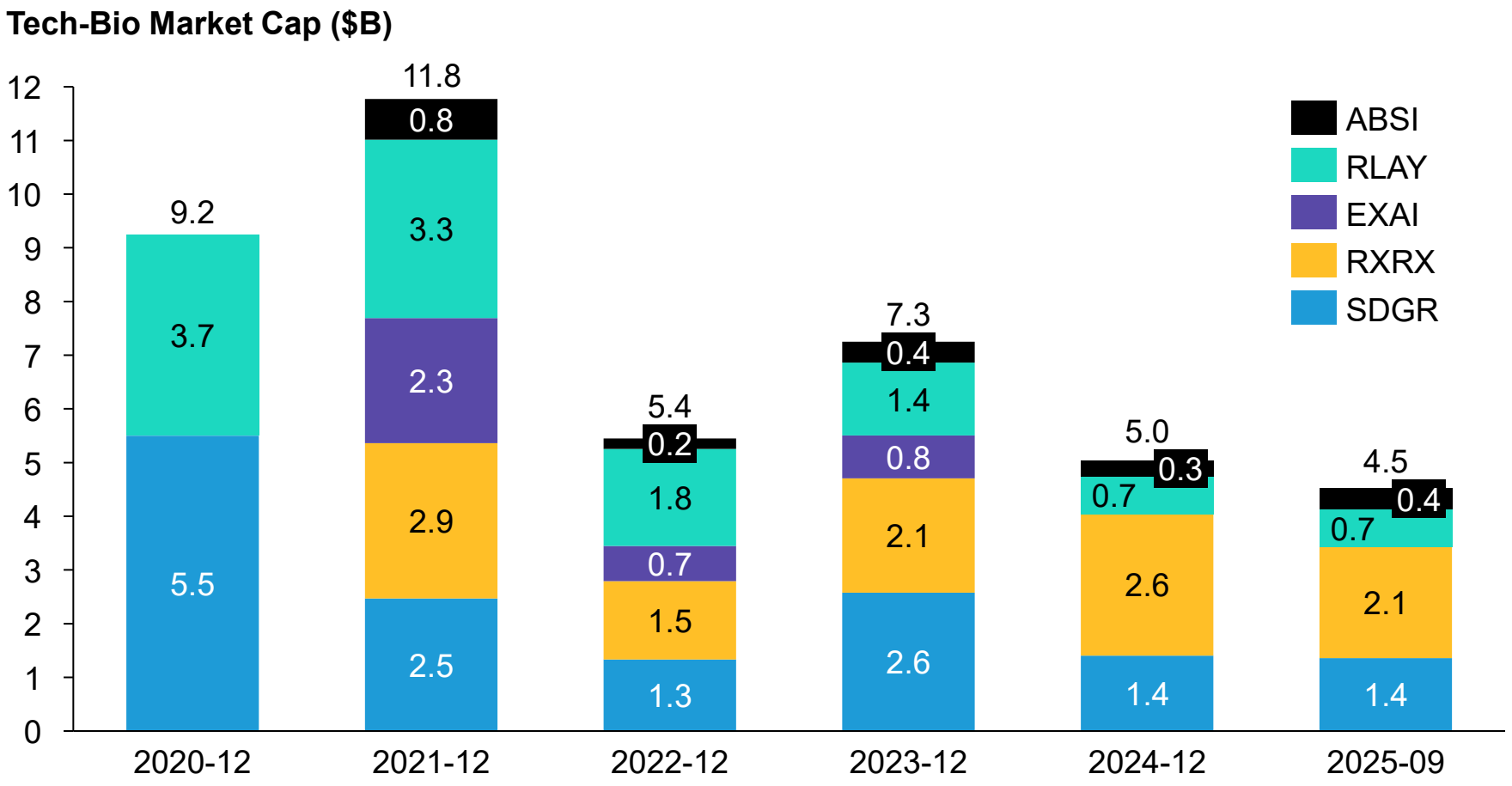
Source: Nature Reviews Drug Discovery 19, 833-834 (2020); Bernstein analysis

We continue to see incredible innovation across therapeutic areas, benefiting patients young and old, with both rare and high prevalence conditions



Source: FDA, Reuters, NEJM, Endpoints, Bernstein analysis

AI | The market is telling us that AI drug discovery is overhyped. Is it?



Source: Bloomberg, Bernstein analysis

AI | Our expectations for market evolution and structure over 10 year period

Where we stand

We have already seen tremendous advances that support AI-enabled drug discovery and development…

- ML techniques, development of novel databases and tools, computational power

And while market participants are investing accordingly, we have yet to see the sort of full-scale disruption some may envision

- Thus far, more akin to Tesla's slow journey toward full self-driving as opposed to ChatGPT
- Value chain: Chemistry more validated, biology and clinical development more white space

Where we are going

- The key to sustainable competitive advantage is proprietary datasets… advantages from algorithms alone will be rapidly competed away
- Bias toward valuing companies based on their pipeline vs. capabilities
- Pharma companies will internalize these capabilities over time, expec to see few if any of these companies still standing in 10 years

Source: Bernstein analysis

What we'll cover today

1. Biotech fundamentals: Sector performance, valuation framework, segmentation

2. Recent trends

BERNSTEIN TICKER TABLE

Ticker	Rating	Cur	9 Oct 2025 Closing Price	Price Target	TTM Rel. Perf.	Reported EPS Cur	Reported EPS 2024A	Reported EPS 2025E	Reported EPS 2026E	Reported P/E (x) 2024A	Reported P/E (x) 2025E	Reported P/E (x) 2026E
ALLO	M	USD	1.51	1.60	(58.6)%	USD	(1.32)	(1.09)	(1.08)	(1.1)	(1.4)	(1.4)
ALNY	O	USD	456.95	471.00	47.7%	USD	(0.02)	3.80	11.61	N/M	120.4	39.3
ARWR	M	USD	36.06	17.00	87.4%	USD	(5.00)	1.88	(3.43)	(7.2)	19.2	(10.5)
BEAM	O	USD	27.87	32.00	4.7%	USD	(4.58)	(4.11)	(4.45)	(6.1)	(6.8)	(6.3)
BIIB	M	USD	149.61	155.00	(37.0)%	USD	16.47	15.97	16.22	9.1	9.4	9.2
BHVN	O	USD	17.23	34.00	(82.8)%	USD	(9.28)	(6.47)	(6.28)	(1.9)	(2.7)	(2.7)
BMRN	O	USD	53.85	95.00	(39.2)%	USD	3.52	3.93	5.84	15.3	13.7	9.2
CRSP	M	USD	74.92	43.00	48.8%	USD	(4.34)	(6.34)	(4.43)	(17.3)	(11.8)	(16.9)
DYN	M	USD	14.68	12.00	(71.2)%	USD	(3.37)	(3.64)	(3.75)	(4.4)	(4.0)	(3.9)
NTLA	O	USD	25.46	14.00	26.8%	USD	(5.25)	(4.65)	(4.75)	(4.8)	(5.5)	(5.4)
IONS	M	USD	70.27	50.00	68.9%	USD	(2.17)	(1.63)	(1.64)	(32.3)	(43.1)	(42.8)
REGN	O	USD	569.90	781.00	(59.2)%	USD	45.62	37.46	39.90	12.5	15.2	14.3
RNA	O	USD	50.77	52.00	(1.5)%	USD	(2.89)	(3.86)	(3.91)	(17.6)	(13.1)	(13.0)
SRPT	M	USD	23.13	18.00	(97.4)%	USD	3.69	(4.05)	4.07	6.3	(5.7)	5.7
VRTX	M	USD	414.86	471.00	(29.2)%	USD	0.43	18.56	18.99	967.4	22.3	21.8
SPX			6,735.11									

O - Outperform, M - Market-Perform, U - Underperform, NR - Not Rated, CS - Coverage Suspended

ALNY, BIIB, BMRN, IONS, REGN, SRPT, VRTX estimate is Adjusted EPS; ALNY, BIIB, BMRN, IONS, REGN, SRPT, VRTX valuation is Adjusted P/E (x);

Source: Bloomberg, Bernstein estimates and analysis.

I. REQUIRED DISCLOSURES

References to "Bernstein" or the "Firm" in these disclosures relate to the following entities: Bernstein Institutional Services LLC (April 1, 2024 onwards), Sanford C. Bernstein & Co., LLC (pre April 1, 2024), Bernstein Autonomous LLP, BSG France S.A. (April 1, 2024 onwards), Sanford C. Bernstein (Hong Kong) Limited 盛博香港有限公司, Sanford C. Bernstein (Canada) Limited, Sanford C. Bernstein (India) Private Limited (SEBI registration no. INH000006378), Sanford C. Bernstein (Singapore) Private Limited and Sanford C. Bernstein Japan KK (サンフォード・C・バーンスタイン株式会社).

On April 1, 2024, Société Générale (SG) and AllianceBernstein, L.P. (AB) completed a transaction that created a new joint venture in which their respective cash equities and research businesses operate in a new business combination. Although their respective ownership percentages in the joint venture differ between North America and the rest of the world, the creation, production and publication of research is handled collaboratively on a global basis across the two research brands, "Bernstein" and "Autonomous". Unless specifically noted otherwise, for purposes of these disclosures, references to Bernstein's "affiliates" relate to both SG and AB and their respective affiliates.

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- Outperform: Stock will outpace the market index by more than 15 pp
- Market-Perform: Stock will perform in line with the market index to within +/-15 pp

- Underperform: Stock will trail the performance of the market index by more than 15 pp

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Not Rated: A rating assigned when the stock cannot be accurately valued, or the performance of the company accurately predicted, at the present time. The covering analyst may continue to publish research reports on the company to update investors on events and developments.

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