The ABCs of Biotechnology

We are issuing our Guide to Biotechnology. Since the prior publication, the COVID-19 pandemic drove significant capital investment in the sector, resulting in a proliferation of small- and mid-cap companies (accounting for ~$400B in current total market cap vs. $110B in 2017); the ten largest (AMGN, REGN, VRTX, GILD, ARGX, ALNY, MRNA, BIIB, BNTX, GMAB) account for >$690B in market cap. Within, we provide a refresher on valuation and potential returns (XBI has outperformed the S&P500 for 11 of the last 17 years), and review the key stages of drug development and commercialization. We provide an analysis of the funding environment, review recent regulatory changes, and take a deeper look at disease areas and technologies driving the next wave of innovation within the industry. While we acknowledge the sector's recent underperformance, which has persisted for more than three years, we believe it offers the potential for attractive idiosyncratic returns given underlying innovation, emerging product cycles and business development/M&A (where we highlight $280B in losses-of-exclusivity by 2030 with $490B+ in large-cap balance sheet capacity at 2.5x Debt/EBITDA).

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Biotechnology by the numbers

INDUSTRY SIZE

$690B+

The combined market capitalization of the ten largest biotechnology companies[1]

REVENUE GENERATION

17%

Percent of companies within the XBI with 2023 revenue >$500mn

LOW PROBABILITY OF SUCCESS

10-12%

The percent of drugs entering clinical trials that make it to patients

COSTLY DEVELOPMENT

$30B

The combined 2023 R&D expenditures of the ten largest biotechnology companies[1] (vs. $14B in 2016).

GENERATED SIGNIFICANT REVENUE

$100B

The combined 2023 revenue of the ten largest biotechnology companies[1] (vs. $70bn in 2016).

BLOCKBUSTER SALES POTENTIAL

$25B

2023 sales for Keytruda, the highest selling drug in the world. Other 2023 standouts were Eliquis ($19B), Comirnaty ($16B), Humira ($14B), and Ozempic ($14B).

HIGH APPROVAL RATES

84%

The percent of new drug/biologic applications received in 2023 that were approved by the FDA on first pass (similar to 85% in 2016)

HIGH DOMESTIC SALES EXPOSURE

70%

The percent of 2023 sales generated in the US by the ten largest biotechnology companies[1]

IMPENDING PATENT CLIFFS..

$280B

The combined peak sales for drugs with <= 2030 LOE across ~50 products

..CONTINUED ELEVATED FIREPOWER

$490B

The amount of firepower assuming 2.5x Gross Debt/EBIDTA. US and EU biopharma[2] could purchase 1.8x of the total biotech market

1. The top 10 largest biotech companies per GS coverage include AMGN, REGN, VRTX, GILD, ARGX, ALNY, MRNA, BIIB, BNTX, and GMAB (in order of decreasing market-cap);
2. See Exhibit 21

PM Summary

We first issued this report in 2017, in order to provide investors - including non-specialists - with an overview of the biotechnology sector and the building blocks to aid an investment process. We wrote at the time that "biotechnology is one of the more specialized sectors within the public markets," which remains true today. However, since our 2017 report, the biotech sector came to the forefront of the public conscience in the context of the global COVID-19 pandemic and the rapid development of a vaccine by key players in the industry, highlighting the innovation potential within the industry. We continue to view the sector as offering opportunities for secular growth, though we acknowledge macroeconomic (i.e. the interest rate environment) and regulatory factors (i.e. Inflation Reduction Act) have been headwinds to the sector, and the industry is otherwise characterized by significant volatility around clinical, regulatory, and commercial events.

Within we provide context on how to think about valuations across the spectrum of biopharma companies, from blue-chip pharmaceutical companies to small-cap biotechnology companies, and update the drivers and outlook for M&A within the sector. Further, we introduce a discussion on the biotech funding environment, which plays an essential role in the discovery and development efforts by smid-cap biotechnology companies.

We again describe the entire life cycle of a drug - from bench (laboratory) to bedside - with a focus on therapeutic areas of key interest (i.e. obesity, Alzheimer's disease, pain, and others), emerging therapeutic modalities (i.e. gene editing, radiopharmaceuticals), updated insights on new technology used to discover drugs (including AI - i.e. byte-ology), and changes in the regulatory landscape across stages of drug development, commercialization and business development (i.e. Food and Drug Administration, IRA implementation, Biosecure Act, Federal Trade Commission). We provide considerable detail on the commercialization of new drugs, including on the drug reimbursement process, regulatory policies governing pricing models, generic/biosimilar entrants, and patent protection. Similarly, we review biotech manufacturing, including with respect to complicated processes (i.e. cell/gene therapy) and the complexity associated with manufacturing for the obesity market.

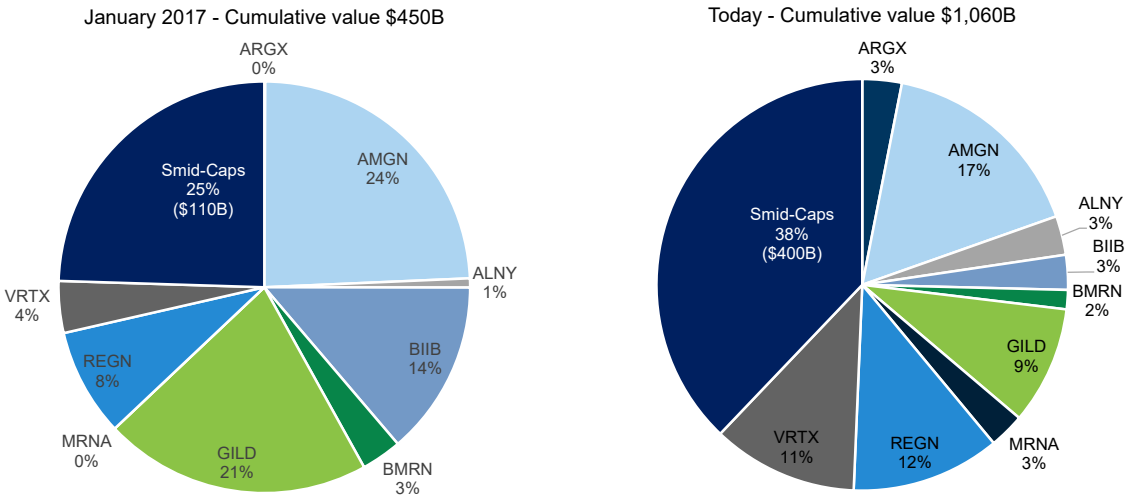
Biotechnology: overview and key risks

Biotechnology can be defined as the field focused on developing medicines derived from living organisms rather than chemical reactions (which defines pharmaceuticals). However, when discussing the sector, we broadly encompass companies focused on the development of drugs in both categories: noting the distinction between the two traditional sectors (biotechnology and pharmaceuticals) has become increasingly nebulous, leading to the sector's other moniker: biopharma. The US large-cap biopharma industry now comprises eleven public companies and forms 5.6% of the S&P 500.

Only a minority of the biotech companies on the market today are profitable, while the majority are focused on discovering and developing new drugs, an expensive endeavor,

and are therefore unprofitable. The sector's largest players are: AMGN, REGN, VRTX, GILD, ARGX, ALNY, MRNA, BIIB, BMRN; since we last wrote this report, ALXN and CELG were acquired, ALNY, ARGX and MRNA built their way onto this list, and INCY no longer sits among the large cap stocks of the sector (>$20B). Small- and mid-cap companies now comprise a greater portion of the biotech market, both on an absolute and relative basis (38% vs. 25% in 2017) and are a greater focus of this update compared to the last iteration of the Hitchhiker's Guide, reflecting in large part the proliferation of biotechnology companies in the public markets during the COVID-19 pandemic (discussed in greater detail below).

Exhibit 1: Historical and recent market caps of biotech companies



Source: FactSet, Goldman Sachs Global Investment Research

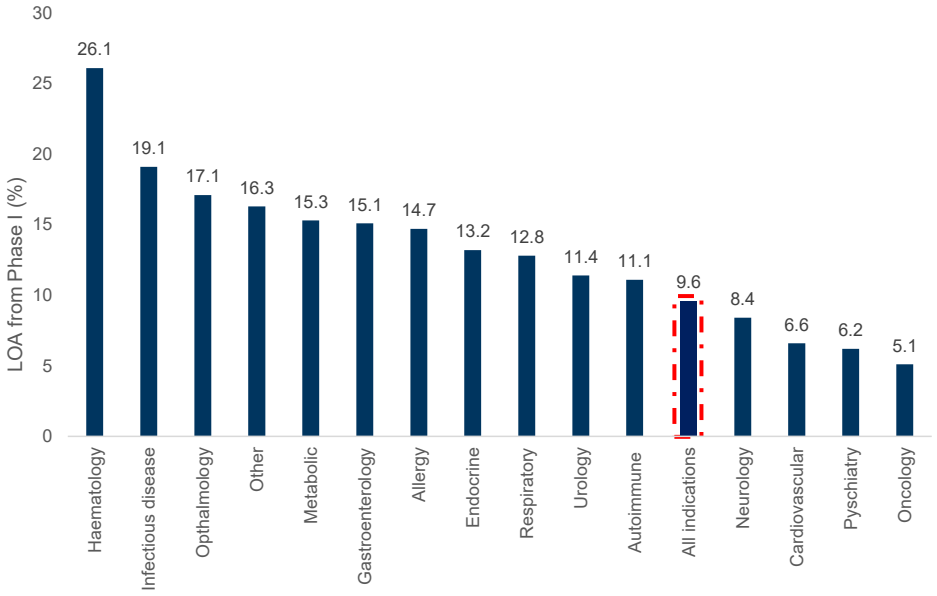
While these companies offer potential for tremendous returns, drug development is an inherently long, challenging, and risky endeavor:

Biotech Risk #1: development

Estimates for the cost of drug development range from $0.8B to $2.3B, depending on selection of companies/drugs; estimates at the lower bound do not encompass the cost of development for failed drugs (underestimating the total expenditure required to bring a new drug to market), while estimates at the upper bound may reflect selection bias. Further, R&D costs have increased ~8.5% annually over the past decade.

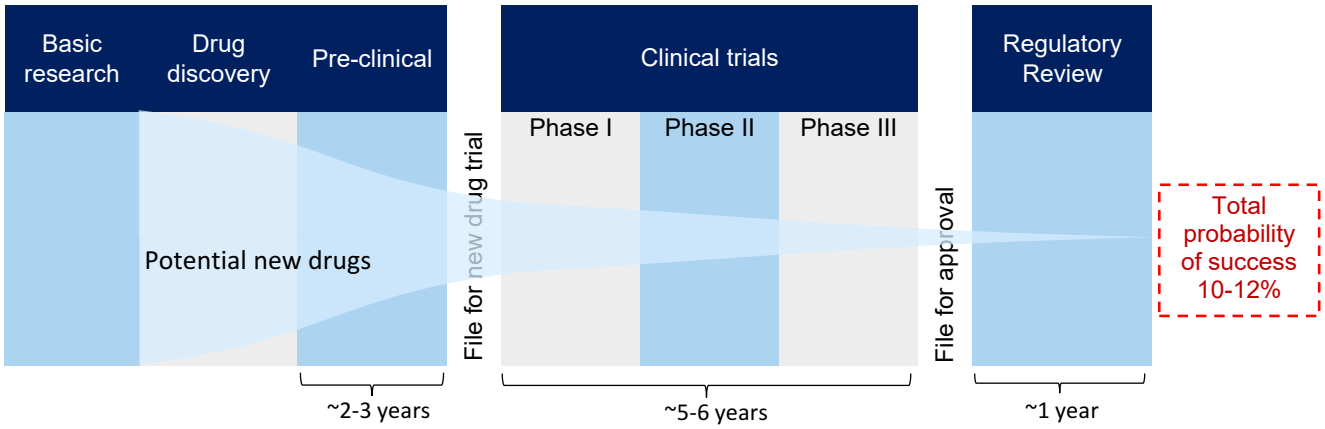
The R&D spend necessary to bring a new drug to market reflects in part the cost of failure: some estimates suggest that 60% of R&D costs are attributed to attrition (failed drugs). In fact, only ~10% of drugs that enter Ph1 study will be approved, though we note considerable variability by therapeutic area (Exhibit 2). By stage, the probability of success is 63% from Ph1 to Ph2, 31% from Ph2 to Ph3, 58% in Ph3 trials and 85% during the regulatory review process.

Exhibit 2: Likelihood of approval from Phase I



Source: Nature Reviews, Goldman Sachs Global Investment Research

Exhibit 3: Path to drug approval – vast majority of drugs do not reach the finish line



Source: PhRMA, BIO

With this in mind, biotech companies must invest significant resources into R&D to advance and replenish their pipelines, yet if the drug fails to demonstrate safety and/or efficacy, they may lose all or part of their investments.

Exhibit 4: Biotech vs. pharma R&D spend on absolute $ basis - EU pharma (light blue), US pharma (gray), US Biotech (dark blue)

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
#1	ROG-CH	ROG-CH	ROG-CH	ROG-CH	ROG-CH	ROG-CH	ROG-CH	ROG-CH	ROG-CH	MRK
#2	NOVN-CH	JNJ	NOVN-CH	JNJ	JNJ	JNJ	JNJ	JNJ	JNJ	JNJ
#3	JNJ	NOVN-CH	JNJ	MRK	MRK	NOVN-CH	BMY	PFE	MRK	ROG-CH
#4	PFE	PFE	PFE	NOVN-CH	NOVN-CH	MRK	PFE	MRK	PFE	PFE
#5	MRK	MRK	MRK	PFE	PFE	PFE	MRK	NOVN-CH	AZN	AZN
#6	GSK	AZN	AZN	AZN	BAYN-DE	GILD	NOVN-CH	BMY	BMY	LLY
#7	AZN	GSK	LLY	LLY	AZN	BMY	BAYN-DE	AZN	NOVN-CH	BMY
#8	LLY	LLY	BAYN-DE	BAYN-DE	ABBV	BAYN-DE	ABBV	LLY	LLY	NOVN-CH
#9	BAYN-DE	BAYN-DE	GSK	ABBV	BMY	LLY	AZN	ABBV	BAYN-DE	ABBV
#10	AMGN	ABBV	GILD	GSK	LLY	GSK	LLY	BAYN-DE	ABBV	GSK
#11	BMY	AMGN	BMY	BMY	GSK	ABBV	GSK	GSK	GSK	BAYN-DE
#12	ABBV	BMY	ABBV	GILD	GILD	AZN	GILD	GILD	GILD	GILD
#13	GILD	GILD	AMGN	AMGN	AMGN	AMGN	AMGN	AMGN	AMGN	AMGN
#14	NOVO.B-DK	BIIB	NOVO.B-DK	BIIB	BIIB	REGN	BIIB	VRTX	NOVO.B-DK	NOVO.B-DK
#15	BIIB	NOVO.B-DK	BIIB	NOVO.B-DK	NOVO.B-DK	BIIB	REGN	REGN	REGN	MRNA
#16	REGN	REGN	REGN	REGN	REGN	NOVO.B-DK	INCY	NOVO.B-DK	MRNA	REGN
#17	VRTX	VRTX	VRTX	INCY	VRTX	VRTX	NOVO.B-DK	BIIB	VRTX	VRTX
#18	BMRN	BMRN	BMRN	VRTX	INCY	INCY	VRTX	MRNA	BIIB	BIIB
#19	INCY	INCY	INCY	BMRN	BMRN	BMRN	MRNA	INCY	INCY	BNTX
#20	ALKS	ALKS	ALNY	MRNA	ROIV	ALNY	ROIV	BNTX	BNTX	INCY
Sum (bn)	$84	$85	$88	$95	$98	$106	$118	$133	$132	$159

This list is based on current GIR coverage

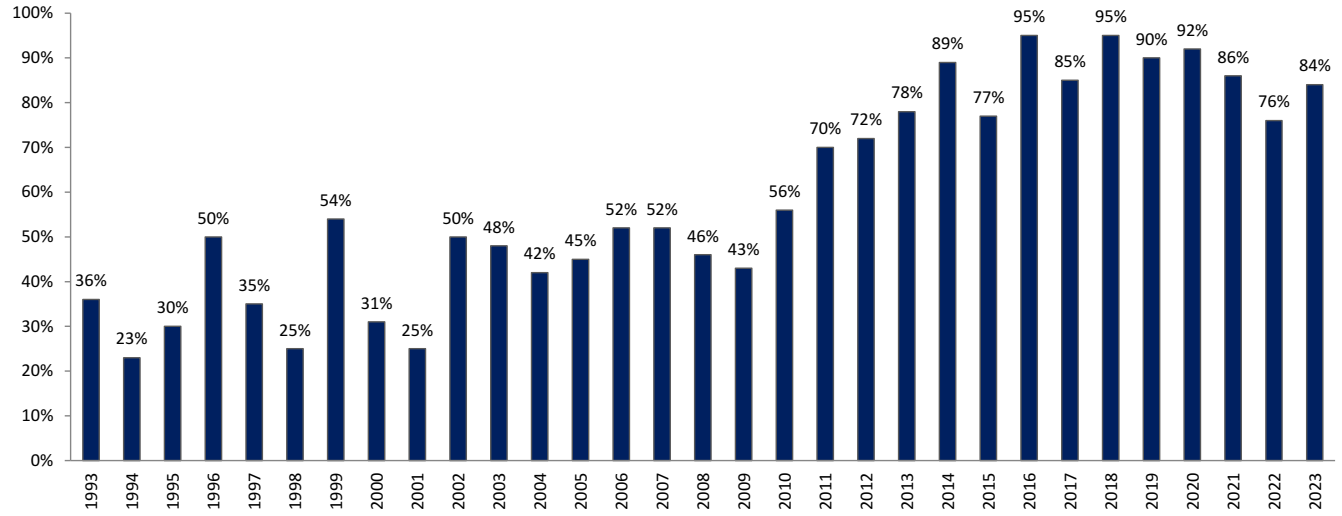
Source: FactSet, Goldman Sachs Global Investment Research

Biotech Risk #2: regulatory approval

One of the trade-offs that biotech companies face is in how to best design clinical trials for expediency, while generating data in the broadest patient population appropriate for the drug, and meeting regulatory standards necessary for approval and reimbursement. Thus, companies will meet with regulators throughout the development process, and file for approvals once all data has been collected. If regulators deem the clinical data produced incomplete, they may require additional studies be run.

Following a detailed review of the clinical data, regulators will determine whether to approve the drug (a complete response letter is issued when the drug is not approved). In the US, this approval rate has improved considerably since the '90s, largely due to enhanced communication between sponsors and regulators throughout drug development, with additional points of contact throughout the development process, and increased flexibility/novel regulatory pathways for select indications (discussed in more detail below).

Exhibit 5: FDA approval rates on first pass



Source: FDA

Biotech Risk #3: commercialization

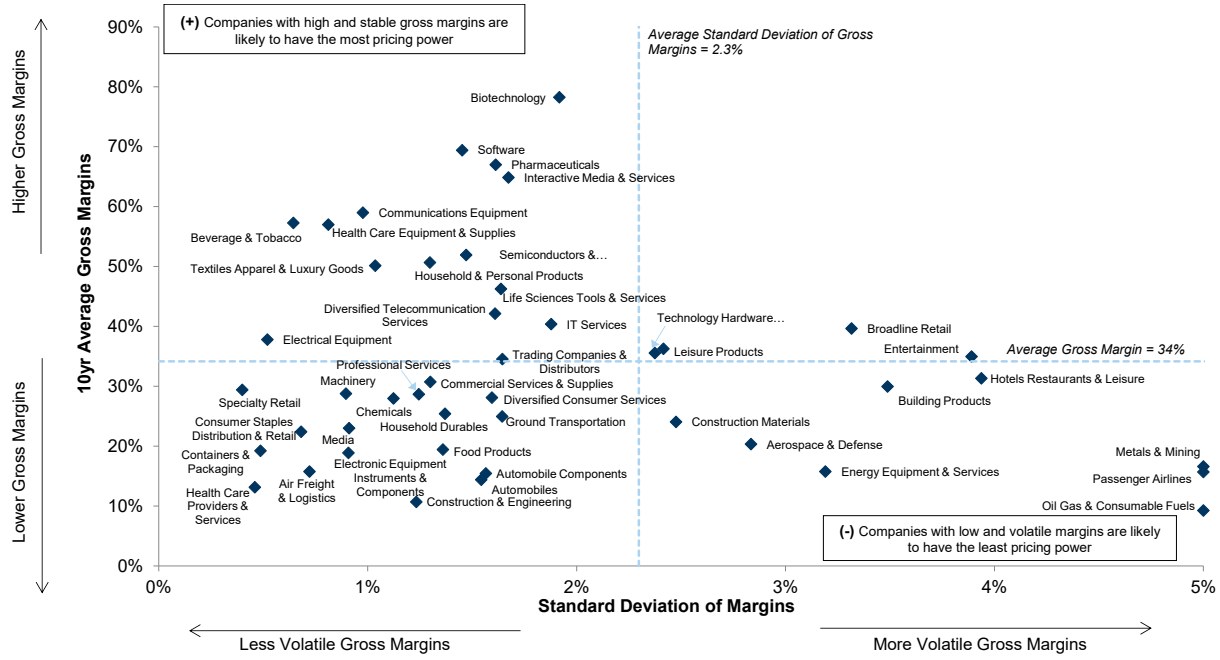
Following approval, biotech companies will launch drugs into the marketplace, leveraging a sales force (ranging from 10s to 100s of people), patient support services, and in some cases, direct-to-consumer advertising (only allowed in the US and New Zealand). Drug developers cannot promote a drug for use beyond the prescribed label granted by regulators, but physicians have discretion to prescribe approved drugs where they see fit.

To incentivize drug development, governments issue patents to grant limited-duration monopolies (typically 20 years from when the patent is filed, which can be well before approval). Beyond patents, regulatory authorities may also grant specific exclusive rights to market a product for a set period of time. We cover this in detail within.

Drugs that deliver substantial clinical value (meaningful improvement over existing standard-of-care) have considerable pricing power. This is reflected in biopharma gross margins, which are the highest and relatively stable across industries.

Exhibit 6: The absolute level and the volatility of gross margins are two potential indications of pricing power

10yr average gross margin by sector vs. 10yr standard deviation of gross margins (2014-2023)



Note: We calculate each industry's gross margins on a rolling LTM aggregated basis (using total industry sales and total industry COGS) - for current Russell 1000 constituents (exclude Financials, Real Estate & Utilities) with sufficient historical data. 2.3% is the average 10 yr standard deviation of industry gross margins for our sample. 34% is the average industry gross margin over the 10yr period. Standard deviation capped at 5% for the purposes of presentation.

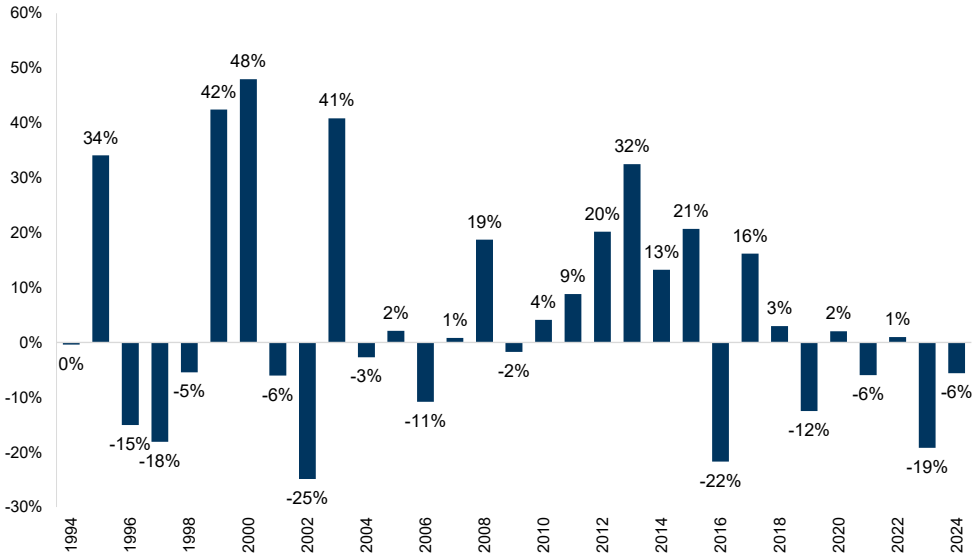
Source: FactSet, Goldman Sachs Global Investment Research

However, drug pricing is an evergreen focus of policymakers, payers, patients, and other stakeholders. Recent legislation included in the 2022 Inflation Reduction Act (IRA), which instates a negotiation for drugs following a set period on the market, is expected to significantly impact the outlook for pharma pipelines, M&A decisions, and therapeutic/technology focus areas. We address this in more detail later in the note.

Rewards for biotech investing

Investors bear the risks involved with biotech investing for a chance at outsized returns. The NBI (NADSAQ Biotechnology Index) has outperformed the S&P 500 during 17 out of the last 30 years, and the XBI outperformed 11 of the last 17 years.

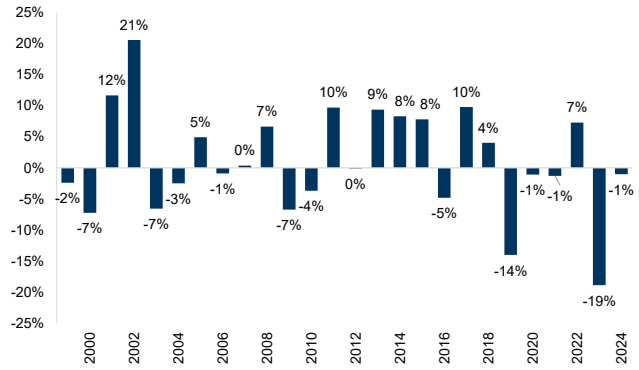
Exhibit 7: NBI YTD performance relative to the S&P 500 - Last 30 years



Data available since 1994; performance for all years based on YTD (as of 09.09)

Source: FactSet

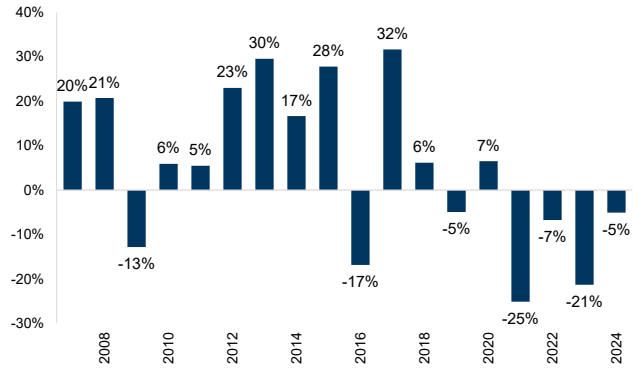
Exhibit 8: XLV YTD performance relative to the S&P 500 - Last 25 years



Data available since 1999; performance for all years based on YTD (as of 09.09)

Source: FactSet

Exhibit 9: XBI YTD performance relative to the S&P 500 - Last 17 years



Data available since 2007; performance for all years based on YTD (as of 09.09)

Source: FactSet

Even in the context of the recent biotech bear market (which has persisted for more than three years now), companies with clinical, regulatory, and commercial successes can still deliver outsized returns, pointing to the role for stock selection within the XBI. Similarly, regardless of a bull market, biotech returns can significantly underperform in the case of failed clinical studies, regulatory rejections, or disappointing commercial performance (Exhibit 10).

Exhibit 10: Performance of Best 5 and Worst 5 Biotech companies (2019-2023)

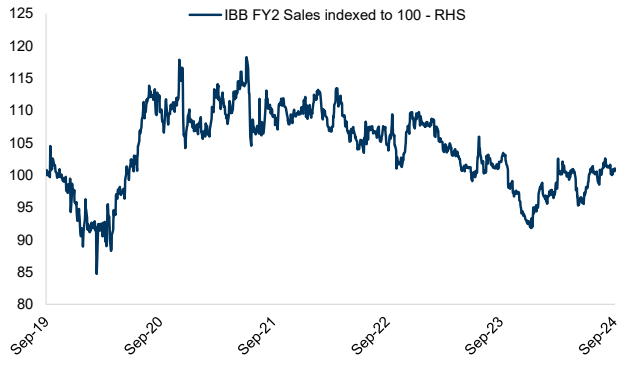
	2019	Perf	2020	Perf	2021	Perf	2022	Perf	2023	Perf
Best performing	AXSM	3565%	NVAX	2702%	PRTA	311%	VRNA	289%	SLNO	1933%
	RCEL	698%	CLDX	686%	BCYC	239%	MDGL	243%	EYPT	560%
	ARWR	411%	TWST	573%	AVXL	221%	RYTM	192%	OLMA	473%
	MDXG	323%	ALT	497%	BNTX	216%	ATXS	176%	BBIO	430%
	ARDX	319%	MRNA	434%	DVAX	216%	ADMA	175%	AUTL	239%
Most underperforming	ANAB	(75%)	EYPT	(58%)	OLMA	(81%)	CCCC	(82%)	ARQT	(78%)
	WVE	(81%)	RCEL	(59%)	IMVT	(82%)	CVAC	(82%)	NVCR	(80%)
	COGT	(84%)	ATXS	(64%)	DCPH	(83%)	FATE	(83%)	BLUE	(80%)
	VRDN	(84%)	EOLS	(72%)	ARDX	(83%)	NVAX	(93%)	VTYX	(92%)
	NVAX	(89%)	SVRA	(74%)	SPRY	(86%)	TRML	(93%)	ACRS	(93%)
XBI		33%		48%		(20%)		(26%)		8%

Source: FactSet, Goldman Sachs Global Investment Research

We highlight several factors that drove the biotech bear market of 2021 to present:

- **Macroeconomic uncertainty.** Persistent inflation, which led to a higher interest rate environment that continues into this year, is negative for long-duration and risky assets. The XBI, by nature, is characterized by its high risk profile. The higher-for-longer rate environment has also been a headwind to funding within the sector, which primarily rely upon equity markets, and M&A, which is a key driver of performance for the group.
- **Negative earnings estimate revisions.** The past three years have been characterized by negative estimate revisions across the large-cap biotech companies, driving underperformance for the biggest names within the index as generalist investors have been unwilling to allocate capital to a sector where earnings revisions are moving lower, with downstream impact on the small- and mid-cap population. Estimates are now 15% lower vs. 2021. We have seen a slight uptick in estimates recently but it is early to say that this is a reversal in trend.

Exhibit 11: Estimate revision across large-cap biotech companies



Source: FactSet, Goldman Sachs Global Investment Research

- **Inconsistent M&A.** While there have been pockets of robust M&A activity (most notably in the late 2023/early 2024 period), and potential acquirers continue to mention balance sheet capacity and a desire to engage in deal activity, the execution of deals has been mixed (particularly among large acquisitions, >$10B) vs. prior

periods. Macroeconomic uncertainty is a contributor, as it can be a headwind to obtaining financing for potential deals (particularly where debt will be required).

- **Clinical and regulatory outcomes.** In addition, clinical and regulatory failures have been a drag on the sector. We note that changes in the complexion of the XBI, driven by an increase in early-stage companies IPOing in 2020/2021 (see below for more detail), naturally increases the rate of clinical failure among public biotech companies given drugs in preclinical development/Ph1 study are ~10% likely to reach the market.
- **IPO activity.** The 2020-2021 period, during which time the biotech sector played a significant role in the global COVID-19 pandemic via the development of vaccines, led to a significant influx of capital toward the sector. As a result, we saw a significant increase in IPOs vs. prior years (74 on average between 2018-2021 vs. an average of ~43 over the rest of the decade), pulling forward deal activity as companies sought to tap robust public markets. As discussed, the complexion of these deals skewed more heavily toward preclinical and early stage biotech companies vs. prior years, leading to an increase in overall risk within the biotech index. The subsequent declines in 2022/2023 in the number of biotech IPOs was significant, reflecting also a challenging market environment for biotech companies in early-stage development that drove companies to remain private for longer.

As we look forward, we continue to see attractive returns available to investors within the biotech sector. We highlight the following reasons for optimism:

- **Innovation remains robust.** Despite industry headwinds, we continue to see innovation across the sector, which will result in new drugs for new markets, and more efficient drug discovery and clinical trial execution.
- **New product cycles in large addressable markets.** Perhaps best exemplified by the recent emergence of anti-obesity medication (which we estimate is a $130B market), there are multiple new product cycles emerging across large addressable markets: Alzheimer's disease ($20B+), pain ($15B+), and others which will drive returns to the sector.
- **M&A is a necessity for acquirers.** While there have been some headwinds in funding M&A, pharma companies have $490B in balance sheet capacityfor new acquisitions and face ~$280B in patent cliffs by the end of the decade. We expect that these companies will need to deploy meaningful capital through the next decade, with returns accruing to the biotech companies driving drug discovery and early development of new agents.

However, we look for the negative estimate revisions cycle to reverse, macroeconomic stability (particularly with respect to the rates outlook), clarity on election outcomes, and a pick up in M&A to provide the backdrop necessary for biotech to emerge from its protracted bear market.

Investing in Biotech

Biotech investing is characterized by high risks offset by the potential for high rewards, with returns driven by idiosyncratic events (clinical, regulatory, and commercial), though these are bolstered by underlying secular growth. We primarily utilize DCF-based analyses to derive valuations for biotech companies, given revenue streams are often many years away.

Key questions / considerations

When evaluating a biotechnology company, it is first necessary to consider a few key aspects of the company:

- **Technology:** What kind of drug does the company develop? Is there a central technology that drives all of its drug development? Is this technology proven by others, or are they the first to deploy it? Is the process for drug development using this technology repeatable or scalable?
- **Pipeline:** How does the company discover drugs? Do they buy assets that are already in development, or discover drugs themselves? How far along in the development process are the products identified in the pipeline? Does this company have a successful track record of drug discovery that will apply to future efforts? Does the company hold full economic rights to its pipeline, or is it partnered on some / all products?
- **Product:** Does the drug show promising signs of efficacy in key patient populations? What is the addressable market for this product? What is the unmet need within that addressable market? What can be expected with respect to peak sales of a given product? If commercial, how will physicians consider and use the drug? What is the competitive landscape? What is the catalyst path for a given product?
- **Intellectual property:** How many patents are listed for each drug? What kind of patents are they, and how strong will they be against potential litigation? When do these patents expire?
- **Team:** What is the senior leadership team's prior experience? What is the experience of the board? Have they ever been in senior leadership at a biotech company before, and have they previously executed well on similar projects? What are the goals of the team (acquisition, or to become large-scale biotech company)?
- **M&A:** Could this asset be attractive to a larger biotechnology or pharmaceutical partner? How would a potential acquirer ascribe value to this asset?

Valuation Framework

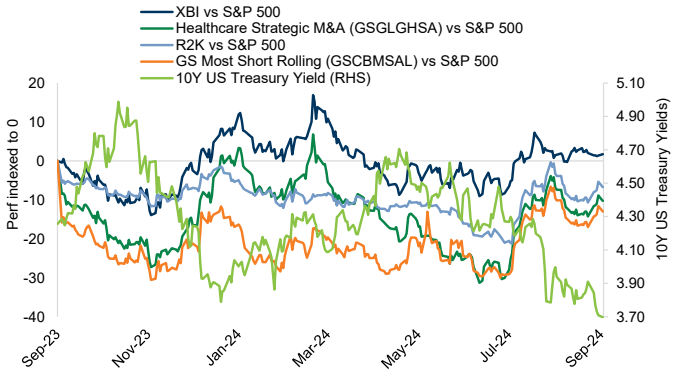
We leverage a few basic valuation frameworks to assess biotech companies, with strengths and weaknesses of each.

- **Discounted Cash Flow analysis.** We primarily leverage a discounted cash flow analysis in our valuation of biotechnology companies, which a) allows for the valuation of companies that are currently unprofitable (and in many cases, are

expected to remain unprofitable for many years), and b) captures the full life cycle of a drug, from approval to loss of patent exclusivity.

- We employ a discount range of 8-21% across our biotech coverage, which reflects stage of development, degree of clinical/commercial risk, and need for additional capital. We also employ a range of terminal growth rates across our coverage from -2% to 5%, reflecting the breadth of a company's pipeline and their ability to leverage discovery and development capabilities to bring additional drugs forward that may not already be reflected in our models.
- In the case of small- and mid-cap biotechnology companies, we generally apply the terminal growth rate to cash flows beyond the patent-protected period of modeled drugs, limiting terminal value to a small portion of the overall value of the company. However, in the case of a company with a deep pipeline and/or technology that can be reproducible and thus leveraged across future programs not necessarily yet in our specific models, our terminal value may be a more significant portion of the overall company valuation.
- Given biotech valuations are primarily derived via discounted cash flow analysis over a long duration of the drug life cycle (in many cases 15-20 years), the rate environment can be a significant driver of biotech performance. In periods when rates are low, cost of capital is also low (informing a lower discount rate, all else equal); by contrast, a rising rate environment will pressure cost of capital across the sector (which also relies on frequent capital infusions), resulting in overall downside to the index. Thus, the XBI often trades relative to the macroeconomic rate environment.

Exhibit 12: XBI performance frequently trends in relation to 10Y yields



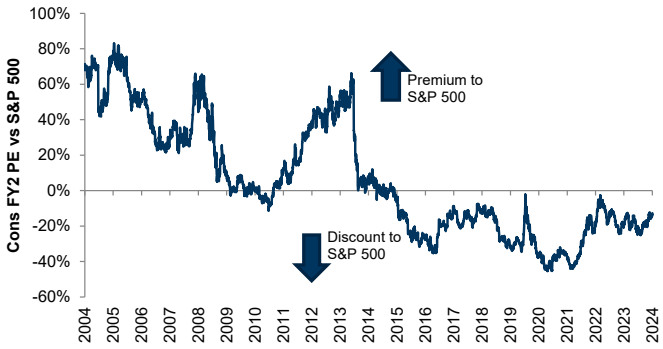
Source: Goldman Sachs Global Investment Research, FactSet

- **Multiples based analysis.** In some cases, we leverage a multiple-based analysis for profitable stage companies. We can also use EV/sales (both near-term and peak) to compare peers across the group and vs. history. In recent years, where clinical stage biotechnology companies have been out of favor, we have also used EV/cash to identify companies trading below cash value and assess the appropriateness of such market valuation.
  - **P/E and EV/EBITDA:** For large-cap biotechnology companies we can use Price/Earnings and/or EV/EBITDA multiples, where we note a historic trading

range of 14x / 10x. Today, large-cap biotech trades at 16x P/E, a premium to history and at a discount relative to the S&P.

- **EV/Sales:** We evaluate companies on an EV to sales basis, including for commercial companies relative to FY1/FY2 sales, which can identify companies trading at a premium or discount to peers. The range of EV/Sales (TTM basis) is 5x today across our large cap coverage, and 8x across our smid-cap group. We also leverage EV/Peak Sales for clinical and in some cases early commercial stage biotech companies, which biotech investors often use as a back-of-the-envelope valuation methodology. Investors will often benchmark to 3-5x peak sales as an appropriate range for biotech valuations, though we note considerable variability depending on therapeutic area, stage of development, and the sophistication of the company's scientific efforts.
- **EV/Cash:** In the context of the recent biotech bear market (from early 2021-present), we have also found EV/cash multiples to be informative. 51% of biotech companies traded below cash at the low point of the market, and 38% do today. While in some cases this is warranted following clinical failure, this valuation methodology can also identify companies that are trading at a deep discount to what their cash + pipelines may be worth.

Exhibit 13: LC Biotech FY2 P/E vs. S&P 500



Source: FactSet, Goldman Sachs Global Investment Research

Exhibit 14: GS-covered Commercial SMID-caps

SMID-cap	EV / TTM sales	EV / NTM sales
ACAD	2x	2x
ADPT	3x	3x
AGIO	65x	24x
ALKS	3x	3x
ALNY	14x	14x
AMRN	0x	0x
APLS	8x	5x
ARQT	9x	5x
ASND	20x	12x
ATRA	2x	1x
BBIO	30x	29x
BIOA.B-SE	48x	18x
BLUE	-7x	
BMRN	7x	5x
BNTX	4x	4x
BPMC	15x	9x
CRSP	10x	11x
DAWN	105x	9x
DVAX	5x	3x
ESPR	2x	2x
EXEL	3x	3x
FGEN	1x	1x
FOLD	8x	6x
GERN	1861x	11x
HALO	10x	8x
HCM	4x	3x
HRMY	3x	3x
IMCR	4x	4x
INCY	3x	2x
INSM	35x	26x
INVA	4x	4x
IONS	7x	9x
IOVA	71x	7x
ITCI	12x	8x
JAZZ	3x	2x
KNSA	5x	3x
KRYS	32x	11x
MCRB	793x	18x
MDGL	276x	14x
NBIX	6x	4x
OGN	2x	2x
PHAT	131x	11x
PTCT	2x	2x
QURE	10x	5x
RARE	10x	9x
ROIV	30x	20x
RPRX	11x	8x
RVNC	4x	3x
RYTM	29x	18x
SAGE	-2x	-3x
SDGR	6x	5x
SNDX	324x	15x
SRPT	8x	4x
SWTX	29x	8x
TARS	11x	4x
TGTX	10x	8x
TSVT	7x	4x
URGN	4x	3x
UTHR	5x	4x
VLA-FR	3x	2x
median for above tickers	**8x**	**5x**
median for all tickers (SMID and large-cap)	**7x**	**5x**
median for all biotech	**6x**	
median for historical recession (all biotech)	**6x**	
median for 2018 sell-off (all biotech)	**7x**	

Source: Goldman Sachs Global Investment Research, FactSet

Exhibit 15: GS-covered non-commercial companies: EV/Cash

Non-commercial companies	
	EV/Cash
ABCL	0.2x
ACRS	
ALEC	0.2x
ALLK	
ALLO	0.4x
ALT	2.0x
AMLX	
APGE	3.1x
ARVN	0.5x
ARWR	6.2x
ATHA	
AUTL	1.0x
AVBP	2.1x
BAI-NL	
BCYC	0.5x
BOLD	
BTAI	1.2x
CGON	3.4x
CLLS	0.1x
CNTA	4.7x
CTNM	1.1x
CVAC	2.3x
CYTK	5.3x
DBVT	0.4x
DNLI	4.0x
DTIL	
ELVN	2.6x
ERAS	0.8x
EWTX	2.2x
EXAI	0.7x
FATE	0.8x
FDMT	0.6x
FHTX	0.9x
FULC	1.0x
GOSS	0.2x
GRTS	2.1x
IDYA	3.1x
IMTX	
IMVT	6.8x
IPH-FR	
KOD	0.4x
KRON	
KROS	3.9x
KYMR	5.9x
LYEL	
MLTX	4.7x
MLYS	0.9x
NKTR	0.8x
NTLA	2.0x
NUVL	7.6x
OLMA	1.9x
OMGA	3.2x
PHIL	
PMVP	
PRME	2.2x
RAPP	1.2x
RAPT	
RCKT	5.7x
RCUS	0.6x
RGNX	1.6x
RLAY	0.8x
RLMD	0.2x
RPTX	
RVMD	3.4x
RXRX	2.4x
SANA	4.0x
SGMT	
TERN	2.7x
TNGX	2.2x
TRDA	0.2x
TSHA	2.4x
VERV	
VIR	0.0x
VOR	0.3x
VRDN	1.1x
VTYX	
XENE	3.2x
ZEAL-DK	5.2x
median for above tickers	**1.9x**
median for all biotech	**2.1x**
median for historical recession (all biotech)	**1.1x**
median for 2018 sell-off (all biotech)	**2x**

Source: Goldman Sachs Global Investment Research, FactSet

M&A

We also employ M&A valuation methodology within our framework for biotech valuations, particularly given the important role M&A plays in the biopharma/biotech ecosystem. Based on a framework that incorporates qualitative (product/pipeline, technology, FTC considerations) and quantitative (valuation, potential returns on investment, synergies with existing franchise) factors, we ascribe a probability of M&A to each company, ranking these 1-3: a "1" implies a high probability of acquisition (30-50%), "2" implies a moderate probability (15-30%), while "3" represents a low probability (10-15%). For companies ranked 1 or 2, in-line with our standard departmental guidelines, we incorporate an M&A component into our valuation of the company. Within this context we, ascribe an M&A component to the following:

Exhibit 16: GS biotech coverage with M&A rank of 1 or 2

Ticker	Company	Market Cap ($ mn)	Rating	M&A Rank	Price	Target Price (12 mo)	Primary Therapeutic Area(s)
ALT	Altimmune	$702	Neutral	1	$6.96	$10	Obesity/liver disease
APLS	Apellis Pharmaceuticals	$5,360	Buy	1	$39.18	$74	Immunology (C3)/othalmology
BPMC	Blueprint Medicines	$5,382	Buy	1	$85.99	$167	Oncology/I&I
BBIO	BridgeBio Pharma	$5,612	Buy	1	$29.99	$50	Cardiovascular
CGON	CG Oncology	$2,407	Buy	1	$36.12	$52	Bladder cancer
DAWN	Day One Biopharmaceuticals	$1,258	Buy	1	$14.34	$45	Oncology
IMCR	Immunocore	$1,713	Buy	1	$34.26	$83	Oncology
INSM	Insmed*	$11,928	Buy	1	$71.57	$103	Rare disease/gene therapy
IOVA	Iovance Biotherapeutics	$2,729	Buy	1	$9.18	$21	Oncology
KRYS	Krystal Biotech	$5,311	Buy	1	$185.00	$193	Rare disease/gene therapy
MDGL	Madrigal Pharmaceuticals	$5,115	Buy	1	$235.69	$511	Metabolic disease
SRPT	Sarepta Therapeutics	$12,012	Buy	1	$126.94	$219	Rare disease/gene therapy
AGIO	Agios Pharmaceuticals	$2,532	Neutral	2	$44.52	$57	Hemotology
ARGX	Argenx	$31,991	Buy	2	$535.00	$565	Immunology
ARVN	Arvinas	$1,735	Buy	2	$25.51	$70	Oncology/Neurology
ARWR	Arrowhead Pharmaceuticals	$2,667	Neutral	2	$21.47	$28	Cardiometabolic/Pulmonology
BMRN	BioMarin Pharmaceutical	$16,152	Buy	2	$84.85	$139	Rare disease/gene therapy
DNLI	Denali Therapeutics	$4,466	Buy	2	$26.34	$46	Neurology
GERN	Geron	$2,582	Buy	2	$4.34	$6	Hematologic malignancy
MLYS	Mineralys Therapeutics	$597	Buy	2	$12.01	$29	Hypertension
MLTX	MoonLake Immunotherapeutics	$2,930	Neutral	2	$46.60	$62	Inflammation
NBIX	Neurocrine Biosciences	$12,342	Buy	2	$119.10	$170	Neurology
OLMA	Olema oncology	$706	Buy	2	$12.33	$27	Oncology
RYTM	Rhythm Pharmaceuticals	$3,125	Buy	2	$49.09	$58	Rare genetic disease of obesity
RCKT	Rocket Pharmaceuticals	$1,794	Neutral	2	$19.59	$34	Cardiovascular/gene therapy
RLAY	Relay Therapeutics	$1,191	Buy	2	$9.00	$20	Oncology
SNDX	Syndax Pharamaceuticals	$1,606	Buy	2	$18.81	$30	Oncology
XENE	Xenon Pharamaceuticals	$2,938	Buy	2	$38.93	$60	Neurology

* On the US Conviction list

Source: Goldman Sachs Global Investment Research

Overall, smid-cap biotech companies are more likely to be acquired vs. large-caps, due to valuation (large-cap balance sheets are sufficient to acquire without incurring significant leverage), ease of integration (these are often single product or few product companies), and potential for Federal Trade Commission concerns regarding anti-competitive deals (a recent focus given scrutiny on Horizon [by AMGN] and Seattle Genetics [by PFE] acquisitions). Since 2007, we highlight a median multiple of 11x EV/FY2 sales for biotech companies (where these data are available).

Exhibit 17: Major M&A Transactions 2023-2024

Deal Timing (Announced)	Acquirer	Target	Stage	Primary Therapeutic Area	Value ($bn)	Premium	EV/Sales Multiple
			2024				
8/12/2024	Crown Laboratories	RVNC	Commercial	Aesthetics	$0.9	89%	3x
8/1/2024	OTSKY	Jnana Therapeutics	Ph1	Rare disease/I&I	$0.8	-	-
7/29/2024	COLL	Ironshore Therapeutics	Commercial	CNS	$0.5	-	-
7/8/2024	LLY	MORF	Ph2	I&I (bowel disease)	$3.2	79%	12x
529/2024	MRK	EyeBio	Ph2/3	Opthalmology	$1.3	-	-
5/28/2024	JNJ	Yellow Jersey Therapeutics	Ph1/2	I&I	$1.3	-	-
5/28/2024	Asahi Kasei	CALT	Commercial	Rare diseases	$1.1	83%	4x
5/22/24	BIIB	HI-Bio	Ph2/3	Immunology	$1.2	-	-
5/16/24	JNJ	Proteologix	Ph1	I&I	$0.9	-	-
5/2/24	NVS	Mariana Oncology	Preclinical	Oncology (radiopharmaceutical)	$1.0	-	-
4/29/2024	OPHLY	DCPH	Commercial	Oncology (small molecule)	$2.4	75%	12x
4/23/2024	INCY	Escient Pharma	Ph1/2	I&I	$0.8	-	-
4/11/2024	VRTX	ALPN	Ph2/3	Immunology	$4.9	67%	14x
4/3/2024	GMAB	Profound Bio	Ph1/2	Oncology (ADC)	$1.8	-	-
3/19/2024	AZN	FUSN	Ph2	Oncology (small molecule)	$2.0	97%	12x
3/14/2024	AZN	Amolyt Pharma	Ph3	Endocrinology	$0.8	-	-
2/12/2024	GILD	CBAY	Regulatory	Liver Disease	$4.3	27%	10x
2/5/2024	NVS	MOR	Ph3	Oncology (small molecule)	$2.9	18%	14x
1/23/2024	SNY	INBX	Regulatory	Oncology/rare diseases	$1.7	-	10x
1/9/2024	GSK	Ailos Bio	Ph2	Respiratory	$1.4	-	-
1/8/2024	JNJ	AMAM	Ph2	Oncology (ADC)	$2.0	105%	10x
1/8/2024	MRK	HARP	Ph1	I&I / Cell therapy	$0.7	118%	10x
			2023				
12/26/2023	AZN	GRCL	Ph1	Oncology (CAR T)	$1.0	62%	11x
12/26/2023	BMY	RYZB	Ph3	Oncology (RPT)	$4.1	104%	24x
12/22/2023	BMY	KRTX	Ph3	Neurology	$14.0	53%	12x
12/12/2023	AZN	ICVX	Ph2	Infectious disease	$1.1	43%	3x
12/6/2023	ABBV	CERE	Ph3	Neurology	$8.7	26%	17x
12/4/2023	ROG	Carmot Therapeutics	Ph2	Diabetes / Obesity (GLP-1)	$2.7	-	-
11/30/2023	ABBV	IMGN	Commercial	Oncology (ADC)	$10.1	95%	16x
10/23/2023	ROG	Televant	Ph3	I&I	$7.1	-	-
10/8/2023	BMY	MRTX	Commercial	Oncology (small molecule)	$4.8	35%	7x
10/3/2023	LLY	Point Biopharma Global	Ph3	Oncology (radiopharmaceutical)	$1.4	87%	5x
9/26/2023	Alfasigma	ICPT	Commercial	Liver	$0.8	82%	3x
7/28/2023	BIIB	RETA	Commercial	Rare Disease/Neuro	$7.3	59%	9x
6/20/2023	LLY	Dice Therapeutics	Ph2	I&I	$2.4	42%	14x
6/12/2023	NVS	Chinook	Ph3	Rare Disease/Kidney	$3.2	67%	11x
5/22/2023	Ironwood	VectivBio	Ph2/3	Bowel (GLP-2)	$1.1	43%	-
5/10/2023	Sobi	CTI Biopharma	Commercial	Oncology (small molecule)	$1.7	95%	9x
4/30/2023	Astellas	Iveric Bio	Commercial (pre-PDUFA)	Ophthalmology	$5.9	64%	17x
4/18/2023	GSK	Bellus Health	Ph3	Respiratory	$2.0	103%	8x
4/16/2023	MRK	Prometheus	Ph3	I&I	$10.8	75%	24x
3/31/2023	Sartorius Stedim	Polyplus	n/a	CRO (cell/gene therapy)	$2.6	-	-
3/3/2023	PFE	SGEN	Commercial	Oncology (ADC)	$43.0	42%	12x
3/13/2023	SNY	Provention Bio	Commercial	Diabetes	$2.9	273%	9x
1/9/2023	AZN	CinCor Pharma	Ph3	Heart/Kidney	$1.3	121%	9x
1/8/2023	Chiesi Farmaceutici	Amryt Pharma	Commercial	Rare Disease	$1.5	107%	-
					Mean	**78%**	**11x**
					Median	**75%**	**10x**

Reflects either EV/NTM consensus sales or EV/FY2 consensus sales where applicable

deals >$500M in 2023 and 2024

Source: Goldman Sachs Global Investment Research, Visible Alpha Consensus Data, Company data

We note particular focus within certain therapeutic areas (neuroscience, oncology, rare disease, and cardiometabolic disease) and technologies (antibody drug conjugates, radiopharmaceuticals), as well as concentration toward de-risked assets and platforms, which is consistent with recent commentary from pharma companies.

Exhibit 18: Recent commentary across large-cap biopharma

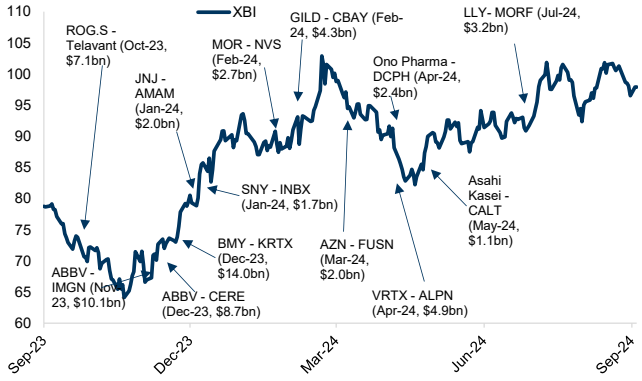
Company	Area of Focus
JNJ	JNJ's BD strategy remains disciplined and agnostic to size and sector, noting an emphasis on areas with existing internal capabilities and knowledge. For Innovative Medicines (Pharmaceuticals), hematology, solid tumors, immunology, and neuroscience are areas of interest with a preference for assets near proof-of-concept stages. For MedTech, JNJ highlighted cardiovascular, robotics/surgery, vision, and ortho.
BMY	Following an active series of M&A announcements last year (MRTX, KRTX, RYZB), while BMY intends to pay down debt and continue to integrate these acquisitions, BD still remains a priority for the company. Notably, BMY are focused on "fit" for potential BD in strategic areas where they currently operate in and are focused on, with the goal of continuing to diversify the portfolio and strengthen the company's longer-term growth profile later into the 2030s.
PFE	Pfizer has signaled their current priorities reside in paying down debt (goal to de-lever to 3.25x) from the Seagen acquisition, as well as in commitment to the dividend and to dividend growth. However, we note that within this process, management has said they continue to keep an active eye on prospective opportunities that could strengthen key franchises where the company can excel (i.e., oncology, but e.g., not rare disease where they believe they do not have an advantage versus smaller companies and have dialed back R&D). Within this framework, it would be unlikely that M&A in the near to intermediate term would go beyond a bolt-on in terms of deal size.
LLY	We expect LLY will continue to be active in external business development given their significant capacity to allocate capital, with a focus on BD activities related to earlier-stage, less-validated assets. Most recently, LLY proposed acquisition of clinical stage IBD company MORF for $3.2B, which fits within this deal framework and helps potentially move towards strengthening the company's pipeline portfolio in Immunology. Capital allocation priorities are focused on R&D, business development, and bolstering manufacturing capacity, evidenced by $18+B committed since 2020.
MRK	Capital allocation priorities remain focused on internal investment in the business, though capacity for M&A remains strong, with deal size likely to focus in the <$15bn range given the recent trend (though this does not necessarily preclude larger deals under the right circumstances). MRK notes interest in expanding beyond oncology and diversifying within oncology. Collaborations and partnerships will also continue to be a part of the company's external BD strategy, which ultimately remains unchanged in 2024.
ABBV	Following the IMGN and CERE transactions, management notes interest in primarily smaller size, early-stage opportunities to drive growth for the next decade. Capital allocation priorities are to support a strong growing dividend, continued debt repayment, and continued business development to further augment the portfolio.
AMGN	Management has reiterated they are on track to deleverage to pre-HZNP acquisition levels by YE25, and, while they are always monitoring opportunities, they are currently focused on the HZNP integration/execution, as well as investment in their late-stage pipeline (e.g., obesity program).
BIIB	Management has noted capacity of ~$8-10bn within the next 24 months, highlighting rare disease and immunology as key areas of interest, with the focus likely on smaller deals albeit will remain opportunistic.
INCY	Management has noted that given their current pipeline and R&D capabilities, management views BD as more of a supplement to growth vs. a key driver; that said, they noted continued strong balance sheet optionality, post the recent Escient deal and share repurchase program.
GILD	Management has reiterated that post the recent CBAY acquisition and given the current pipeline they have the necessary assets to achieve diversification goals and do not expect meaningful M&A in the near-term, with a focus on earlier-stage deals and ordinary course partnerships. Longer-term, GILD emphasized that IMMU-sized deals are not likely, but it could do CBAY-sized deals every few years.
REGN	Management is focused on internal R&D, and will be selective on evaluating external opportunities, noting interest in platforms that are complementary or synergistic.
NOVN.S	Focus continues to remain on bolt-on acquisitions in the sub-$5bn space that are considered value-creative in its 4 core therapeutic areas and 3 platform technologies. Vast majority of deals likely to be in the sub-$1bn space (but will continue to look at the full range) give the company's view that the most significant opportunity for value creation, as well as differentiated views vs. the markets, is on the lower end of the range of deal values.
GSK.L	First priority remains to invest in the business, with capital allocated towards development of the pipeline, both organic and targeted BD (with GSK noting it having the balance sheet capacity to do BD). Focus remains on four core therapeutic areas, and for earlier deals, a focus on underpinning technologies. The company is generally interested in assets that will be delivering more for the end of the decade.
MRCG.DE*	Strategic priority for M&A remains with Life Science given: (i) its leadership position in the space; (ii) attractive growth and margins; and (iii) this segment providing an optimal risk/reward profile for the group. For the Healthcare business, the company notes a focused leadership approach in therapeutic areas where it already has a presence, or potential adjacent opportunities beyond these areas. The company expects >50% of future Healthcare launches to come from external innovation, with Merck noting a preference for licensing deals. The company also considers value-creating bolt-ons, with the criteria being: (i) ROCE above WACC of the company; (ii) EPS pre accretion; and (iii) maintaining a strong investment grade rating.
ROG.S	Focus on early-stage assets that can be launched in the mid-term with best or first-in-class potential. The company has pointed to an annual budget of around CHF $10bn for M&A.
BAYGn.DE	Focus on early-stage assets and licensing rather than large M&A deals given limited balance sheet flexibility.
AZN	Feel comfortable with internal technology platforms after recent acquisitions and plan to focus on integration instead of more deals.
NOVOb.CO	Novo Nordisk have communicated that they would complement their internal innovation with external innovation, but have a clear approach of looking at assets in late preclinical/early clinical development allowing higher value creation. Novo Nordisk commented they are disciplined and focused on a few core therapeutic areas (diabetes, obesity, cardiovascular disease and rare blood diseases), and recently commented at a competitor conference that the cardiovascular and cardiometabolic space is an obvious place for them to invest. We also note Novo Nordisk's announcement to acquire 3 fill-finish sites from Novo Holdings in connection with the Catalent transaction for $11bn upfront.

***Coverage suspended**

Source: Company data, Goldman Sachs Global Investment Research

While important for company-specific returns, XBI performance on aggregate is not affected by one-off acquisitions. However, sustained deal activity can be a driver of outperformance, as observed in the period from late 2023-early 2024 where M&A offset a rising rate environment (albeit this was not sustained as M&A activity tailed off).

Exhibit 19: XBI performance vs. major M&A announcements



Source: Goldman Sachs Global Investment Research, FactSet

A key driver of M&A within the biopharma landscape is impending patent cliffs across key products within existing pharma company pipelines. With products expected to lose market exclusivity in the back half of this decade, continued pharma company growth beyond the patent expirations will require these companies to purchase and develop assets with commercial opportunities that are in aggregate greater than the peak sales opportunity for franchise assets (i.e. MRK's Keytruda, BMY's Ocrevus, JNJ's Darzalex; Exhibit 20). Against this backdrop, commercial and near-commercial de-risked assets that will contribute meaningfully to revenue within the next ~3-5 years are at a premium, and this is where we have seen a concentration in acquisitions over the past several years.

Exhibit 20: Revenue impact from impending patent cliffs

Ticker	Peak sales for drugs with ≤2025 LOE (in $M)	Peak sales for drugs with ≤2030 LOE (in $M)	# of key products
ABBV	$21,237	$28,318	3
AMGN*	$6,786	$14,096	5
BIIB	$4,928	$10,004	4
BMY	$25,707	$51,219	8
INCY	-	$2,950	1
JNJ	$27,777	$50,962	11
LLY	$7,538	$19,529	5
MRK	$1,061	$63,049	7
PFE	$6,792	$38,445	8

**Sales the year prior to LOE*

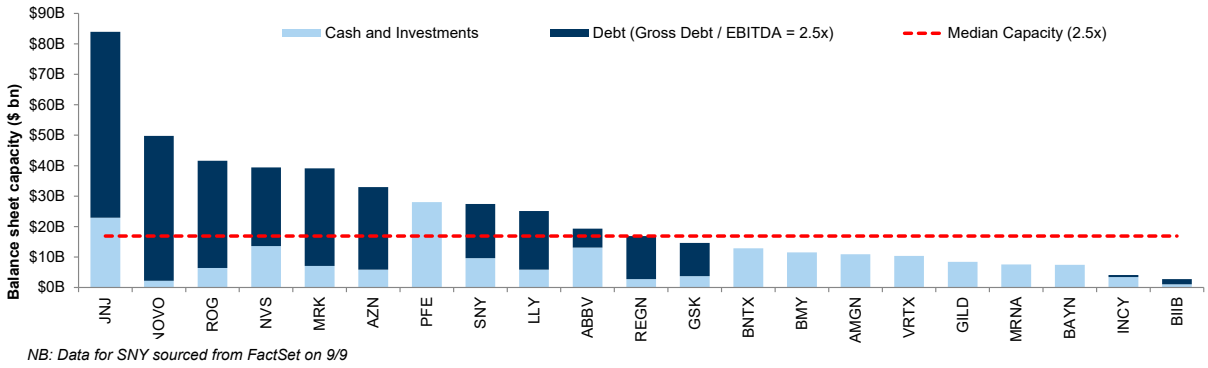
Only reflects the key products

Source: Data compiled by Goldman Sachs Global Investment Research

Despite the need for acquisitions to drive revenue growth and ample balance sheet capacity, large-cap biopharma companies have been somewhat reticent to deploy capital over recent years. Biopharma balance sheet capacity has been at elevated levels for the greater part of the last decade. In fact, in 2017 we highlighted $420B in balance sheet capacity (assuming 2x Net Debt/EBITDA), which today measures at $490B (assuming 2.5x Gross Debt/EBITDA). Compared to the total valuation of the XBI at $1,300B, pharmaceutical companies in the US and Europe could

conceivably purchase 1.8x of the total biotech market (exc. companies with market cap >$10B). While elevated valuations were a headwind to deal activity in the 2019-2021 period, rate volatility and uncertainty creates an environment wherein it is more difficult to obtain financing.

Exhibit 21: Global large cap biopharma M&A capacity for 2024



Source: FactSet, Goldman Sachs Global Investment Research

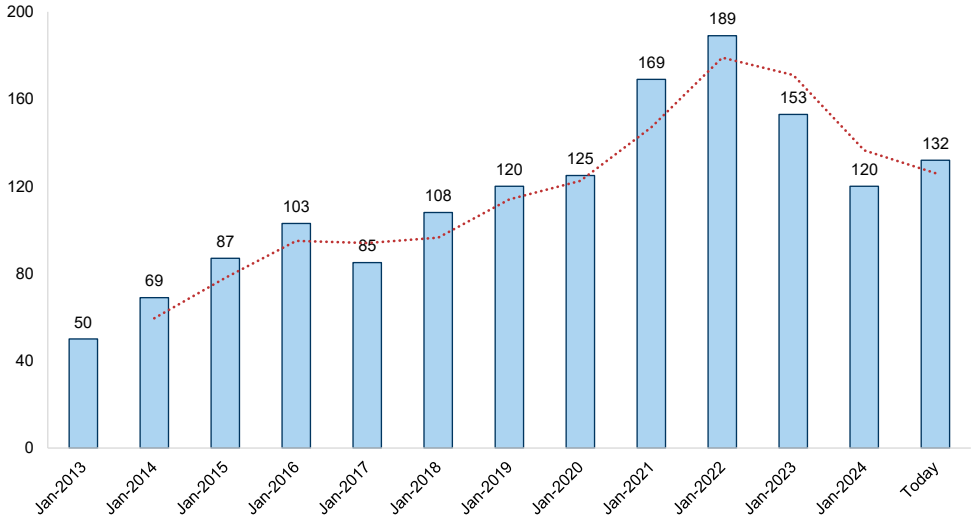
FTC considerations have become more restrictive in recent years. The Federal Trade Commission, responsible for consumer protection law enforcement to prevent (among other things) unfair business practices, has increased scrutiny of M&A within the biopharma sector. Draft guidelines introduced in July 2023 focus on mergers that either: i) preclude a potential competitive entrant within a concentrated market, or ii) increase concentration within an already concentrated market. This scrutiny played out in the agency's challenge to AMGN's acquisition of HZNP, despite limited precedent for that challenge, and via the extended review of PFE's acquisition of SGEN. With anti-trust considerations at the forefront, banker panels at our recent conferences have cited an increase in interest in bolt-on styles acquisitions, which favor smid-cap acquisitions over mergers between companies of similar size/scale.

Funding in biotech: long road to profitability

The past several decades have witnessed a proliferation in the number of biotech companies, driven by innovation, access to capital, and unmet need; there are 133 listed biotech companies in the XBI today vs. 65 when we last wrote this report and 50 a decade ago. We note that there has been a contraction since the peak in number of listed biotech companies over the prior three-year period, reflecting a combination of acquisitions, reverse mergers, de-listings, and bankruptcies, though recent IPOs have driven a slight uptick year-to-date.

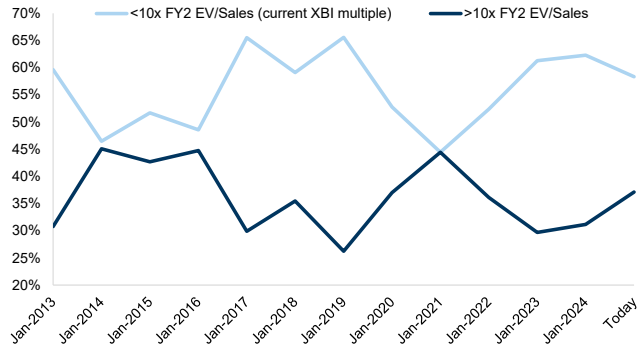
With the expansion, we also observe a shift in the complexion of XBI constituents, with a smaller portion of these companies more than two years from revenue than at peak in 2022. Consistent with this observation, there is also a relatively greater portion of companies trading <10x FY2 sales compared to the 2021 peak of the market.

Exhibit 22: The number of constituents in the XBI has increased since Jan amidst the recent pick up in IPOs



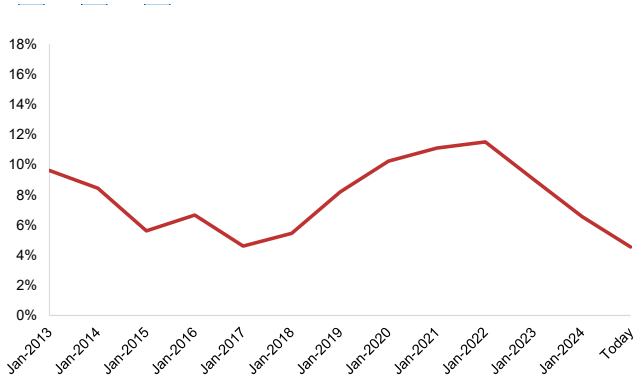
Source: Goldman Sachs Global Investment Research

Exhibit 23: XBI constituents EV/sales breakdown



Source: FactSet, Goldman Sachs Global Investment Research

Exhibit 24: % of XBI constituents with no FY2 sales



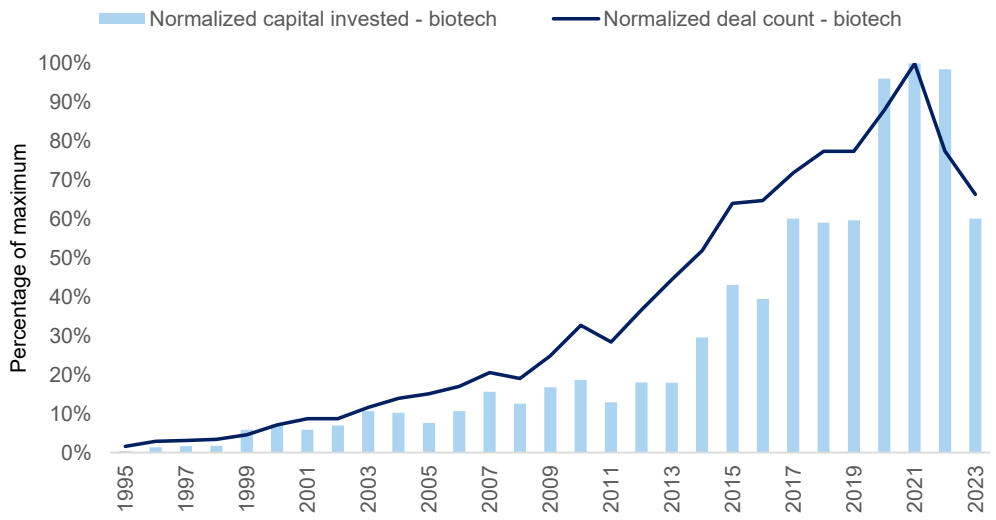
Source: FactSet, Goldman Sachs Global Investment Research

Central to the proliferation of biotech companies has been access to capital. Drug development is a long process, characterized by many failures offset by a few large successes (which "pay for" the development costs associated with these failures), and biotech companies will require multiple capital infusions throughout their life cycle. Private and public markets investors contribute to this ecosystem, via early series funding rounds, initial public offerings, and often multiple secondary financing rounds prior to the company becoming cash flow profitable (or acquired); many never reach this phase.

Private funding: Private markets are the primary sources of capital for early stage biotech companies (through Ph1/Ph2 studies), although biotech companies may become public at various stages of development. Over the past three years we have seen a decline in the number of biotech deals executed in the private markets, however,

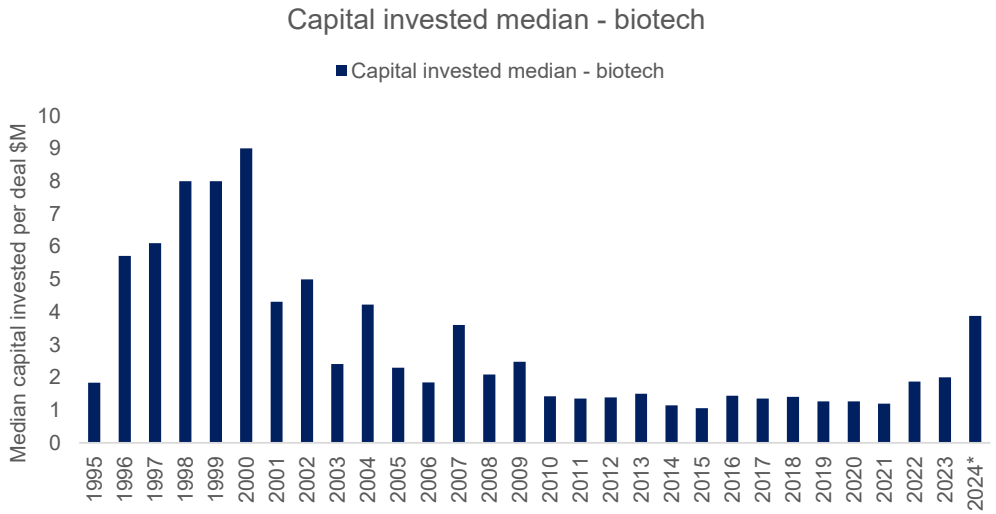
absolute levels of deal activity remain above normal and the capital invested per deal has also increased off trough. We believe that this reflects consolidation around higher-conviction and/or later-stage assets, particularly as public market funding has become more challenging.

Exhibit 25: Normalized deal count and invested venture capital trends for biotech



Source: PitchBook, Goldman Sachs Global Investment Research

Exhibit 26: Median invested venture capital per deal in biotech



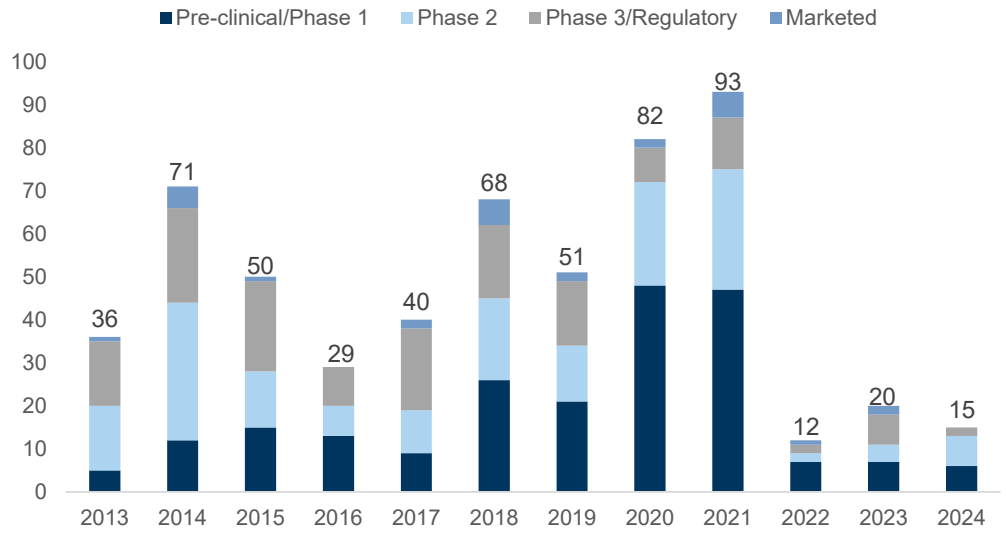
2024 data based on YTD (as of 09/09/2024)

Source: PitchBook, Goldman Sachs Global Investment Research

Initial public offerings: Often a pivotal moment in the life cycle of a biotech company is the initial public offering. While these have historically occurred during mid-to-late stage development (Ph2/Ph3 or commercial stage), we saw a mix shift in stage of company at IPO toward earlier stage (and thus riskier) assets during the most recent XBI bull

market. This trend has reversed to some degree, but we continue to see >40% of IPOs pre-Ph2 development year-to-date in 2024. We also monitor the number of IPOs per year, which peaked in 2021 (amid COVID-informed capital infusions into the biotech sector); the number of IPOs declined rapidly in 2022-2023. IPO performance is a closely watched metric within biotech markets, where we highlight performance by class is related to stage of development at IPO.

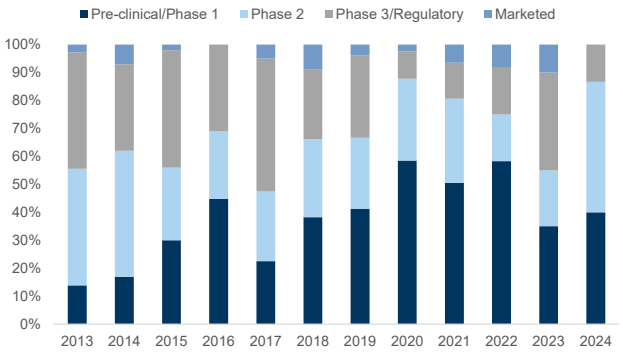
Exhibit 27: Significant increase in biotech IPOs over the past decade include an increase in preclinical/Ph1 assets



2024 data as of 09.09.2024

Source: Goldman Sachs Global Investment Research, FactSet

Exhibit 28: with >50% of IPOs in 2019-22 preclinical/Ph1 at the time of IPO (vs. <30% in 4 of the 6 prior years)



Source: Goldman Sachs Global Investment Research, FactSet

Exhibit 29: Performance post-listing has skewed better for later-stage companies

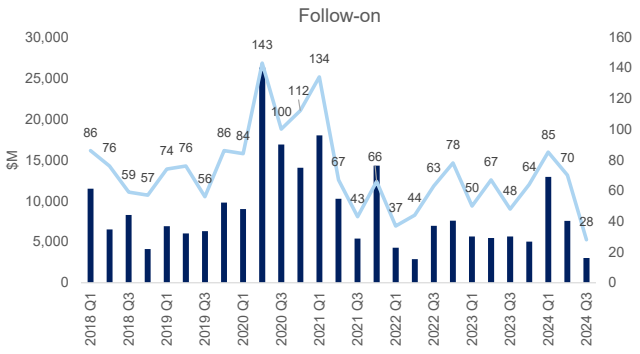
			Performance vs. XBI		
Phase at IPO	Ticker	Offer date	Listing day	Follow-through post listing day	vs. IPO price
Preclinical	GUTS	02/01/24	-13%	-86%	-88%
Preclinical	MGX	02/08/24	-33%	-79%	-90%
Preclinical	TELO	02/08/24	-31%	12%	-24%
Phase 1	BOLD	03/27/24	-11%	-81%	-83%
Phase 1	CHRO	02/15/24	-20%	-86%	-90%
Phase 1	RAPP	06/06/24	24%	-13%	10%
Phase 2	ACTU	08/12/24	6%	-5%	1%
Phase 2	ANRO	02/01/24	30%	-43%	-22%
Phase 2	ALMS	06/27/24	-17%	-17%	-32%
Phase 2	ARTV	07/18/24	0%	0%	0%
Phase 2	CTNM	04/04/24	-5%	5%	0%
Phase 2	KYTX	02/07/24	35%	-85%	-78%
Phase 2	OSTX	07/31/24	-37%	67%	5%
Phase 3	AVBP	01/25/24	11%	28%	43%
Phase 3	CGON	01/24/24	95%	-9%	88%

Source: FactSet, Data compiled by Goldman Sachs Global Investment Research

Secondary offerings: Given biotech companies will often require multiple capital

infusions prior to commercialization and reaching profitability, a robust secondary market is also necessary for a healthy biotech market. Companies will most frequently raise capital following key clinical read-outs and regulatory actions, though they may raise money in the interim of such events. The secondary market has been somewhat more resilient than that for IPOs over the past several years, and is expected to recover ahead of the more risky initial public offerings. Despite a contraction in 2022-2023, compelling clinical evidence was sufficient to support attractive secondary financing rounds in select cases. We note the expectation of a raise can in some cases limit performance following a positive event, as investors anticipate dilution and a better entry point via the secondary offering.

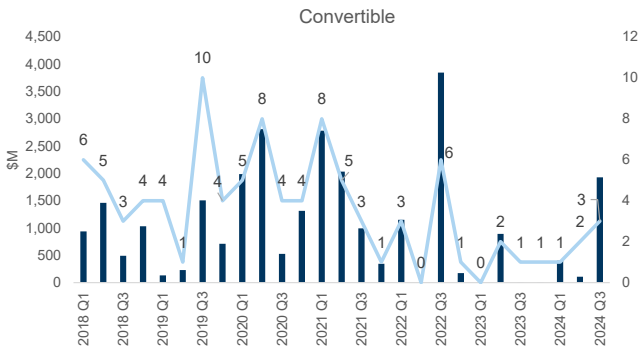
Exhibit 30: Deal value and number of follow-on offerings across biotech from 2018 to-date



2024 Q3 data as of 09-06-2024

Source: Dealogic

Exhibit 31: Deal value and number of convertible offerings across biotech from 2018 to-date



2024 Q3 data as of 09-06-2024

Source: Dealogic

Private investments in public equities: A recent and closely watched trend within the biotech sector is private investments in public equities (known as PIPEs), wherein a select group of investors provide direct financing to a public equity. This structure may include selective disclosures relating to upcoming clinical events, and has drawn scrutiny in recent months.

Catalyst path

Biotech performance, particularly among clinical stage companies, is primarily driven by "catalysts": events wherein investors gain additional insight into the likelihood a drug will work, come to market, and compete. These include:

- **Results from a clinical study.** Data can be provided through a press release (termed "topline results" because there are limited details and the results are generally provided as soon as possible following the collection of data), at a medical conference, or via publication in a medical journal. Results may be presented in multiple of these forums.
- **Results from a competitor.** As above, results can be disclosed in a variety of formats, but will inform investors on the competitive landscape for a given product.
- **Regulatory actions.** These include activity during drug development (minutes from regulatory planning meetings, clinical holds) or in the process of approving a new

drug (acceptance of the filing, decision to host an Advisory Committee meeting, Advisory Committee panel vote, and PDUFA [approval date]).

Depending on the event, these can come at expected or unexpected times, and can have highly variable impact on biotech stocks. Positive results, particularly from a late-stage study, can solidify positive expectations that a drug will work and come to market. By contrast, a negative outcome could cast doubt on the probability that the drug will reach patients. Thus, step changes in probability of success for the product are often the result of these catalysts, driving the large stock moves characteristic of the sector.

Ahead of catalysts that are planned, investors will predict the most likely outcomes (based on analysis of the drug, market, trial design, and statistical assumptions), and will seek to understand expectations ahead of the event, in order to take positions that can be rewarded if correct about the outcome.

In a healthy market, positive results will be rewarded with significant and sustained outperformance, sometimes offering the opportunity for a secondary offering. However, a characteristic of the recent biotech bear market has been lack of follow-through momentum on the back of even positive clinical events as investors seek to take profits where they are available.

Exhibit 32: 2024 catalyst reactions

Event Date	Ticker	Event	Outcome	Day 1 Perf	Follow Through Perf	Follow Through Perf vs XBI
9/10/2024	CNTA	Positive Ph1 ORX750 data in acutely sleep deprived healthy volunteers for NT1, NT2, IH	Positive	-2%	-6%	-7%
9/10/2024	ROIV	Introduction of new asset (mosliciguat) in PH-ILD	Positive	-2%	2%	1%
9/10/2024	TERN	Positive Ph1 data for TERN-601 in obesity	Positive	23%	-5%	-6%
9/10/2024	VRDN	Topline Ph. 3 THRIVE data for veligrotug (VRDN-001) in moderate-to-severe active TED	Positive	32%	6%	5%
9/9/2024	AVBP	Positive Ph1b FURTHER data for firmo in PACC EGFRm NSCLC patients	Positive	-1%	-9%	-10%
9/9/2024	IMVT	Detailed Ph2 data of batoclimab in Graves' disease	Positive	-8%	-8%	-9%
9/9/2024	RLAY	Positive data in PI3Ka-mutated HR+/HER2- breast cancer	Positive	52%	-18%	-19%
9/9/2024	CYTK	Early Phase 1 data support advancement of CK-586	Positive	3%	-4%	-5%
9/5/2024	VOR	Positive additional Ph1 trem-cel data in R/R AML	Positive	-2%	28%	28%
9/3/2024	VLA-FR	Positive Ph2 data for Lyme booster vaccination VLA15	Positive	1%	-3%	-4%
9/3/2024	ATHA	Fosgo missed primary endpoint of Ph2/3 LIFT-AD study	Negative	-8%	-83%	-83%
9/4/2024	BMRN	Investor Day including long-term financial guidance	Positive	-2%	-6%	-6%
9/3/2024	DNLI	FDA alignment on accelerated approval pathway in Hunter syndrome	Positive	3%	8%	8%
9/3/2024	RXRX	Mixed efficacy data in CCM	Mixed	-17%	6%	6%
9/2/2024	ARWR	Positive Ph3 PALISADE data in FCS	Positive	0%	-12%	-10%
8/30/2024	ALNY	Detailed Ph3 HELIOS-B data	Positive	-8%	0%	2%
8/30/2024	KRYS	Ph1 KB301 data in lateral canthal lines and wrinkles of the decollete	Positive	0%	2%	4%
8/27/2024	NBIX	Positive but underwhleming Ph2 data for NBI'568 in schizophrenia	Mixed	0%	-20%	-18%
8/22/2024	JAZZ	Ph3 Epidyolex Japan study failed	Negative	0%	-8%	-7%
8/22/2024	BIOAb.ST	Eisai announced the approval of Leqembi in the UK for the treatment of MCI and mild dementia due to Alzheimer's disease	Positive	3%	6%	7%
8/14/2024	SNDX	Niktimvo approval ahead of PDUFA	Positive	-1%	-6%	-9%
8/13/2024	ASND	PDUFA for Yorvipath (TransCon PTH) in hypoparathyrodism	Positive	9%	-19%	-21%
8/12/2024	RVNC	Proposed acquisition by Crown Laboratories	Positive	87%	0%	-4%
8/8/2024	APLS	Ph3 data for subcutaneous Empaveli in IC-MPGN and C3G	Positive	12%	2%	-2%
8/8/2024	NTLA	Topline Ph2 results for NTLA-2002 in hereditary angioedema (HAE)	Positive	5%	-10%	-14%
7/31/2024	FGEN	Topline results from Phase 3 studies of pamrevlumab in pancreatic cancer	Negative	-48%	-27%	-26%
7/29/2024	SNDX	Revumenib PDUFA pushed out	Negative	-10%	-17%	-15%
7/26/2024	BIOAb.ST	CHMP issues negative opinion on Leqembi's approval in the EU in Alzheimer's disease	Negative	-34%	15%	18%
7/25/2024	SAGE	Ph2b data for SAGE-324 in essential tremor	Negative	1%	-28%	-26%
7/22/2024	IONS	Six-month Ph1/2 data on antisense oligonucleotide (ASO) ION582 in Angelman syndrome	Positive	6%	-16%	-16%
7/18/2024	PHAT	PDUFA for Voquezna (vonoprazan) label expansion to non-erosive GERD (NERD)	Positive	-8%	67%	66%
7/18/2024	RARE	Alignment reached with the FDA on the Ph3 study for ASO GTX-102 in Angelman syndrome	Positive	-3%	32%	30%
7/17/2024	FDMT	24-week 4D-150 data from the broader population extension in wAMD; and safety update in wAMD and DME	Positive	-32%	-14%	-13%
7/10/2024	ARQT	Approval in Atopic Dermatitis a relief. Label inline with expectations	Positive	-2%	7%	4%
7/10/2024	AMLX	Acquisition of relatively de-risked asset builds late-stage pipeline	Positive	25%	24%	21%
7/9/2024	IDYA	Positive Ph2 IDE397 clinical data update	Positive	-2%	-6%	-11%
7/9/2024	QURE	Additional Ph1/2 data from gene therapy AMT-130 in Huntington's disease	Positive	76%	-18%	-23%
6/6/2024	BMRN	Decision to retain Roctavian in hemophilia A	Positive/Neutral	1%	5%	-2%
6/28/2024	PTCT	CHMP issues negative opinion again though Translarna expected to remain on the market through year-end	Negative	-12%	6%	-1%
6/28/2024	RCKT	Kresladi CRL in LAD-I due to CMC requests	Negative	0%	-12%	-18%
6/26/2024	LYEL	First ROR1 CAR T data is confounded by safety signal	Negative	-36%	-12%	-19%
6/26/2024	RPTX	Positive MINOTAUR phase I trial presented at ESMO GI Congress 2024	Positive	-1%	-17%	-24%
6/25/2024	TRDA	Preliminary ph1 data in ENTR-601-44 in DMD / 100mn registered direct offering	Positive	4%	1%	-6%
6/24/2024	ALNY	Positive Ph3 HELIOS-B in ATTR-CM (positive readthrough to IONS and NTLA)	Positive	35%	18%	12%
6/24/2024	HRMY	FDA approval for Wakix in pediatric patients with excessive daytime sleepiness	Positive	0%	24%	18%
6/24/2024	ARGX	Vyvgart Hytrulo FDA approval in CIDP	Positive	12%	22%	16%
6/24/2024	HCM	EU approval of fruquintinib in later line mCRC received by commercial partner	Positive	0%	-7%	-12%
6/24/2024	RXRX	Download Day	Positive	6%	-31%	-36%
6/21/2024	ZELA.CO	Phase 1b MAD data for amylin analogue petrelintide in obesity	Positive	19%	17%	10%
6/20/2024	JAZZ	Ph2b suvecaltemide study in ET failed	Negative	-5%	-2%	-12%
6/20/2024	SRPT	FDA approval for broad label for Elevidys in DMD	Positive	5%	4%	-6%
6/20/2024	PTCT	Interim results from Ph2 study of PTC-518 in Huntington's Disease	Positive	-7%	-3%	-13%
6/18/2024	ITCI	Positive Ph3 data for Caplyta in major depressive disorder	Positive	10%	-1%	-11%
6/18/2024	TSHA	Ph1/2 TSHA-102 gene therapy data in adult and pediatric Rett patients	Mixed	-26%	-22%	-32%
6/17/2024	AGIO	Full Ph3 Pyrukynd data in non-transfusion dependent thalassemia at EHA	Positive	-3%	4%	-5%
6/17/2024	KROS	Regulatory update for KER-050 in LR-MDS	Positive	-10%	23%	14%
6/17/2024	BNTX	Clinical hold on HER3 ADC trial due to safety concerns	Negative	-4%	12%	3%
6/13/2024	URGN	12-month durability data from Ph3 study of UGN-102 in LG-IR-NMIBC	Positive	38%	-21%	-27%
6/11/2024	SAGE	Positive Ph2 SURVEYOR data to support HD-CAB as a logical endpoint for evaluation of dalzanemdor in Huntington's disease	Positive	-3%	-29%	-36%
6/7/2024	ZELA.CO	Survodutide Phase 2 data in NASH presented at EASL	Positive	0%	38%	30%
6/7/2024	FDMT	Additional Ph1/2 4D-710 dose exploration data in CFTR modulator-ineligible/intolerant cystic fibrosis	Positive	1%	-31%	-39%
6/7/2024	GERN	Rytelo approved with label in-line with best-case scenario	Positive	18%	-4%	-13%
6/7/2024	RLAY	New Program & Platform event	Positive	9%	-2%	-10%
6/6/2024	MCRB	MCRB sells VOWST to Nestle Health Science	Negative	-25%	23%	17%
6/6/2024	VTYX	Positive preclinical data for NLRP3i VTX3232 in obesity	Negative	-38%	-36%	-43%
6/5/2024	BBIO	Ph2 data of infigratinib in achondroplasia at 12 and 18 months	Positive	3%	0%	-5%
6/5/2024	RPTX	Lunresertib plus camonsertib combination granted Fast Track Designation by FDA	Positive	14%	-30%	-35%
6/5/2024	VIR	Updated Ph2 combination data of tobevibart and elebsiran in hepatitis B	Positive	20%	-38%	-43%
6/4/2024	NTLA	Positive long-term Ph1 data from gene-edited therapy NTLA-2002 in HAE	Positive	-1%	-13%	-21%
6/4/2024	AGIO	Positive Ph3 data for Pyrukynd in transfusion-dependent thalassemia	Positive	8%	-6%	-15%
6/4/2024	RCUS	GILD and RCUS Initial Ph1b/2 etruma (A2a/2b) combo data in 3L mCRC and updated Ph2 data for domvanalimab (anti-TIGIT) combos in 1L gastric cancer	Positive	1%	6%	-2%
6/3/2024	IONS	Ph3 donidalorsen data in HAE	Positive	3%	10%	2%
6/3/2024	IDYA	Darovasertib investigator-sponsored trial and Ph2 company-sponsored data in neoadjuvant uveal melanoma presented at ASCO	Positive	6%	-7%	-15%
6/3/2024	ARWR	Positive topline Ph3 plozasiran PALISADE data support a path to approval	Positive	7%	-15%	-23%
6/3/2024	RPRX	RPRX announces pricing of $1.5bn in senior unsecured notes	Negative	-2%	4%	-5%
6/3/2024	ALKS	Positive ALKS-2680 ph1b data for NT1 population	Positive	3%	10%	2%
6/3/2024	GMAB	Acasunlimab (PD-L1x4-1BB) Phase 2 data in 2L+ NSCLC presented at ASCO	Positive	2%	-7%	-15%

Source: Goldman Sachs Global Investment Research, FactSet

Exhibit 33: 2024 catalyst reactions (continued)

Event Date	Ticker	Event	Outcome	Day 1 Perf	Follow Through Perf	Follow Through Perf vs XBI
5/31/2024	RARE	Positive topline Ph3 data of DTX401 in GSD1a	Positive	4%	40%	29%
5/31/2024	IMCR	Data update from Phase 1/2 trial in late-line, advanced cutaneous melanoma presented at ASCO	Positive	5%	-33%	-44%
5/28/2024	INSM	Positive Ph3 ASPEN data in bronchiectasis	Positive	118%	51%	40%
5/23/2024	TNGX	Deprioritization of USP1 and extension of the cash runway into 2027 (vs prior through late 2026)	Negative	-4%	37%	26%
5/23/2024	RPRX	Expansion of RPRX's deal with CYTX (~$575mn total deal)	Negative	-2%	3%	-7%
5/22/2024	EXAI	Headcount reductions, extension of the cash runway, and positive initial pkc-theta data	Positive	5%	1%	-6%
5/20/2024	ERAS	Deprioritization of ERAS-007 and ERAS-4 coupled with headcount reductions of ~18%; Addition of ERAS-0015 and ERAS-4001 into the pipeline	Positive	14%	37%	30%
5/15/2024	OLMA	Ph.1b/2 ribo combo data update at ESMO Brest Cancer Conference	Positive	-3%	25%	18%
5/14/2024	DVAX	PDUFA for Heplisav-B sBLA for label expansion in hemodialysis population	Negative	0%	-1%	-10%
5/14/2024	ASND	PDUFA for TransCon PTH in hypoparathyrodism postponed to August	Mixed	-5%	-10%	-18%
5/13/2024	CYTK	Detailed results from Phase 3 SEQUOIA-HCM study at ESC Heart Failure in Lisbon	Positive	-7%	-7%	-17%
5/9/2024	INSM	Positive Ph2 TPIP PH-ILD data	Positive	1%	176%	165%
5/6/2024	GOSS	Strategic partnership with Chiesi Group to commercialize and develop seralutinib	Positive	5%	14%	5%
5/3/2024	CGON	Ph3 BOND-003 data update, including 12-month DoR	Mixed	-8%	1%	-9%
4/29/2024	TERN	Positive Ph1 interim PK data of TERN-701 in chronic myeloid leukemia	Positive	4%	109%	94%
4/23/2024	DAWN	Ojemda approved for relapsed pLGG	Positive	8%	-15%	-32%
4/17/2024	SAGE	Negative topline Ph2 data of SAGE-718 in mild cognitive impairment (MCI) in Parkinson's Disease (PD)	Negative	-20%	-40%	-57%
4/16/2024	ITCI	Positive Ph3 data of Caplyta in major depressive disorder & FPO	Positive	23%	-6%	-22%
4/15/2024	RARE	Ph1/2 dose escalation and expansion data of GTX-102 in Angelman syndrome	Mixed	-9%	31%	17%
4/12/2024	ELVN	□Positive initial Ph1a ELVN-001 data in chronic myeloid leukemia (CML)	Positive	-12%	9%	-3%
4/11/2024	ARVN	Prostate cancer program outlicensed to Novartis	Positive	1%	-33%	-42%
4/10/2024	AMLX	Positive Ph2 interim data of AMX0035 in Wolfram syndrome	Positive	-8%	4%	-5%
4/5/2024	CYTK	48-week open label extension data from FOREST-HCM study	Positive	5%	-26%	-36%
4/4/2024	AMLX	Withdrawal of Relyvrio from US and Canada markets	Negative	-1%	-2%	-12%
4/2/2024	FGEN	Topline results from Phase 1 monotherapy study of FG-4346 in prostate cancer	Negative	-8%	-82%	-91%
4/2/2024	VERV	Halted enrollment in Ph1b heart-1 for gene-editing VERVE-101 for HeFH following observance of a safety signal	Negative	-35%	-29%	-39%
4/2/2024	ROIV	Positive Ph2a data in non-infectious uveitis	Positive	5%	13%	4%
4/2/2024	KNSA	Topline data from Cohort 4 of Phase 2 study of abiprubart in rheumatoid arthritis	Negative	-5%	30%	21%
4/1/2024	GRTS	GRANITE Ph2 PFS and ctDNA data in 1L MSS-CRC	Negative	-9%	-79%	-84%
3/29/2024	UTHR	UTHR's motion for a temporary restraining order and preliminary injunction for Tyvaso in PH-ILD are denied	Negative	0%	51%	46%
3/20/2024	TSHA	Positive longer-term Ph1/2 TSHA-102 gene therapy data in Rett syndrome	Positive	32%	-22%	-26%
3/19/2024	ELVN	PIPE and qualitative first results in CML	Positive	39%	32%	26%
3/15/2024	MDGL	MDGL Rezdiffra approval	Positive	11%	-14%	-18%
3/15/2024	GERN	FDA AdCom panel votes in favor of compelling benefit/risk of imetelstat in lower-risk myelodysplastic syndrome	Positive	92%	31%	26%
3/13/2024	TSVT	Briefing documents for FDA ODAC meeting	Mixed	-15%	12%	10%
3/12/2024	ACAD	Negative topline Ph3 data for Nuplazid in negative symptoms of schizophrenia	Negative	-17%	-20%	-23%
3/11/2024	VTYX	clinical data from NLRP3 portfolio and corporate strategy updates	Positive	-19%	-74%	-76%
3/10/2024	MLTX	Positive 24-week data from ARGO trial of sonelokimab in PsA	Positive	0%	2%	2%
3/8/2024	AMLX	Phase 3 misses in amyotrophic lateral sclerosis	Negative	-82%	-24%	-23%
3/4/2024	BBIO	Out-license of the European rights of acoramidis to Bayer AG in exchange for $310mn in upfront and near-term milestone payments and tiered royalties in the low 30s percent	Negative	-9%	-13%	-12%
2/26/2024	ZELA.CO	Fibrosis benefit in MASH/NASH a positive surprise	Positive	36%	38%	36%
2/20/2024	RAPT	Clinical hold pauses further zelnecirnon development	Negative	-74%	-72%	-79%
2/20/2024	IOVA	Amtagvi in 2L+ melanoma is first approved TIL therapy	Positive	31%	-22%	-29%
2/5/2024	FDMT	Wet AMD gene therapy moving to Ph3 post strong results	Positive	85%	-51%	-63%
1/27/2024	PTCT	Negative CHMP decision on Translarna and product removal from the EU market.	Negative	0%	19%	7%
1/22/2024	SGMT	Positive Ph2b FASCINATE-2 biopsy data confirm compelling profile in NASH	Positive	170%	-80%	-91%
1/16/2024	ALLK	Dual Phase 2 misses for lirentilimab in atopic dermatitis (AD) and chronic spontaneous urticaria (CSU)	Negative	-60%	-49%	-60%
1/10/2024	SANA	Positive Ph1 CD19 data and preclinical type 1 diabetes data	Positive	39%	-31%	-37%

Source: Goldman Sachs Global Investment Research, FactSet

Biotech 101

Quick history

Human Genome Project provided the foundation for accelerating biotechnology innovation. Drug development in biotechnology accelerated due to the Human Genome Project (the human genome was sequenced in 2003), enabling scientists to identify novel genetic targets that cause disease and leading to the genome revolution. In addition, since 2001, the cost of sequencing the human genome has declined faster than Moore's law would predict, to <$1K from $100M. As the cost of sequencing a single genome improved, so too did the drug developer's ability to 1) identify key biological genetic targets to address underlying disease, 2) generate animal models with

predictive potential to ascertain clinical benefit in humans, and 3) identify biomarkers that are early indicators of drug activity and safety.

Moreover, this era witnessed the emergence of new technological modalities such as cell therapy, antibody drug conjugates, RNA-based therapies (RNAi, mRNA, etc), CRISPR, and bi-specific antibodies (described in greater detail below). This stood in contrast to the prior decades, where the exclusive therapeutic modalities comprised small and large molecules (i.e. antibodies). These technologies can potentially be leveraged across multiple indications and/or therapeutic categories, which provides the theoretical potential for biotech to be scalable and spread clinical risk across a greater number of indications.

COVID-19 drove investment toward biotechnology assets. Given the role biotechnology and pharmaceutical companies played in addressing COVID-19 there was a significant influx of capital into the industry throughout the pandemic. While this began with investment into COVID-specific market participants (e.g. MRNA, BNTX), returns accrued via those investments were then available for re-investment into the industry more broadly. Further, investors began seeking additional exposure to the biotechnology sector, with perception of the total addressable market and path to clinical success for nascent companies informed by the vaccine successes, and sometimes inflated vs. the realities of drug development.

For example, Operation Warp Speed facilitated a rapid path for COVID-19 vaccines through the clinic, with approvals less than one year after the drug candidates were identified. By contrast, it takes an average of eight years (96.8 months) to develop a new drug, with an estimated cost of >$2B (including the cost of failed candidates). Similarly, the probability of clinical success (as described above) is generally low for drugs that have not yet reached Ph3 development.

Multi-year return to normal. In the wake of the pandemic driven exuberance in the biotech sector, the realities of drug development (an estimated 90% of drugs entering Ph1 will fail to reach patients), a negative estimate revision cycle across the sector (Exhibit 11), and the backdrop of inflation/rising rates led to a three year (and ongoing) period of significant XBI underperformance. While the rate environment remains difficult to navigate, biotech markets have now absorbed a significant portion of the pulled-forward new issuance that characterized 2020/2021 (Exhibit 27), and the estimate revision cycle has demonstrated early signals that it is turning. Further, a spate of M&A in late 2023/early 2024 drove renewed interest in the returns available within the sector. While too early to call a full reversal in biotech markets, the operating environment is incrementally improved (albeit this improvement has not been linear) and we view the backdrop as supportive of a stock-picker's market.

Therapeutic areas

Within biotech, we divide diseases into subcategories called "therapeutic areas", which broadly map to medical specialties: cardiometabolic disease, oncology, neurology, immunology, virology, and others. Companies may operate within a single or across multiple therapeutic areas.

We also discuss specific therapeutic areas in more detail within the Appendix. However, at a high level the areas of greatest interest across the industry can be sorted across key verticals, including (non-exhaustive):

Cardiometabolic disease: heart and blood vessel diseases, obesity, diabetes, liver disease, and others. Obesity is a therapeutic area of considerable interest, given its prevalence within the US and globally.

Neurology: disease of the central and peripheral nervous system, which can be further categorized into neurodegeneration (e.g. Alzheimer's disease, Parkinsons' disease, ALS/Lou Gehrig's disease) or neuropsychiatry (e.g. depression, schizophrenia, bipolar disorder).

Oncology: cancer, which can also be categorized further into solid tumors (cancer within specific tissues, like the lung or breast tissue) and liquid tumors/hematology (blood cancer). There are many subtypes within the broader umbrella of cancer, based on the type of cells and tissue location of the cancer, but all are characterized by uncontrolled cell growth.

Hematology: blood disorders, including blood cancers, anemia, bleeding disorders, among others.

Opthamology: diseases of the eye.

Nephrology (renal disease): there are many potential diseases of the kidney, sometimes leading to kidney failure requiring dialysis and/or kidney replacement.

Inflammation and Immunology: a large umbrella comprising diseases of the immune system, wherein immune cell populations are (over)activated when they should not be, against self-targets (i.e. autoimmune diseases) or foreign substances (i.e. allergies).

Infectious disease: illnesses caused by germs, including viruses, bacteria, and fungi.

Rare disease: diseases that affect a small percentage of the population, which are often due to genetic abnormalities.

Major types of drugs

There are many different technologies that can be used to address disease, though which technology is best suited will depend on the cause of that disease, the goal of treatment, and safety requirements. In some cases, drugs across multiple technologies will be available. Some of these technologies are fully de-risked (small molecules, monoclonal antibodies), while others are in early days and have significant room for optimization (e.g. base editing, cell therapy).

Understanding drug nomenclature

Drug candidates are called different names at various stages of development.

- Chemical names – correspond to the molecular structure of the drug. Early-stage drugs are generally named a prefix of the company's abbreviated name followed by a number.

- Proprietary (branded) names – the trademarked drug name that appears on marketing material. Regulatory agencies ensure that the name will not confuse physicians by sounding too similar to another drug. This is the drug name patients are most familiar with via advertising and usually begins in uppercase.
- Nonproprietary (generic) names – a simplified name used to describe the molecule. During clinical development companies apply to regulatory and/or international bodies for a unique nonproprietary drug name. The suffix of the generic name usually indicates which class of drugs the candidate belongs in (e.g., "-tinib" in ibrutinib indicates it is a tyrosine kinase inhibitor; drugs that end in "-mab" are antibodies).

Types of drug candidates

Small molecules: low molecular weight, organic compounds with simple chemical structures that can pass through cellular membranes to reach intracellular targets (such as proteins within the cell vs. on its surface), lending predictable PK/PD (drug behavior) profiles compared to biologics (described below). Small molecules are highly stable, require simple manufacturing and regulatory procedures, and are more sensitive to generic competition. This category includes aspirin, penicillin, and atorvastatin (Lipitor).

Biologics: drug products synthesized from biological sources, containing highly complex structures that are more sensitive to degradation. This translates to more expensive and complicated drug manufacturing processes and diversified avenues for therapeutic benefit. This category includes monoclonal antibodies, proteins, gene therapies, and adalimumab (Humira).

Vaccines: biological preparations that contain a pathogen (disease-causing agent) variant to stimulate the body's immune response and build immunity against existing disease.

- Live-attenuated: contains weakened, live pathogens from either bacteria or virus, which stimulates a significant immune response such that additional boosters are not always necessary.
- Inactivated: introduces a dead virus/bacterium to the host cell, which is weaker than live-attenuated and usually requires multiple rounds of doses.
- Subunit: delivers parts (rather than the whole) of a pathogen, such as surface proteins, secreted toxins, or polysaccharide chains, which are suitable for immunocompromised individuals.
- Toxoid: employs inactivated toxins ("poison" or protein produced by organisms that are harmful to other organisms) to disrupt the toxic activity created by bacteria (rather than directly targeting the bacteria), which is important in toxin-mediated diseases.
- Viral vector: delivers the genetic code of the antigen (any substance that causes the body to initiate an immune response) to the host cell via a harmless viral shell.
- messenger RNA: delivers a piece of mRNA (molecules that carry the genetic instructions to make proteins) corresponding to a viral protein.

Peptide therapy: use of peptides (short chains of amino acids [the building blocks of

proteins] capable of easy absorption) to improve functioning, cellular communication, and increase the concentration of proteins such as creatine, testosterone, and collagen for muscle growth, hormone regulation, and age-related decline.

- PEGylated agents: pegylation is the process of attaching repeating units of polyethylene glycol to polypeptide drugs (long chains of amino acids). Polypeptide drugs are limited in therapeutic effectiveness by their rapid degradation by enzymes (proteins that build up and break down substances) in the body. Pegylation can enhance drug stability, improve half-life, and limit immune reactions against the drug, by shielding the drug from this type of breakdown.
- Protein Degraders: biologics that leverage the body's natural protein disposal system to selectively target and break down disease-causing proteins, which offers the potential advantages of potency, iteration (allowing a single molecule to degrade multiple target proteins) and engagement of historically difficult ("undruggable") targets. There are multiple distinct approaches approved and in development within this class of therapy.
- Protein Replacement Therapy: treatments to replenish or supplement protein shortages in patients with absent or dysfunctional protein expression.

Antibodies (Ab): (also called immunoglobulins) are endogenous proteins (originate within the body) produced by the immune system that bind to molecules on the surfaces of cells (antigens) and elicit an immune response. Antibody therapies are, therefore, derived from the immune system's ability to ward off foreign invaders.

- Monoclonal antibodies (MAb): lab-derived proteins that serve as substitute antibodies and bind to an antigen to enhance the immune system's attack on cancerous, diseased, and foreign cells. Specifically, MAbs function to flag cancer cells for destruction, block immune system inhibitors, and deliver treatments via conjugation (the union of two chemical and/or biological structures).
- Bispecific antibodies: bispecifics can bind to two different antigens or two epitopes (part of the antigen that is recognized by an antibody) of the same antigen simultaneously. They have the potential to drive synergistic treatment effects leading to better clinical efficacy. Clinical validation of efficacy has been achieved for this class of drugs, but safety/tolerability is a key consideration and potential liability for the class. On the forward, several investigational treatments aim to improve tolerability, initial response, durability, combinability, and breadth of targets.

Conjugated agents: modality that enables targeted delivery of therapeutics using antibodies to deliver potent drugs to specific settings.

- Antibody-drug conjugates: biologics that combine the target specificity of an antibody with the anti-tumor efficacy of cytotoxic (toxic to living cells) agent (payload) via connection with a linker for potent and selective tumor cell targeting. Key areas of interest on the forward include expanding existing indications (i.e., into earlier lines and across tumors), developing next-generation technologies (via novel targets/antibodies, payloads, and linkers, noting that the earlier-generation ADCs are associated with a high level of potency but challenging toxicity profiles), and

evaluating combination strategies.

- Radiopharmaceuticals: radioactive agents conjugated to antibodies that are selectively taken up into certain organs and, in small doses, aid in tumor diagnosis via nuclear medicine imaging equipment. In larger amounts, radiopharmaceuticals are utilized in oncology treatments, as the radioactive properties can destroy cancerous tissue.
- Antibody oligonucleotide conjugates (AOC): biologics that combine antibody targeting and directed tissue delivery with high-precision oligonucleotide therapeutics via conjugation with a linker. Oligonucleotide therapeutics include either siRNAs or ASOs (described in more detail below).

Cell therapy: process wherein cells are genetically modified to enhance their therapeutic properties, amplified, preserved, and subsequently infused into a patient. Treatments can either be autologous (use the patient's own cells) or allogeneic ("off-the-shelf", uses healthy donor cells).

- Chimeric antigen receptor T-cell (CAR-T): engineered T cells (white blood cells that confer adaptive immunity ["built-up", specialized immunity that forms as a specific response to a foreign substance]) programmed to express CAR protein on their cell surface, which recognizes and binds to specific antigens (typically CD19 or BCMA proteins) on B cells (antibody-producing white blood cells) in order to kill the diseased B cells. B cells are responsible for mounting the hyperactive immune responses seen in inflammatory auto-immune diseases, and they are typically the target in B cell hematologic oncology cases.
- Natural Killer (NK): NK cells are white blood cells that destroy harmful, diseased cells without needing prior exposure to the pathogen. These fighters are part of the innate immune system (non-specific, first line of defense against pathogens) and recruit other immune cells via cytokine signaling (protein signaling that affects the immune system). NK-cell based therapeutics include autologous NK cell transfer, allogeneic NK cell transfer, and CAR-NK, which incorporates CAR-engineering to recognize tumor specific antigens, and enhance NK cells' killing of cancer cells.
- Regulatory T cells (Tregs): anti-inflammatory helper T cells that regulate the immune system's response in order to guard against the body attacking itself. CAR-Treg therapies are aimed at targeting antigens on inflamed tissues and suppressing the hyperactivity and inflammation seen in autoimmune diseases, transplant rejection, and graft versus host disease (GvHD).

Genomic medicine: uses a patient's genomic information to inform and personalize diagnosis and treatment.

- Gene Therapy: one-time delivery of a functional gene to replace an abnormal, disease-causing one. This irreversible gene modification process consists of a protein capsid binding to surface proteins on a cell, injecting their DNA or RNA into the cell, and depending on the type of vector (lentivirus, retrovirus, adenovirus, or adeno-associated virus) it will integrate the foreign DNA into the host DNA of non-dividing and dividing cells or just non-dividing cells. This has important

implications for whether the therapeutic gene will be copied with each cell division and will confer downstream effects. Gene therapy has made significant advances over the past decades, including the development of those with transformative disease-modifying impact. Current research efforts include the design of next-generation viral and non-viral delivery vectors and manufacturing improvements to address challenges such as high COGS, immunogenicity (ability to provoke an immune response against the drug), waning benefit over time, and limitations in carrying capacity.

- CRISPR/Cas9: gene editing tool that functions as a 'molecular scissor' capable of disrupting, deleting, or replacing a defective DNA section with normal, non-mutated section of DNA. This gene editing system consists of a guide RNA complementary to the target gene and Cas9 (enzyme) that creates a double-stranded break in the DNA to enable gene modification.
- Prime and base editing/Gene writing/alternative nucleases: next-generation gene editing tools that limit double-strand DNA breaks, thereby increasing precision, aim to achieve higher rates of editing efficiency, lower rates of off-target editing, and the ability to generate three or more edits simultaneously without the risk of chromosomal abnormalities. We note that there is some overlap in the capabilities of such tools and expect that each class of editor will co-exist within a toolbox wherein different technologies are leveraged based on the type of edit required, delivery vehicle, and genetic profile of the disease.

RNA-based therapy: process that enables the interception of genetic abnormalities at the level of RNA before it gets translated into dysfunctional proteins.

- messenger RNA (mRNA): therapies that instruct the patient's own cells to produce proteins. They have relatively low toxicity, high transfection efficiency, diminished risk for accidental DNA mutation, and are therapeutically beneficial in diseases lacking specific protein expression.
- RNA interference (RNAi): RNAi is the efficient biological process of gene silencing via mRNA knockdown. Small interfering RNA, also known as silencing RNA (siRNA), are double-stranded RNA sequences programmed to target specific mRNA sequences, bind, and recruit proteins to slice and/or repress the mRNA. The therapeutic benefit of this strategy is the silencing of disease-causing genes. Micro RNA (miRNA) are non-coding RNAs that regulate gene expression via gene silencing. miRNA is coming into view given its ability to address multiple targets, specifically providing tumor suppressor effects in oncology.
- Antisense Oligonucleotides (ASO): ASOs are stable, single-stranded DNA that bind complementarily to mRNA and prevent translation into protein. The field of ASOs have previously been challenged with renal toxicity, coagulation inhibition, stability, and thrombocytopenia, among other hurdles, which companies often aim to address via chemical modifications and advances in delivery technology.

Key considerations

There are two key questions a biotech investor must ask when evaluating a new

product:

Question #1: Will it work?

We call the way a drug exerts its effect its "mechanism of action" (MOA); for example, a small molecule drug might bind a mutated or faulty protein, turning off the action of that protein that has been causing disease. Identifying the mechanism of action is the first step in evaluating whether a drug will work.

From there, we can evaluate:

- **Is the drug effectively achieving its target?** Preclinical and clinical data can demonstrate that the drug is effectively achieving its target via changes in biomarkers (molecules in the blood and/or tissue associated with certain biological activity). For example, if the drug is designed to turn off a protein signaling network, decreases in the activity of proteins within this network would provide evidence of target engagement.
  - A related question will be whether there are "off-target" effects of the drug. Drugs often interact with molecules they are not explicitly designed to target, given there can be considerable similarities in the structure of molecules that play very different roles in the body. This can inadvertently impact biological processes that are not disease causing, and in some cases lead to safety considerations.
- **Do we know that the target it is hitting is relevant in this disease?** In some cases, we have a clear idea of what causes a given disease: a mutated protein (common in cancers), a miscoded gene (often a hallmark of rare disease), molecule levels that are too high (e.g. elevated cholesterol) or too low (e.g. hypoparathyroidism). When we evaluate a drug, it is important to understand whether the target of that drug is relevant to fixing the cause of the disease (or its symptoms). We call this "mechanistic rationale", and if the target is well-established we call it a "validated target".
  - Sometimes these targets play good roles and bad roles within the same individual. When the target is relevant to the disease, but also relevant to a necessary process for the health of the patient, the drug can cause "on target" effects, or negative consequences inherent to the drug. These can be managed, but not eradicated.
- **Is this type of drug the best one to hit this target or address this disease?** As described above, there are myriad types of drugs that can be employed to address disease; depending on the context, one technology might be better or worse than another. Some technologies are also less risky that the others, because there are many prior examples in similar disease areas (i.e. antibodies, small molecules). Others are more risky, often because there are a lot of component parts (i.e. CAR T therapies, antibody drug conjugates) which must each be optimized for the best possible drug candidate.

These questions inform our expectations for the efficacy and the safety of a drug, which together we call the clinical benefit/risk. The best drugs deliver efficacy at dose levels

that do not create safety issues (called the therapeutic index), though what is acceptable from a safety perspective depends on the severity of disease and magnitude of benefit delivered.

The risk profile for whether a drug is likely to work varies along each of these axes, which we call target risk, biology risk, and technology risk. Companies generally get rewarded for taking some risk in drug development (otherwise products are likely to be "me too" drugs, similar to those already on the market). However, taking risk along multiple of these axes at the same time (for example, using novel technology against an unproven target) can increase the likelihood a drug will fail in clinical studies. Collectively, the answers to these questions inform the probability of success we apply to each drug candidate in a given disease.

Question #2: How big is the market opportunity?

Sizing the market opportunity for a new drug is required to ascribe value to the program. As with any product, it all comes down to price and volume.

Volume:

- **Patient population.** Drugs may be developed to treat large indications (diseases) with millions of patients (e.g. cholesterol drugs), while others can be developed for extremely niche patient populations (e.g. gene editing programs). The number of patients who have a given disease is called the prevalence (the pool), while the number of patients that develop the disease in a given year is referred to as the incidence (amount of water going into the pool). For diseases with high mortality rates, the incidence and prevalence might be similar; for chronic conditions that do not impact lifespan, prevalence will be much larger than incidence. It is important to identify which of these populations is relevant for a given drug.
- **Diagnosis rate.** In order to receive a drug, a patient must know that they have the disease. In some diseases, the diagnosis rate is significantly lower than the incidence or prevalence of the disease. This may improve once a drug becomes available (as doctors have more motivation to run diagnostic screening).
- **How broad (narrow) the label will be.** Drugs will be approved based on the clinical population they are studied in, and in some cases this will reflect a narrow portion of the patient population with the disease (for example, lung cancer drugs that are only approved for patients with certain genetic signatures). It is generally difficult for drugs to be used outside of populations identified in the label, but off-label use (treatment of patients not specified in the label) can occur.
- **Market penetration.** The rate of uptake is driven by its clinical profile (see Question #1 above), competitive landscape, and reimbursement.
- **Adherence and compliance.** Patients do not necessarily remain on a drug indefinitely once they are prescribed the therapy. Adherence refers to the act of filling and acquiring a new prescription on time, while compliance refers to consistency in taking the drug as prescribed. Patients may not refill a drug if they do not like the side effects, or if it is not convenient for them.

Price:

- **Gross price.** In the US, companies set the price of the drug (gross price) based on the perceived value of that medication, the number of patients eligible for treatment, and other options available to patients on the market.
- **Net price.** However, companies will also negotiate rebates to Pharmacy Benefit Managers (PBMs) or the government (Medicaid and the VA), such that the realized price of the drug (net price) will be lower than the listed gross price. This difference is referred to as the gross-to-net discount.
- **Other considerations.** Biotech companies can employ different mechanisms to encourage use of a drug, including co-pay assistance or patient assistance programs. In some cases, PBMs and/or insurance companies will seek to restrict use of a drug via "prior authorization" requirements, sometimes called step edits: patients will be required to try and fail other, cheaper therapy before insurance will cover the drug.
- **Ex-US pricing.** Ex-US the price of a drug is often negotiated based on a value assessment, and this negotiation is required prior to launch in that country. As a result, launches in the EU are often delayed relative to the US.

Drug Development

Drug development is a long and arduous process, with many stages which are gated on the success of prior steps. While there are many differences depending on the kind of drug and the medical condition it seeks to address, the basic stages include: discovery, clinical, and regulatory development. We break each down in further detail below.

Exhibit 34: Stages of drug development

Discovery stage			
Basic Research - Scientists contribute knowledge about diseases and identify potential druggable targets for future research	**Goal:** target identification	**Time:** Ongoing **Scope:** Worldwide by government, academia, research institutions and companies	
Drug Discovery - Researchers design or select one of many possible drug candidates to move forward into later studies	**Goal:** candidate identification	**Time:** Varies	
Preclinical testing - Extensive laboratory and animal testing to determine drug activity and safety prior to human use	**Goal:** Investigational New Drug application	**Time:** 2-3 years	
Clinical development stage			
Investigational New Drug (IND) Application - IND filing must be accepted by the FDA before beginning clinical trials; application describes preclinical data and plans for future studies	**Goal:** initiate clinical study	**Time:** Studies may initiate 30 days after receipt of IND by FDA	
Phase I Clinical Trials - Primarily conducted to determine a drug's pharmaceutical actions, safe dosage range, pharmacokinetics in the body and duration of action	**Goal:** determine safety	**Time:** 6-12 months **Scope:** 20-80 individuals, typically healthy volunteers	After Phase I, 59.5% advance into Phase II
Phase II Clinical Trials - Controlled testing to evaluate optimal dosing, efficacy and safety	**Goal:** identify optimal dose	**Time:** 1-2 years **Scope:** 30-300 individuals	After Phase II, 35.5% advance into Phase III
Phase III Clinical Trials - Extensive testing to confirm efficacy and safety	**Goal:** establish clinical benefit/risk	**Time:** 2-4 years **Scope:** 500-3,000 individuals	
Regulatory stage			After Phase III, 62.0% advance to NDA/BLA submission
Filing for Approval - Company submits New Drug Application (NDA) or Biologic License Application (BLA) to FDA with preclinical, clinical and manufacturing data		**Time:** FDA has 60 days to decide to accept application for review	
FDA Advisory Committee - The FDA may choose to convene an Advisory Committee Panel made up of independent experts to review the company's data and make a non-binding recommendation on approval		**Time:** If convened, typically occur no later three months (standard review) or two months (priority review) from PDUFA date	After application filing, 90.3% probability of approval
Regulatory Approval - The FDA and in some cases expert panels evaluate drug applications for approval; FDA will approve or issue a Complete Response Letter (CRL) to the sponsor company		**Time:** FDA goal is to act on at least 90% of standard filings no later than 10 months from filing acceptance (6 months for priority review)	**Total probability of success from Phase I to approval is only 10-12%**
Post-approval safety monitoring and ongoing research			
Phase IV Clinical Trials - All companies must monitor drug usage for safety events. Some companies may be required by the FDA to conduct further Phase IV studies to confirm safety and or efficacy	**Goal:** monitor clinical profile	**Time:** Varies **Scope:** Varies	
Further research - Companies may conduct additional research to expand the drug's use into new disease settings and/or patient populations, or to create new formulations and delivery methods	**Goal:** identify new indications for label expansion	**Time:** Ongoing **Scope:** Varies	

Source: FDA, PhRMA, Tufts, Bio, Goldman Sachs Global Investment Research

Discovery. The first step in drug discovery is basic research, wherein researchers

attempt to identify which molecules and/or genes are involved in causing the disease, known as the disease pathogenesis. Once identified, these become the target for drug development: thousands of drug candidates may be tested for how they interact with the targeted molecule. The lead candidate will then be selected as the best of these.

Following lead candidate selection, drug developers will seek to optimize the drug. For example, chemical or biological modifications may extend the half-life or the drug (how long it persists in the body following administration), increase its potency (how tightly it binds the target), or reduce its side effects, among other desirable qualities.

The identification of a lead candidate is the goal of this stage, often called "candidate selection".

Artificial intelligence (AI)/machine learning (ML)

The convergence of biotechnology and technology (e.g., neural networks, natural language processing, generative AI and cloud infrastructure, among others) could enable advances in drug discovery and development, where applications include the ability to screen massive chemical and biological datasets to identify and design drugs with desired properties, predict protein structures and drug-target interactions, better understand underlying disease pathology and discover novel therapeutic targets, and drive efficiencies in clinical trial design/operations and commercialization while reducing the cost and time associated with traditional approaches. Biopharma companies have historically utilized some level of computational biology and data analytics capabilities, and the availability of large datasets and a greater understanding of human genomics (next-generation sequencing, the Human Genome Project) coupled with technological advancements (e.g., the development generative AI, which can effectively create new content vs. the traditional application of classifying data) have increased the interest and adoption of AI (the ability of a machine to simulate human intelligence)/ML (the process by which a machine learns and improves on its own) for predictive purposes in drug development.

The field remains in early stages with regard to validation per approved drugs, albeit proof-of-concept supporting the integration of AI/ML in drug discovery/development is emerging. Broadly, analyses on AI-discovered drugs have found an 80–90% success rate in Ph1 studies (i.e. development of the asset continues post Ph1 results), meaningfully higher than the historic average of 40-65%, suggesting that AI is capable of designing or identifying molecules with promising drug-like properties - when assuming these early success rates hold in the future, the analysis estimated that the probability of a molecule succeeding across all clinical phases end-to-end would increase from the 5-10% average to ~9-18%, roughly doubling biopharma R&D productivity. Regarding specific cases, we note AI/ML's role in the response to the COVID-19 pandemic (MRNA, PFE, ABCL) and encouraging early clinical data from RLAY (positive efficacy data in cholangiocarcinoma and HR+/HER2- breast cancer) and SDGR (software contributed to the approvals of Tibsovo and Idhifa) – however, other AI-enabled biotech companies may have promising potential but are seen as less de-risked given the lack of meaningful data in humans for key programs (EXAI, RXRX, ABSI) or have faced clinical setbacks calling their platform into question (BAI). Meanwhile, larger biopharma companies, such as AMGN and ROG, are focused on gaining access to innovative technologies by building up internal capabilities and/or through external business development deals (we expect the partnering environment to remain robust, noting the risk associated with acquisitions given the early-stage of the field, limited proof-of-concept and rapid innovation where a given technology may

become obsolete).

We continue to monitor the landscape for further proof-of-concept data, successful implementations, and business development activity to increase enthusiasm as investors look for differentiation and value creation among players – to this end, we are focused on understanding the integration of biological and computer science talent and capabilities, strategic execution on milestones per the management team, and the extent to which the company's platform is validated per clinical data indicating the ability to reproducibly develop best-in-class/first-in-class products (and proprietary features, such as expertise in data generation). Overall, we believe AI/ML's advantages will be closely studied and increasingly implemented over time, and companies who integrate and leverage such technologies will be at an advantage to those who do so suboptimally or not at all.

GS research on AI/ML in healthcare includes the following reports and events:

- GS HealthcAIre Series – a call series with various healthcare management teams and thought leaders in the space
- Healthcare: Byte-ology and takeaways from the Healthruption Conference (April 13, 2023)
- Research Unplugged: Byte-ology: A broadening convergence (April 6, 2023)
- Report: Byte-ology: A broadening convergence (March 27, 2023)
- Generative AI - Part I: Laying Out the Investment Framework (March 26, 2023)
- Byte-ology: The beginning of the convergence (December 12, 2021)
- Byte-ology: The Convergence of Biotechnology and Technology (December 8, 2021)

Companies in focus: RLAY RXRX, BAI , EXAI, SDGR, ABCL, CERT, ABSI, MRNA, AMGN.

Pre-Clinical Development. Once a drug is selected, it must undergo considerable laboratory (in vitro) and animal (in vivo) testing. These tests are designed to establish initial signals of safety and efficacy, with animal models specifically designed to mimic human biology (for example, obese mice might be used to test weight loss drugs). Animal testing is conducted primarily in rodents. However, there are diseases where other animals provide better fidelity to human biology and thus dogs and monkeys may also be used.

Animal studies also provide insight into a drug's carcinogenecity (propensity to cause cancer) and pharmacokinetics (how the drug moves within the body).

The goal of this process is to generate sufficient data to transition to human studies. The FDA requires substantial information and an Investigational New Drug (IND) application. If the FDA does not respond to an IND within 30 days, the company is cleared to proceed with human studies. The commensurate paperwork in the EU is called a Clinical Trial Application.

Clinical Development. Clinical testing (drug testing in humans) includes up to four phases:

- **Phase I trials** are the first studies of a drug in human patients, and are primarily intended to evaluate safety. These studies can last 6-12 months, and typically enroll 20-80 patients. They generally enroll healthy volunteers, but may include patients in the case of high mortality diseases (e.g. cancer). These studies are designed to assess pharmacokinetics (effect the body has on the drug), pharmacodynamics (effect the drug has on the body), and safety. These studies help to identify the drug's maximally tolerated dose (MTD; highest dose level without unacceptable side effects), minimally efficacious dose (lowest dose at which a clinical effect is observed), and dose-limiting toxicities (DLTs).
- **Phase II trials** are typically conducted in 30-300 patients, with a focus on safety and efficacy. During this phase, developers will seek to narrow down or select the optimal dose level for the drug. These trials may or may not include a control arm, and can last 1-2 years. While these studies are expected to demonstrate a signal of efficacy, they are not necessarily expected to show a statistically significant benefit vs. a control arm. They will inform patient selection, dose, and endpoint for Phase 3 studies.

Project Optimus

The Oncology Center of Excellence introduced Project Optimus to reform dose optimization and selection within oncology. Per the agency, poorly characterized dose and schedule can result in higher toxicity without additional efficacy benefits, leading to several adverse effects: higher dose reductions, intolerable toxicities, premature discontinuations, and loss of benefit. Draft guidance for this program addresses preclinical strategies, trial design recommendations (to compare multiple dosages), recommendations to incorporate symptomatic adverse reactions that impact compliance/adherence, and to evaluate dose regimens by indication.

As a practical matter, this has required certain biotech companies to explore more doses and dose regimens within early stage dose escalation and expansion studies within cancer indications than were previously undertaken, adding cost and time to dose identification processes.

- **Phase III trials** evaluate the drug in a large number of patients over a typically 2-4 year period to confirm the efficacy and safety of the drug. The number of patients in a Ph3 study is a function of the number of patients with disease, the FDA requirements for safety data (how many patients have been exposed to a drug prior to approval), and the magnitude of benefit expected between drug and control arms (the larger the expected benefit, the fewer patients required to demonstrate statistically significant difference vs. control). These are also called pivotal or registrational studies, because data from these trials are the basis for approval (if positive) and will inform the label (approved indications and safety data).
- **Phase IV trials** provide additional safety and efficacy data post-approval, and are sometimes required by the FDA to confirm the drug is well-tolerated.

We note that there may be mixed permutations of these clinical studies, such as Phase 1/2, Phase 2a/2b, and Ph2/3 studies, which are designed for efficiency and to achieve

multiple aims in a streamlined manner. For example, a Ph1/2 study in cancer will establish safety, help determine the optimal dose, and demonstrate initial efficacy with a new agent. In some cases, Ph3 studies are not required for approval, and the Ph2 trial will be referred to as "registrational" or "pivotal". Additional detail below.

Clinical trial design

Successful and efficient drug development is contingent upon well-designed clinical studies. Biotech companies will design their trials based on feedback from regulators (more below), key opinion leaders, and data on disease prevalence, severity, and progression. The goal for any development program is to demonstrate that the drug has clinically meaningful efficacy with acceptable tolerability and safety.

Gold standard drug development relies on randomized, double-blind studies to demonstrate clinical benefit/risk against a clinical endpoint that is meaningful to patients. Patients are randomly assigned to the drug or control arm of a trial (randomization) but neither physician/provider nor the patient will know whether the patient is to receive the drug or control (double-blind).

Key decisions within trial design include:

- **Choice of control treatment.** Trials include a comparator arm in order to determine the specific effect of the drug studied. The control arm can be placebo (inactive agent) or a currently available treatment that the drug arm will ultimately compete with. Head-to-head comparisons against an active treatment may be preferred if the approved treatments are good. Depending on the disease, it may also be unethical to give a patient an inactive control vs. the treatment they could receive outside of the clinical trial context. In some cases, the control will be an active "treatment of physician's choice" where there are a couple of commonly used therapies that can be used within the control. These studies can also help to inform treatment decisions once a drug is available on market (doctors know which agent is "best" from a head-to-head study) and can also facilitate better insurance coverage.

  Single-arm studies are run without a control arm, which may be less rigorous than a controlled trial, but may also be acceptable in certain settings: i) where there are likely to be challenges enrolling patients, or ii) where there are ethical concerns to use of a placebo arm (in the case of high mortality diseases). These studies are often seen in pivotal cancer trials, where they are used to support an "accelerated approval" (see below).

- **Patient selection.** Patients who are to be enrolled in a clinical trial must qualify against set inclusion and exclusion criteria. These may include age, fertility status, prior treatment, stage of disease, other medications, or other specifications to optimize the drug effect within the trial. For example, a cancer drug specifically targeting a protein mutated in some patients will only be tested in patients known to have that specific mutation. Depending on how broad or narrow these criteria are will determine the population included on the eventual drug label.

- **Endpoints.** Endpoints are the results against which the drug candidate and control are measured and compared. Studies will have both the **primary endpoint**, and

many key **secondary endpoints**. As the name suggests, the primary endpoint is the main focus of the study, and the endpoint used to determine whether a drug should be approved or not (in Ph3 studies). Thus, significant statistical planning carried out by biostaticians will be employed to maximize the probability of success, as measured by the primary endpoint. Secondary endpoints provide additional information, and can include other measures of clinical efficacy, safety, and pharmacokinetic/pharmacodynamic effects. The study will not necessarily be designed to show statistical significance on these secondary endpoints, and can thus be positive without them, but they can contribute to an overall view of the drug's effect. Common endpoints include (non-exhaustive):

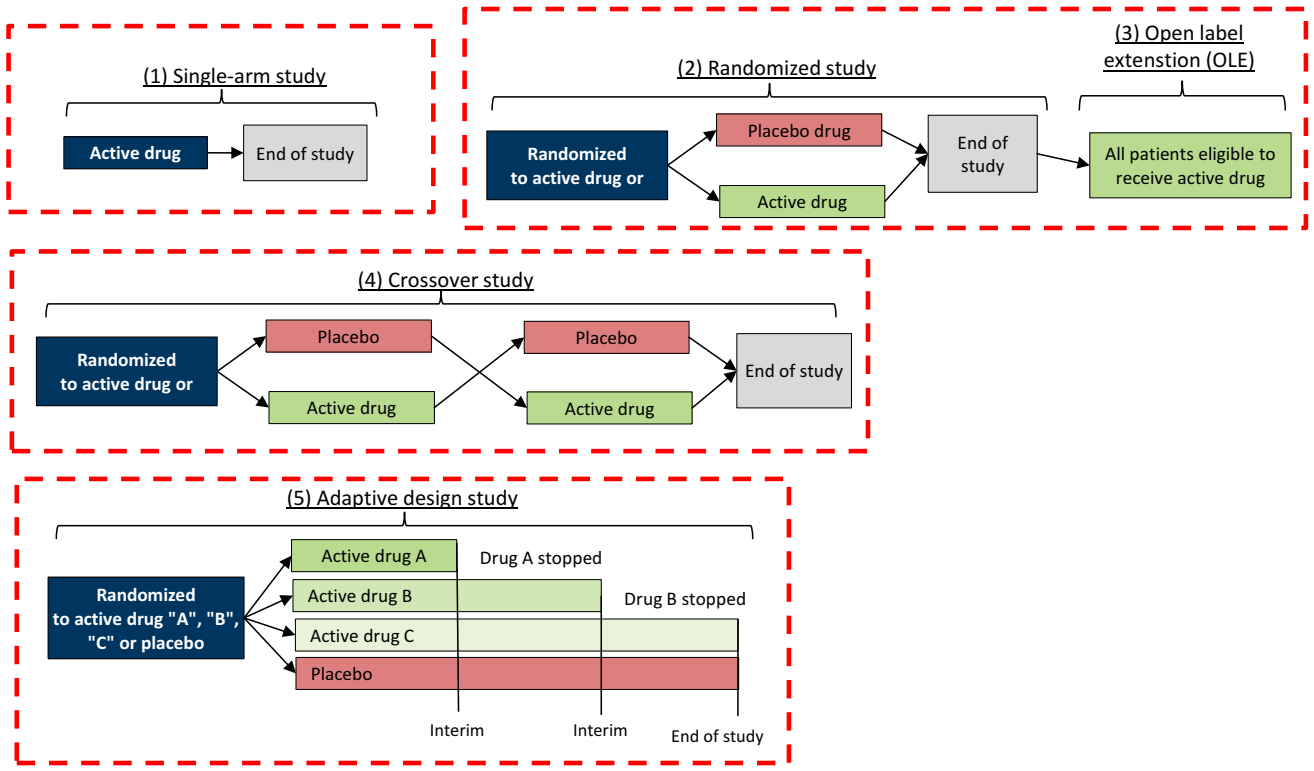
- **Overall survival:** does the drug increase the amount of time patients live vs. control? This is considered the most meaningful endpoint for life-threatening disorders (e.g. cancer).
- **Progression free survival:** does the drug increase the amount of time till patients get worse vs. control? This can be used as a proxy for overall survival, in order to improve the efficiency of drug development and get the drug to patients in an expedited manner.
- **Response rate:** do patients treated with drug achieve a certain threshold of response at a higher rate than patients treated with control? In the case of cancer, this may be a reduction in tumor size (>30% tumor shrinkage; sometimes used to support early approval). In other diseases this may represent response against a measure of disease activity, like the number of patients who achieve certain changes in weight (>5% is the standard threshold) or changes in certain measures of inflammation.
- **Functional endpoints:** do patients improve (or progress more slowly) against measures of disease activity when treated with drug vs. control? Some diseases are measured based on a functional endpoint, wherein patients are measured against their ability to do certain activities over time, and monitored for changes as the disease progresses. These may be compound measures (the ability to do multiple activities, like button a shirt and/or sign a name) or single measures (how far one can walk within six minutes).
- **Disease specific scales/endpoints.** In many disease areas, doctors and professionals have developed over time specific measures of disease activity for use in clinical trials. For example, the Montgomery-Asberg Depression Rating Scale (MADRS) is commonly used in depression studies, while the Eczema Area and Severity Index (EASI) is a frequent measure of atopic dermatitis (eczema).

- **Statistical significance.** This is the probability that differences observed between different groups in the trial occurred because of the treatment vs. chance alone. This is often evaluated based on the "p-value", defined as the probability that the observed results could have occurred due to chance alone. Studies are considered typically considered statistically significant if the p value is less than 0.05, meaning there is less than 5% chance the difference in effect observed was random vs. due to treatment.

- **Confidence intervals** can be informative, as they describe the mean +/- the variation in that estimate. Depending on the "confidence" ascribed, these tell you where the mean is likely to fall if the test were run again.
- **Hazard ratios** are used to describe how often an event happens in one group vs. the other. For example, in a survival analysis, a hazard ratio below 1.0 indicates that patients are less likely to die on drug vs. on control.

- **Statistical power.** The probability of detecting difference between active and control treatments *when a difference actually exists* is called the study's "power". This is determined based on the sample size (number of patients) and expected magnitude of difference between drug and control treatment. The larger the effect size expected, the fewer patients required to adequately power a study. While the minimally accepted power is typically 80%, most studies are powered by 90-95%.
- **Statistical analysis plan.** Prior to the initiation of a study, drug developers will have to lay out their detailed plans for each of the items described above. They will also be required to specify how the study will be evaluated for clinical significance (for example, how will patients be treated if they drop out?). Analysis consistent with this pre-trial plan will be considered "pre-specified", and these analyses are considered more stringent and appropriate. Analysis that is conducted after the data is received is called "post-hoc analysis", and while it can be informative, these results will not be considered as highly, as the developer is able to run the analysis with the full benefit of hindsight on how the data turned out.

Exhibit 35: Examples of treatment studies



Source: Data compiled by Goldman Sachs Global Investment Research

Regulatory process

The Food & Drug Administration (FDA) regulates new drug development and approvals in the US (among other responsibilities). Throughout the span of clinical development, and once the drug is approved, the FDA provides guidance, monitors progress, and makes decisions on how the drug can be developed and then distributed to patients.

FDA touchpoints throughout the development process include:

- **Investigational new drug (IND) filing.** Companies must file preclinical data with the FDA prior to initiating clinical studies. If regulators do not disapprove the filing within 30 days, the company is free to proceed with drug development.
- **Pre- and post-trial meetings.** Companies will meet with the FDA to discuss trial design prior to the initiation of a study in order to ensure developers are on the same page as regulators with respect to what a study must demonstrate (safety and efficacy) for the drug to progress (or be approved). They will also meet with the agency post-trial results to discuss potential next steps. Companies will share limited details of their interactions with the FDA, but will generally wait for formal meeting minutes to disclose takeaways.
- **Monitoring.** Throughout the clinical development process, an independent body (called the Data Safety Monitoring Board or DSMB) will review safety results from the ongoing study, flagging if there are any significant adverse events that require the trial to be paused (called a clinical hold). A clinical hold may also be instituted if preclinical data reveals a particularly concerning potential side effect (e.g. carcinogenecity, or ability to cause cancer). A DSMB may also recognize efficacy, and call for the trial to be stopped early if the drug is so effective that it would be unethical to continue to give sick patients the placebo or control.
- **Regulatory designations.** During drug development, the FDA may ascribe one or multiple "designations" to the agent in question.
  - Fast Track designation (FTD) may be granted (based on application by the sponsor) to a drug that has potential to treat a serious condition and fulfills unmet medical need. Once granted, companies are eligible for more frequent meetings/communication with the FDA, accelerated approval and priority review (if criteria met), and/or rolling reviews. Clinical evidence is not required.
  - Breakthrough Therapy designation (BTD) is requested by the sponsor and ascribed to a drug that treats a serious or life-threatening condition and preliminary clinical evidence indicates the drug may demonstrate substantial improvement on a clinically significant endpoint(s) vs. available therapies. Once granted, companies are eligible for the same as Fast Track designated sponsors, as well as intensive guidance on the drug development program and involvement of senior managers to expedite the process. Clinical evidence is required.

In addition to the FDA, each clinical trial site will have its own review board, called the Institutional Review Board (IRB). This body will evaluate the risks/benefits of a given clinical trial, monitor safety, and monitor adherence to the ethical standards required to protect patients. Each clinical site will have its own IRB, and approval for a new clinical

trial site can take up to many months for approval.

Following the completion of a registrational study, the drug sponsor will submit for approval of the drug. The filing package is called a New Drug Application (NDA) if it is a small molecule drug, or Biologics License Application if it is a biologic agent. These applications are thousands of pages (potentially more than 100K pages) and include:

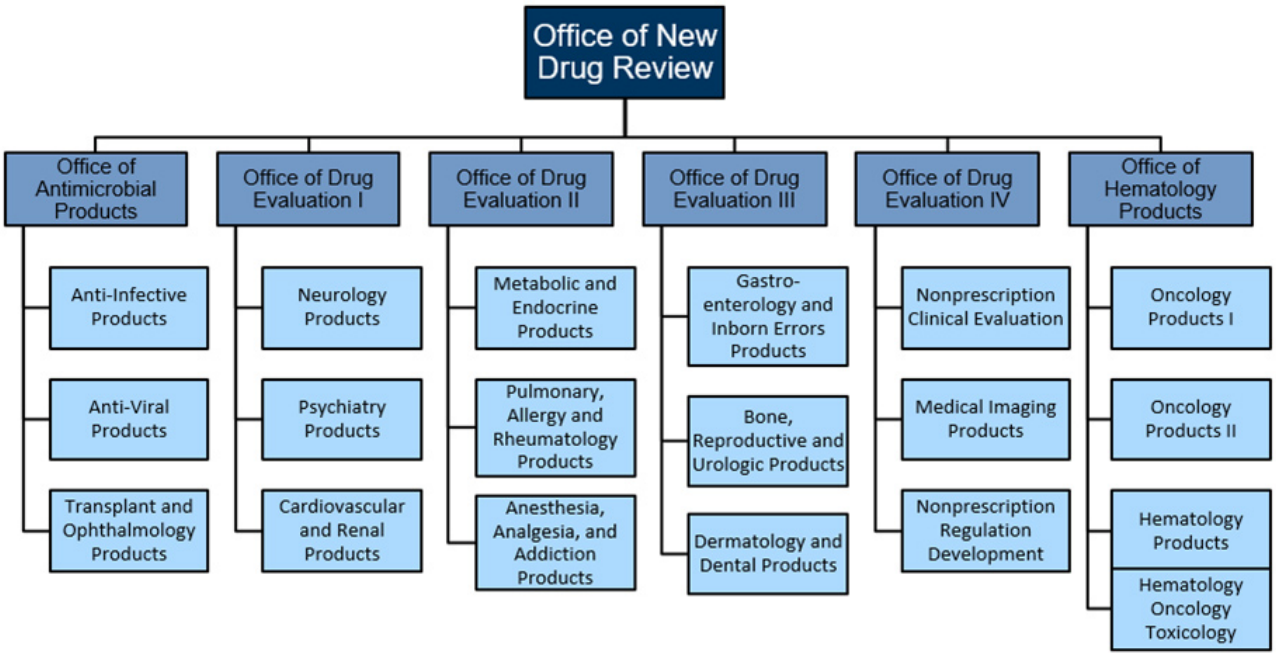
- Study data, including preclinical, clinical, and safety data
- Proposed labeling and directions for use
- Drug abuse information
- Patient information
- Information on chemistry, manufacturing & controls (CMC)
- Institutional review board compliance information

After the company files for approval, the FDA will have 60 days to accept the application (if deemed complete) or issue a refusal to file (RTF) letter describing the deficiencies that warranted the RTF. Once accepted, the FDA review team is assigned, including medical officers, statisticians, and pharmacologists.

New drug review is executed by either the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER). Some biological products are evaluated by CDER, including monoclonal antibodies, enzymes, immuno-modulators, and growth factors. CDER therefore handles the bulk of NDAs and BLAs, though CBER retains oversight over cellular products, gene therapy, vaccines, and clotting factors.

The CDER Office of New Drug Review is divided by therapeutic area, which are each responsible for review applications within their area.

Exhibit 36: Office of New Drug Review Organization Chart



Source: FDA

After the filing is accepted, the FDA will disclose whether the drug will be evaluated via the **standard review** or **priority review** process, and will assign a **PDUFA (Prescription Drug User Fee Act)** action date, the day by which the FDA aims to make a decision on the approval. If a standard review, the PDUFA will be 10 months post acceptance, while a priority review will have a PDUFA 6 months after filing acceptance (12 or 8 months in total). The FDA reserves the right to extend this PDUFA for internal reasons or due to the submission of additional, material data.

Prior to making its decision, the FDA may chose to host an **Advisory Committee panel (AdCom)** made up of independent key opinion leaders to review the company's data during the public meeting, and to make non-binding recommendations on approval, label restrictions, and/or monitoring requirements to the FDA. The FDA typically follows these recommendations, though they are not obligated to (for example, the FDA approved Aduhelm against the recommendation of the AdCom in 2020). If convened, these typically occur 3 months (standard review) or 2 months (priority review) ahead of the PDUFA. While the FDA's plans with respect to an AdCom are often disclosed when the agency accepts a filing, it can institute the AdCom at any time during the review period. However, as it takes ~6 weeks to plan for an AdCom, the chance of one being imposed less than 4.5 months (standard review) or 3.5 months (priority review) ahead of the PDUFA date are low.

Standard vs. priority review

Priority review is granted to drugs that, if approved, would significantly improve the safety or effectiveness of treatment, diagnosis, or prevention of a serious condition. Drugs with Fast Track and/or Breakthrough Therapy designations will be eligible for priority review, and the FDA determines priority review on a drug by drug basis. The company is informed of its status within 60 days of the receipt of the original filing, and the designation does not alter the requirements for the scientific/medical standard for approval or quality of evidence required.

A priority review voucher may be acquired by a company that develops a drug to treat certain diseases (tropical disease, rare pediatric diseases, and illnesses related to public health) that represent significant unmet need but may not be particularly profitable. This can be applied to a future (and more profitable) drug, or resold. The resale value of PRVs can vary, but has recently stabilized at ~$100M.

During the review period, inspectors from the FDA will often travel to study sites to look for evidence of data fraud or withholding. Inspectors may also visit and inspect the manufacturing facility(ies) where the drug will be made. A project manager is tasked with assembling each individual team member's review and analysis into a consolidated action package. Finally, the review team makes a recommendation on approval to a senior FDA official. On behalf of the agency, the officer can then approve the drug or issue a **complete response letter** (CRL) denying the application. A CRL may also contain instructions for remediation and later approval, if available.

Accelerated Approvals: enhanced post-approval requirements as Accelerated Approval policy matures

The Accelerated Approval regulations were instituted in 1992 to allow for drugs that address serious conditions and unmet medical need to be approved based on a surrogate endpoint (later expanded by congress to include an intermediate endpoint). A surrogate endpoint used for accelerated approval is a marker (laboratory measure, radiographic image, physical sign, or other measure) that is well-established to predict clinical benefit. An intermediate endpoint is a measure of therapeutic effect thought likely to predict clinical benefit.

This can save significant time in the drug approval process, however, confirmatory studies are still required. These studies will be expected to verify clinical benefit against gold standard evidence of clinical benefit.

This pathway has been frequently applied in the context of oncology, where Objective Response Rate (ORR; the portion of patients that achieve tumor shrinkage >30%) is believed to be reasonably likely to predict that patients will live longer. Confirmatory studies will then assess the drug on overall survival (how long the median patient lives).

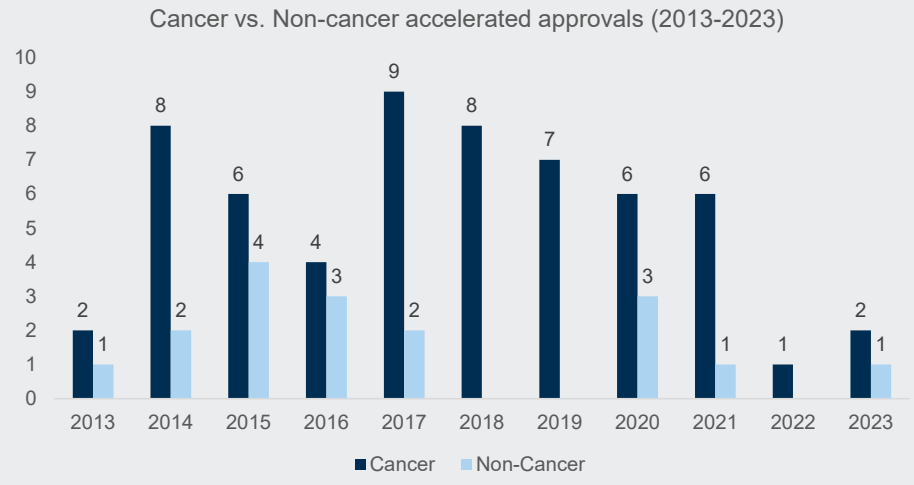
While the Accelerated Approval pathway may save valuable time, and in some cases has facilitated new drug approvals that would not have been likely absent the expedited registrational path, this pathway has recently come under enhanced scrutiny. A recent analysis demonstrated that 63% of cancer drugs approved via this pathway converted to regular approval, despite only 43% demonstrated survival benefit

within five years post-approval. Note that 63% of regular approvals from 2013-2023 came from approval in a different indication (often a broader indication or earlier line of therapy within the same cancer type).

Of particular issue has been sponsor's commitment to fulfilling their post-accelerated approval confirmatory approval requirements (called "dangling approvals"). In 2022, the FDA passed reforms which require confirmatory studies be underway prior to approval, sponsors to submit biannual progress reports, and adopted a streamlined withdrawal process for drugs that do not verify benefit, among other actions. The agency has also hosted discussions with its Advisory Committee on strategies to further mitigate the delay between accelerated approval and confirmatory data.

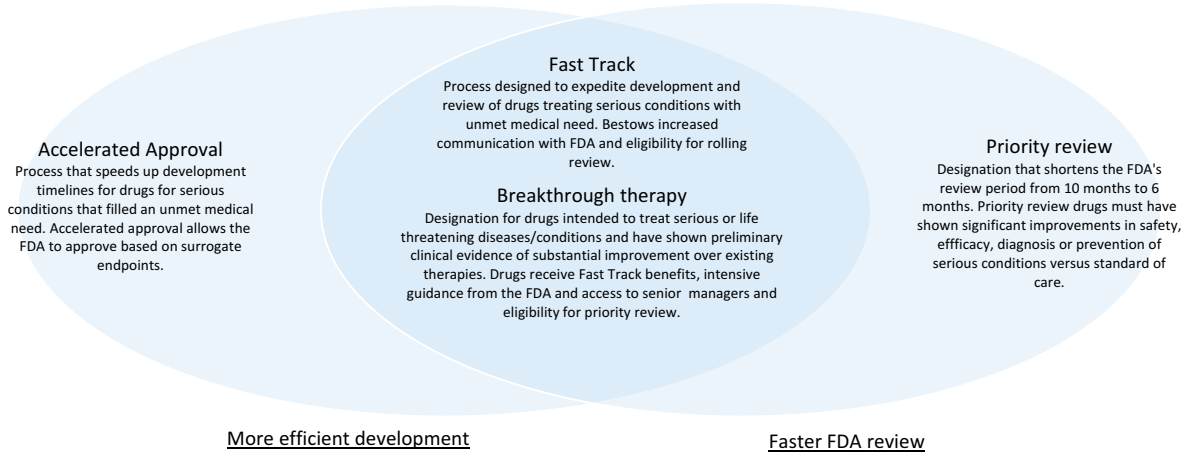
We anticipate that this focus on accelerated approvals will remain stringent as the FDA continues to revisit its approach to accelerated approval.

Exhibit 37: Accelerated approvals: 2013-2023



Source: FDA

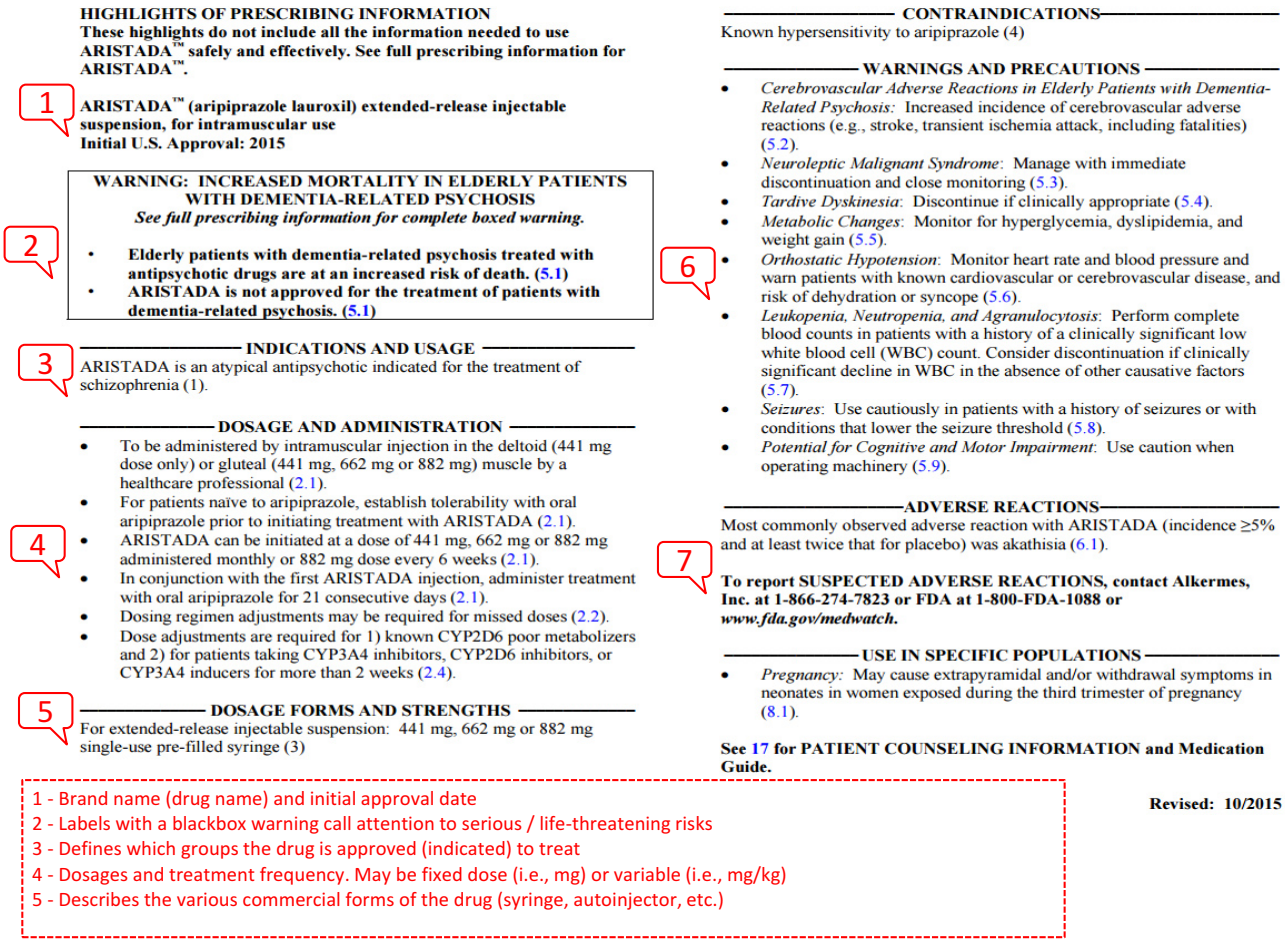
Exhibit 38: Regulatory designations and processes of the FDA



Source: FDA

On approval, the FDA will release the prescribing label for a new drug. The label will always include a number of key components.

Exhibit 39: Front page of an FDA label, explained



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARISTADA™ safely and effectively. See full prescribing information for ARISTADA™.

1

ARISTADA™ (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2015

2

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. (5.1)**
- **ARISTADA is not approved for the treatment of patients with dementia-related psychosis. (5.1)**

3

INDICATIONS AND USAGE
ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia (1).

4

DOSAGE AND ADMINISTRATION
- To be administered by intramuscular injection in the deltoid (441 mg dose only) or gluteal (441 mg, 662 mg or 882 mg) muscle by a healthcare professional (2.1).
- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA (2.1).
- ARISTADA can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly or 882 mg dose every 6 weeks (2.1).
- In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days (2.1).
- Dosing regimen adjustments may be required for missed doses (2.2).
- Dose adjustments are required for 1) known CYP2D6 poor metabolizers and 2) for patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than 2 weeks (2.4).

5

DOSAGE FORMS AND STRENGTHS
For extended-release injectable suspension: 441 mg, 662 mg or 882 mg single-use pre-filled syringe (3)

CONTRAINDICATIONS
Known hypersensitivity to aripiprazole (4)

6

WARNINGS AND PRECAUTIONS
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemia attack, including fatalities) (5.2).
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring (5.3).
- *Tardive Dyskinesia*: Discontinue if clinically appropriate (5.4).
- *Metabolic Changes*: Monitor for hyperglycemia, dyslipidemia, and weight gain (5.5).
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.6).
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.7).
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8).
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery (5.9).

7

ADVERSE REACTIONS
Most commonly observed adverse reaction with ARISTADA (incidence ≥5% and at least twice that for placebo) was akathisia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-866-274-7823 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS
- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates in women exposed during the third trimester of pregnancy (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

1 - Brand name (drug name) and initial approval date
2 - Labels with a blackbox warning call attention to serious / life-threatening risks
3 - Defines which groups the drug is approved (indicated) to treat
4 - Dosages and treatment frequency. May be fixed dose (i.e., mg) or variable (i.e., mg/kg)
5 - Describes the various commercial forms of the drug (syringe, autoinjector, etc.)

Source: FDA

European approval process

The approval process in Europe requires a different application with a separate timeline, as well as coordination with multiple European agencies. The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 30 EEA countries (27 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA. This network is what makes the EU regulatory system unique.

There are three pathways to drug approval in the EU:

1. **Centralized procedure:** The centralized procedure allows the marketing of a medicine on the basis of a single EU-wide assessment and marketing authorization which is valid throughout the EU. Pharmaceutical companies submit a single authorization application to EMA. The Agency's Committee for Medicinal Products for Human Use (CHMP) then carries out a scientific assessment of the application and gives a recommendation to the European Commission on whether or not to

grant a marketing authorization (*see details below*). The CHMP appoints two of its members as "rapporteurs" to evaluate the application. The review period includes two "clock stop" periods where applicants respond to questions from the CHMP. By Day 210 of the active evaluation process, the CHMP issues a recommendation on whether or not a medicine should be granted a marketing authorization and, if so, under which conditions of use. Once granted by the European Commission, the centralized marketing authorization is automatically valid in all EU Member States. The use of the centralized procedure is compulsory for most innovative medicines, including medicines for rare diseases and advanced-therapy medicines. **Accelerated assessment** of medicines in the centralized procedure may take place if they are of major interest for public health, with the assessment period usually reduced to 150 evaluation days, rather than 210 days.

When a company pursues authorization in several EU member states, it may follow one of the following procedures:

1. **Decentralized procedure:** Companies apply for simultaneous authorization of a medicine in more than one EU member state if it has not yet been authorized in any EU country and does not fall within the scope of the centralized procedure.
2. **Mutual recognition procedure:** Applicants obtain a marketing authorization in EU member states for a drug already approved in another EU state. This route is often used by generic filers, and allows member states to rely on each other's scientific assessments.

CHMP review step-by-step:

- Before the review procedure starts, the applicant is required to submit the application to the EMA, and the EMA will conduct a technical validation to ensure all essential materials required for scientific assessment are included.
- The clock starts once the technical validation is finished and the review procedure begins.
- **From Day 1 up to Day 120 (90 if accelerated assessment)**, two teams (rapporteur and co-rapporteur) within the CHMP will review the application and prepare assessment reports independently, which may include recommendations regarding inspection of the medicine's manufacturing site. The CHMP will conduct a peer view meeting to develop a single assessment report including **a list of questions to be addressed by the applicant**.
- **Clock stop 1:** The applicant will normally be required to answer the questions **within 3 months, but an extension of 3 months is possible** if appropriate justification is given. During this time, the review clock is stopped.
- **From Day 121 to Day 180 (Day 91 to Day 120 if accelerated assessment):** The clock will restart after responses are received by the CHMP. The committee will update the assessment report based on the first round of answers from the applicant and raise new questions most of the time.
- **Clock stop 2:** The application will be given 1 to 3 months to answer the new questions.

- **From Day 181 to Day 210 (Day 121 to Day 150 if accelerated assessment):** At this stage, an oral explanation can be requested by the applicant or the CHMP regarding the outstanding questions. Additionally, **the committee may request a Scientific Advisory Group (SAG) meeting**. By Day 210, CHMP will **adopt an opinion on the approval of the drug and publish the opinion**.
- **Re-examination (up to 60 days):** if the applicant disagrees, a request to appeal needs to be raised **within 15 days** of receipt of the opinion. Note that **the applicant is not allowed to bring in new scientific evidence** for the re-examination, meaning it will be based only on the scientific evidence available when the initial decision was made. **We also note that a SAG meeting may be requested by the applicant for re-examination.**
- A final decision will be issued after re-examination.

With investors generally more focused on US FDA regulatory process, the EU process can often be a source of uncertainty. As such we summarize the key differences between the EU process and US FDA process below:

- **Fixed vs. variable timelines:** In contrast to the FDA review times which are typically fixed (10 months or 6 months if priority review is granted), the actual time it takes to get the final CHMP decision depend on the agency's review time (up to 210 days/7 months or 150 days/5 months if accelerated assessment) plus the time it takes the applicant to answer two rounds of CHMP raised questions (up to 9 months). **Note that the CHMP review process usually lasts around a year, per the agency.**
- **EMA decision comes after CHMP recommendation:** The EMA will either grant or refuse drug approval within 67 days after receiving CHMP's final opinion.
- **Non-public SAG (Scientific Advisory Group) meeting:** Unlike AdCom meetings, which are broadcast publicly, SAG meetings are privately held, and results are not revealed to the public.
- **No applicant participation in the SAG meetings:** Whilst the applicant is allowed to present and defend drug applications in AdCom meetings, no such participation is permitted in SAG meetings.
- **CHMP re-examination can be requested:** Although no new scientific evidence is permitted, the applicant can request CHMP re-examination and SAG meetings if it disagrees with CHMP's initial decision.

PRIME

In 2016 the EMA announced that it launched a new initiative called the PRIME priority review program, with the goal of identifying areas of significant unmet need and accelerating drug development in these areas. This is similar to FDA's BTD and priority review designation. Developers of a medicine that benefit from PRIME designation can expect to be eligible for accelerated assessment at the time of a marketing authorization application, and benefit from enhanced support from the EMA.

Drug Commercialization

Modeling new drug launches

The trajectory of new drug launches are closely monitored as leading indicators of the peak sales opportunity for the drug, and whether the drug will ultimately be a success or failure. There are a number of factors to consider when modeling an initial launch: reimbursement/access, insurance coverage determinations, price/rebates, current prescribing trends, patient awareness, physician awareness, and inclusion in industry treatment guidelines. At the end of the day, drug sales are a function of price X volume, no different from any other product. However, the factors that drive Rx volume and net price depend on many factors and differ by market.

Monitoring volume

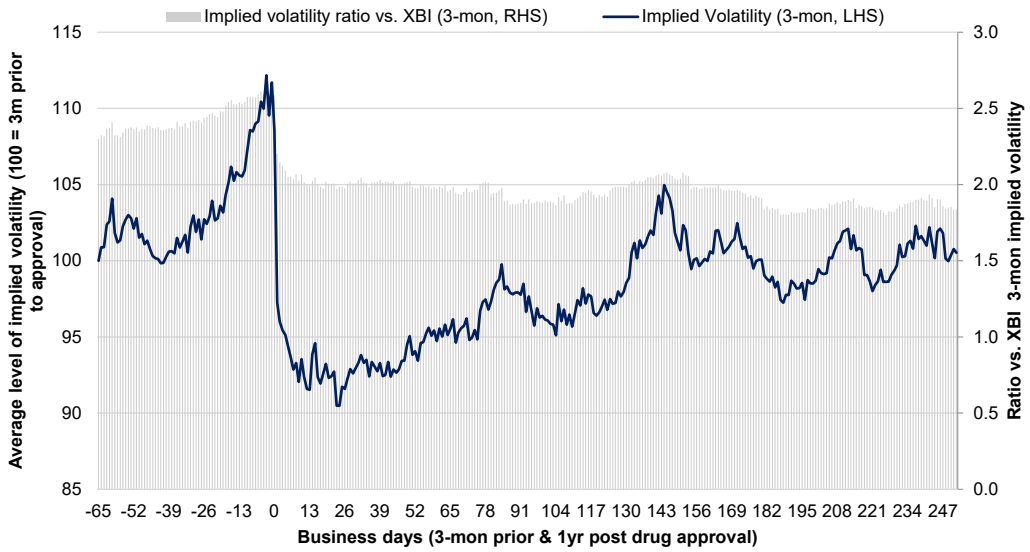
In the case of some new drug launches, data service providers will disclose weekly script data and/or weekly/monthly sales of the new drug. While these data sets do not capture all prescriptions, in some launches they will provide good visibility on the ongoing sales trends prior to the company's quarterly earnings reports. Script data, which is provided by organizations such as IQVIA and Symphony, is best for launches where the drug is distributed via traditional retail pharmacy channels (I.e. CVS, Walgreens). However, when the drug is primarily distributed via specialty pharmacies (often used for complicated and/or rare disease launches), these data providers have much more limited insight into the ongoing launch.

Other key performance indicators that may be provided include:

- **Patient data.** Companies may report patient data, either new patient growth quarter over quarter (net or gross) or average patients on therapy within the quarter. Over time, by monitoring trends, this information may be used to model future sales.
- **Reimbursement levels.** Companies will also disclose the number of patients within the target market that have access to the drug, which is likely to change as government payors (Medicare/Medicaid) and commercial insurance providers set coverage policies for the drug. For drugs covered under the pharmacy benefit, formulary position is crucial to ensuring patients have affordable access to the drug. In the early part of a drug's lifecycle, insurers may approve reimbursement on a case-by-case basis (called medical exception). Drug companies may also disclose the gross-to-net discount between the list price and the average net price they realize for each prescription (additional detail below).
- **Compliance, adherence, or duration of therapy.** Companies may also provide detail on how long patients remain on therapy, what portion are discontinuing drug, or refilling prescriptions.

Regardless, the early stages of a launch can be unpredictable, and the lack of precedent for the drug can make it difficult to accurately predict sales over the first few quarters. As a result, stock performance can be highly volatile during the early launch period.

Exhibit 40: Stock performance during early launch periods



Data compiled by our GS options team

Source: Goldman Sachs Global Investment Research

Forecasting price

The list price of a new drug is disclosed at the time the drug is approved. It is determined based on a myriad of factors, including the clinical benefit offered, the competitive landscape within an indication, and precedent set by other drugs in the same or similar indications. Thus, investors will often predict the likely price of a new agent based on prior similar drugs that were approved.

Additional procedural requirements for new drug products

In addition to reimbursement, certain products that are delivered by physicians (e.g. IV infusions) will also require a specific "J-code" which is used to submit for reimbursement. This J-code must be applied for on a product-by-product basis (not indication specific) subsequent to the drug's approval, and takes ~6 months. While the J-code application and review is ongoing, the drug will be subject to approval for reimbursement via a temporary process. While drugs can and do sell during the review period, an inflection in drug sales is typically expected post the assignation of a J-code as this streamlines the reimbursement process considerably.

Hospital formularies play a role in the administration of drugs within the hospital setting. Drugs that are to be administered within hospitals, such as emergency medicines, will be negotiated on a product-by-product basis for usage within that hospital or health system. Pharmacy & Therapeutics Committees (P&T Committee) evaluate the efficacy and safety of drugs relative to other options already on the market and advise purchasing managers in negotiations with drug manufacturers.

Innovation underpins drug pricing

While appropriate drug pricing remains a central political and societal debate, the

question of value (and how to measure it) is equally important. Value is of particular importance in EU drug pricing decisions, where companies negotiate on a country-by-country basis; this process can take up to multiple years. A drug that presents potential for a cure may be priced highest, with some recent drug launches priced at >$1M for a curative therapy in rare disease. The size of the patient population is also a key factor in determination of price, with smaller markets expected to have higher priced drugs, while drugs for large, chronic conditions will be priced at lower rates.

Exhibit 41: Cell and gene therapies with curative potential
*Not exhaustive

Company	Asset	Indication	Stage	Cell/Gene	US WAC price ($)
BLUE	Zynteglo	Beta thalassemia	Commercial	Gene	$2.80M
BLUE	Lyfgenia	Sickle cell disease	Commercial	Gene	$3.10M
BMRN	Roctavian	Hemophilia A	Commercial	Gene	$90,625
Cardinal Glennon Children's MC	Allocord	Hematopoietic disorders	Commercial	Gene	N/A
FDMT	4D-150	Wet AMD, Diabetic macular edema	Clinical	Gene	N/A
Gamida Cell Inc.	Omisirge	Hematologic malignancy	Commercial	Cell	$338,000
KYKOF	Lenmeldy	Metachromatic leukodystrophy	Commercial	Gene	$4.25M
PFE	Beqvez	Hemophilia B	Commercial	Gene	$3.50M
QURE	Hemgenix	Hemophilia B	Commercial	Gene	$3.50M
RGNX	RGX-202	Duchenne Muscular Dystrophy	Clinical	Gene	N/A
ROG	Luxturna	Inherited retinal disease	Commercial	Gene	$913,750
VRTX/CRSP	Casgevy	Sickle cell disease, beta thalassemia	Commercial	Gene	$2.20M

Source: Data compiled by Goldman Sachs Global Investment Research, PriceRx

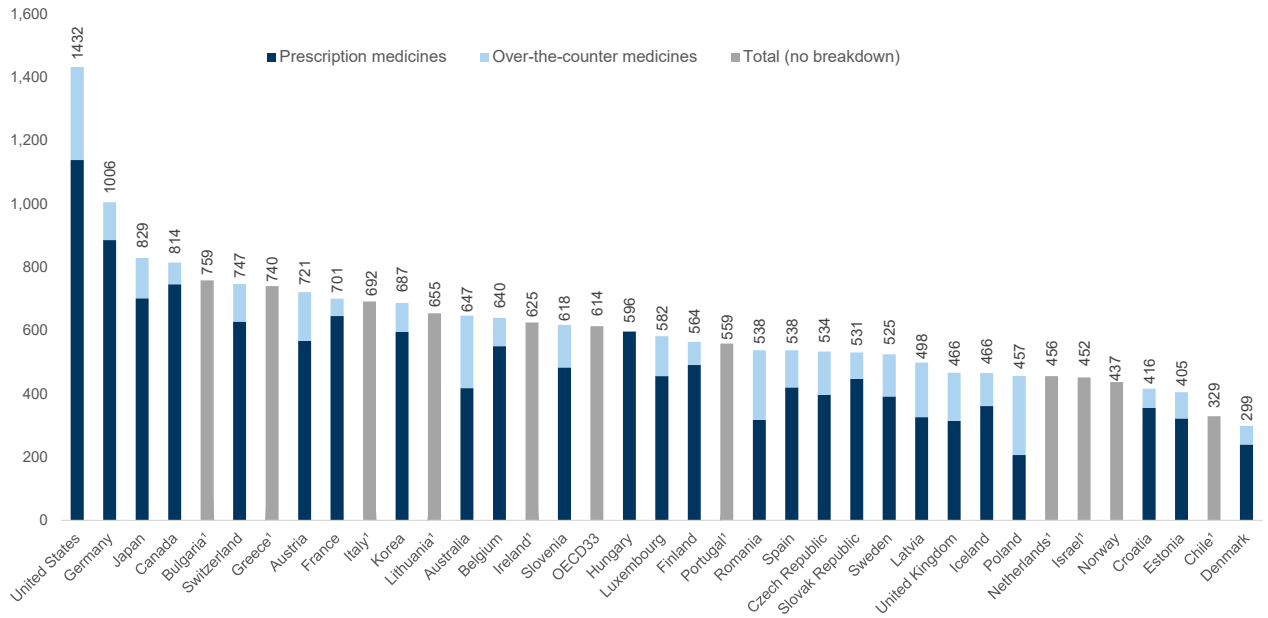
International markets

Drug expenditure per capita is higher in the US than other developed countries, with most international countries negotiating price as a single payor. Another unique feature of the US pharmaceutical market is the relatively high contribution of private insurance in drug expenditures. The US adopted government price negotiation in Medicare on a limited number of drugs via the Inflation Reduction Act. Negotiated pricing for 10 Part D drugs will go into effect starting in 2026. For 2027, the number of drugs involved will rise to 15 Part D drugs. In 2028, 15 drugs will be identified from across Part B and Part D combined, and then 20 drugs will be identified from across Part B and Part D combined starting in 2029 and beyond. The drugs will be selected by CMS from a list of drugs for which there has been the highest level of spending, subject to certain eligibility criteria.

On the forward outlook, while health policy is broadly viewed by investors as being secondary to more pressing items on the agenda (e.g., taxes and tariffs), suggesting a low likelihood of large scale healthcare reform regardless of the outcome of the upcoming presidential election, we note investor interest around the potential impact of a Trump administration on drug pricing, with the general assumption that a Democratic administration would likely maintain the status quo (i.e., provisions of the Inflation Reduction Act (IRA), though we are monitoring VP Harris' platform and note prior calls to expand the number of negotiated drugs to 50 per year). Broadly speaking, there are two potential avenues for further drug pricing policy: (1) legislation (where, per our US political economists, major reforms, including significant changes to provisions within the IRA, are unlikely even in a Republican sweep scenario; that said, smaller changes

(e.g., remediation of the IRA's pill penalty) are possible) and (2) executive action, where a revival of CMS' Most Favored Nation (MFN) model via the Center for Medicare and Medicaid Innovation (CMMI) for the largest Part B drugs (and then potentially Part D) is viewed as the most likely approach by our Washington economists and investors; however, we note the potential for legal challenges to MFN alongside potential impact from the recent overturn of the Chevron doctrine, as well as several outstanding questions around implementation. In addition, we are monitoring how MFN and IRA may intersect (e.g., international prices incorporated into Medicare price negotiations) given many drugs could be eligible for both programs. While a Trump administration would likely add uncertainty around drug pricing policy in the context of MFN, on the other hand, if this model is not pursued we see the potential for a lighter touch on price negotiations if there are changes in staff/leadership at CMS.

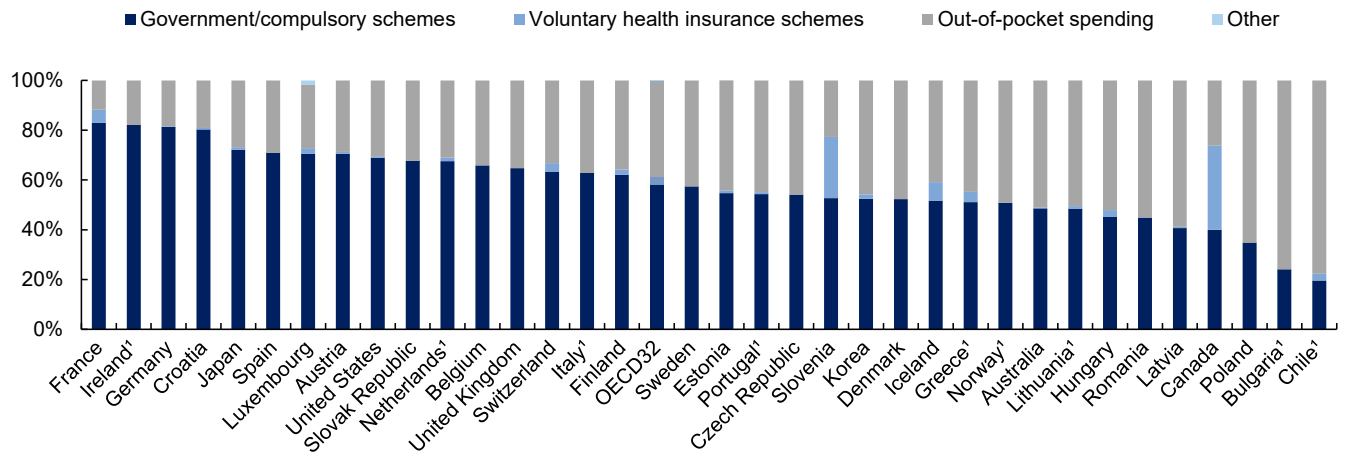
Exhibit 42: Expenditure on retail pharmaceuticals per capita, 2021



1. Includes medical non-durables

Source: OECD Health Statistics 2023

Exhibit 43: Expenditures on retail pharmaceuticals by type of financing, 2021



1. Includes medical non-durables

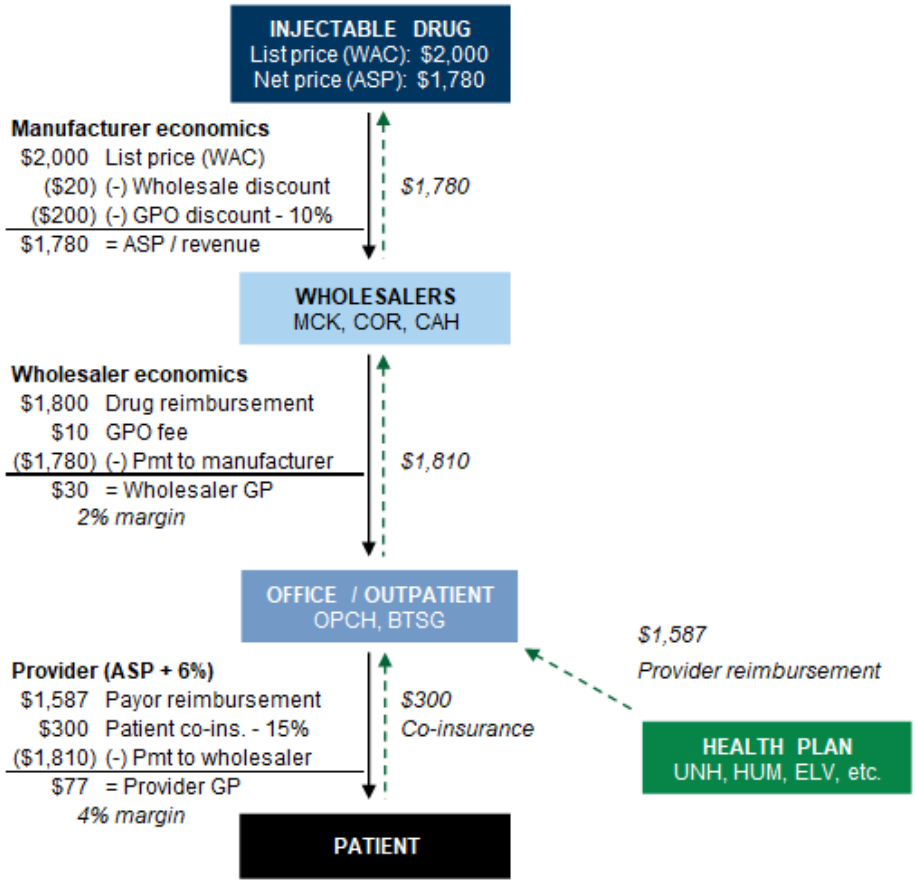
Source: OECD Health Statistics 2023

Drug reimbursement - How price is negotiated with payors?

Drugs are typically designated as falling under the medical benefit (also referred to as Part B drugs) or pharmacy benefit (Part D drugs). There are different mechanisms for reimbursement for drugs covered under the medical benefit vs. pharmacy benefit.

- **Medical benefit:** Drugs that fall under the medical benefit are administered by a physician or nurse practitioner in a hospital, infusion center, physician office, or other outpatient setting. These include many oncology drugs or drugs for other specialty conditions like infused rheumatoid arthritis products (e.g. Orencia) or age-related macular degeneration (e.g. Eylea). Reimbursement for these drugs usually reflect the buy-and-bill method. Under the buy-and-bill system, drug wholesalers negotiate service agreements and contract pricing with drug manufacturers, including discounts achieved via wholesaler-operated group purchasing organizations (GPOs). The wholesaler sells these drugs to providers, who administer them to patients. The provider buys the drugs, and once administered, bills the patient's insurance company for reimbursement. Coverage of these products is determined by the patient's insurance company, and pharmacy benefit managers (PBMs) are usually not involved (except in certain cases like white bagging). For Medicare outpatient drugs, reimbursement is based on average sales price (ASP) + 6%, with average sales price being the WAC price less discounts paid to distributors, providers, or payors in the channel. Commercial reimbursement for these drugs follow a similar formula as Medicare but may include a higher markup (>6%).

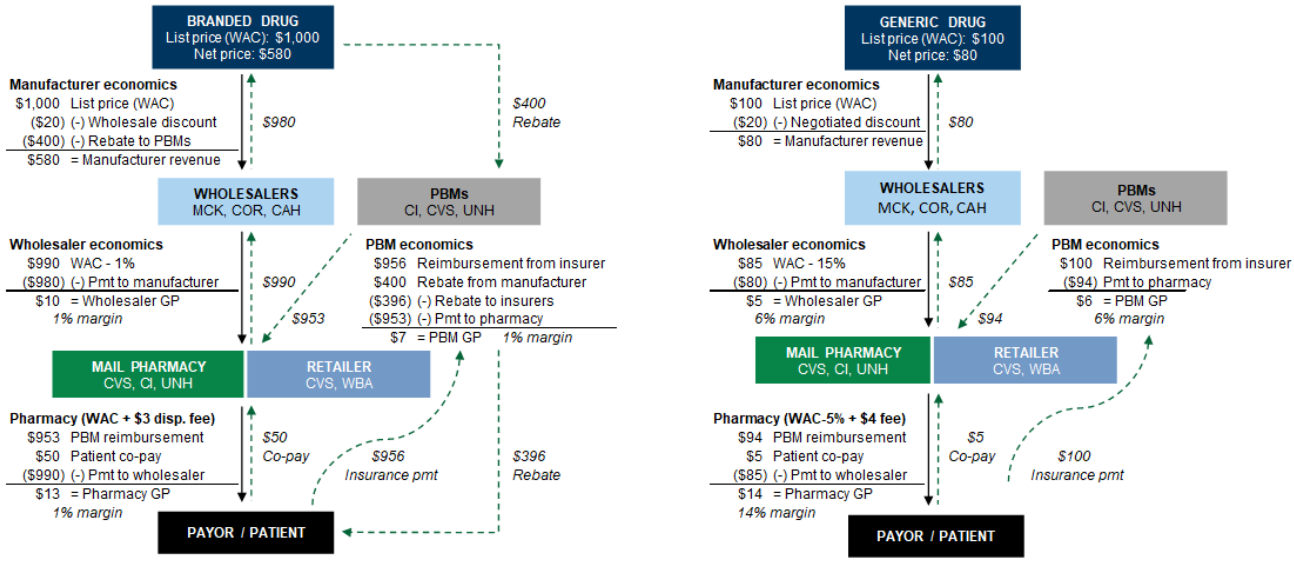
Exhibit 44: MEDICAL BENEFIT: Product and money flow



Source: Goldman Sachs Global Investment Research

- **Pharmacy benefit:** PBMs negotiate drug coverage, formulary tiers, and rebates for drugs covered under the pharmacy benefit. These include self-administered drugs (oral solid doses and patient-administered injectables). Manufacturers will pay rebates and fees in exchange for favorable placement on a PBM's formulary (e.g. ExpressScripts/CI, Caremark/CVS, OptumRx/UNH). PBMs may prioritize a higher list price drug on its formulary vs. a lower list price drug if the amount of rebate results in the lowest net cost despite the higher list price. While PBMs negotiate on a drug-by-drug basis, they aim to deliver the lowest net cost across all drugs for their clients and may consider the combination of drug coverage that will provide the lowest overall cost. Manufacturers may also pay fees to PBM-operated GPOs for pharmacy data, which reduce total net cost, but are not termed a rebate.

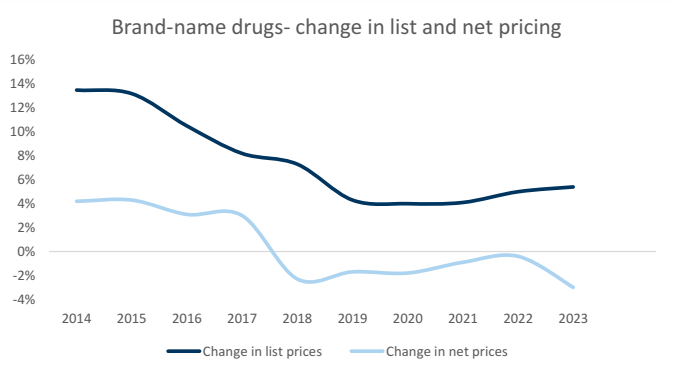
Exhibit 45: PHARMACY BENEFIT: Product and money flow
Brand vs. Generic Drugs



Source: Goldman Sachs Global Investment Research

Gross-to-net pricing for drugs covered under the pharmacy benefit: Pharma sets the list price or WAC (wholesale acquisition cost) of their drugs and are free to raise or lower the list price. Based on prices set by manufacturers, gross margins for biotech companies tend to be around 80%-90%, but can be higher or lower depending on the type of manufacturing and whether royalties are being paid. Reimbursement also depends on any rebates, discounts, fees, and patient assistance paid to the channel. For brand drugs, payors (often via the PBMs) negotiate a rebate for each prescription taken by one of its members under a safe harbor provision to the Anti-Kickback Statute. PBMs also negotiate fees associated prescription adjudication and data processing. These rebates and fees reduce the net cost of the drug and therefore the reimbursement paid to manufacturers. Insurers can use formulary exclusions or other reimbursement hurdles to negotiate pricing concessions from drug companies, and the actual gross-to-net ratio for a drug is dependent on the outcome of contract negotiation. The actual gross-to-net (GTN) ratio for a drug can vary widely and is not directly disclosed. The gross-to-net spread includes rebates passed back to payors, distribution/data fees, and patient assistance. Typically, we view the vast majority of the GTN spread as the rebate, though patient assistance could also be a meaningful portion of this spread before insurance coverage expands. By statute, Medicaid must receive the lowest net price, with limited exception, under the Medicaid Drug Rebate Program. In certain circumstances, a lower net price in a market like Medicare could have implications for Medicaid pricing as an example.

Exhibit 46: Widening of the GTN spread: Net prices moved lower despite list price increases
WAC price vs. net price change for select brand drugs (2014-2023)



Source: Drug Channels Institute, SSR Health

Utilization management: Payors and pharmacy benefit managers (PBMs) leverage utilization management (UM) strategies to control drug spend, especially in a competitive drug class. The most common techniques include formulary placement, prior authorizations (PA) and step therapies (ST). For drugs covered under the pharmacy benefit, the 'Big 3' PBMs, which include CI's Express Scripts, CVS's Caremark, and UNH's OptumRx, negotiate for 80%+ of the prescriptions in the US.

- **Formulary placement:** PBMs employ drug formularies to drive utilization to low net price drugs. Formularies typically have 3-5 tiers that classify drugs as generic (Tier 1) and preferred/non-preferred brand or specialty products (Tiers 2-5). Drug manufacturers negotiate with PBMs and offer rebates in exchange for favorable placement on formulary (e.g. on a lower tier with lower cost sharing). Each tier has unique cost sharing responsibilities for the member, with higher cost sharing for higher tiers. Brand drugs often have coinsurance where patients pay a percentage of the brand's list price, regardless of the rebate associated with that drug.
- **Prior authorization** requires that the patient obtain approval from the health plan before the plan will pay for a drug. This process enables the plan or PBM to determine if a drug is medically necessary for a patient or if treatment alternatives may exist.
- **Step therapy** is a process that requires patients to try lower cost drug options when an alternative exists before moving to the higher cost therapy. In this case, the health plan will typically not pay for a drug until the member has tried and not responded to a lower cost alternative, requiring the prescribing physician to certify that the lower cost option was attempted. These are most often used for common chronic conditions.

Types of health insurance

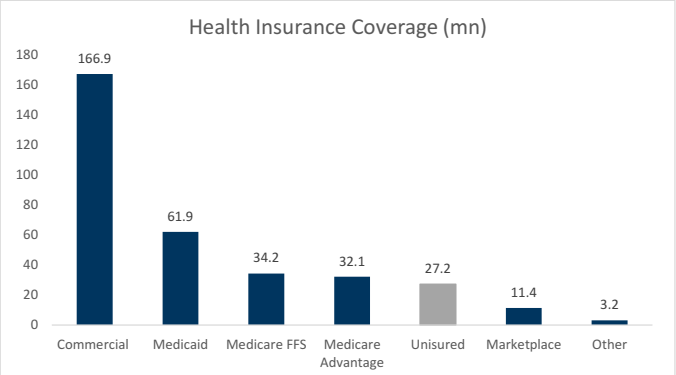
- **Private Health Insurance:** The commercial insurance market, with coverage via an employer or purchased by individuals, is the largest insurance market. Patients generally have one of two primary forms of insurance: a health maintenance

organization (HMO) or preferred provider organization (PPO). HMO plans are generally more restrictive and cost less than PPO plans.

- **Government Insurance:** Government insurance through Medicare and Medicaid provides ~44% of all prescriptions in the US, albeit the degree of exposure to government payers varies considerably by indication (i.e. cancer most frequently occurs in elderly populations covered by Medicare, whereas many rare diseases have limited exposure to Medicare).
  - **Medicaid** is a federally-administered, state-run program that provides health insurance to low income individuals and families. Two-fifths of Medicaid enrollees are children, and the program provides financial assistance to low income seniors who are dually eligible for both Medicaid and Medicare. Medicaid includes benefits for doctor visits, hospital stays, medications, vision/dental care and other items, depending on the state. Patients typically do not have to pay for covered medical costs.
    - **Medicaid Reimbursement:** The Medicaid Drug Rebate Program (MDRP) negotiates with manufacturers to set a National Drug Rebate Agreement (NDRA), and in exchange, covers the majority of a manufactures drugs under state Medicaid programs. In 2024, the MDRP works with ~780 manufacturers. In addition to the NDRA, the manufacturer also agrees to the Section 340B drug pricing program and the Federal Supply Schedule.
  - **Medicare**: Medicare is a federal program providing insurance to Americans over the age of 65 and people with some disabilities (e.g. ALS, ESRD). The Medicare market is has two offerings: **(1)** Traditional Medicare (FFS), which is run by the federal government and **(2)** Medicare Advantage (MA), which is a privatized form of Medicare.
    - **Medicare Part A** covers impatient care that is administered by hospitals, and post acute care including hospice, skilled nursing facilities, and home health care.
    - **Medicare Part B** covers outpatient services, mainly those delivered in a physician's office or outpatient clinics. This includes most preventive services as well as vaccines, lab tests, and medical equipment (e.g., wheelchairs). Part B covers medications that are administered in an office or outpatient setting including infusion drugs and provider-administered injectables.
    - **Medicare Part C** is also known as Medicare Advantage (MA). It includes all the benefits and services under Part A/B as well as benefits not provided by traditional Medicare, including Rx, dental, vision, hearing, fitness, and reduced cost sharing. It also gives patients the choice to enroll in a health maintenance organization (HMO)-type plan provided by a Medicare-approved private insurance company. MA plans that include a prescription drug benefit are called MA-PD plans.
    - **Medicare Part D** provides prescription drug coverage for self administered medications, and is available for anyone entitled to Part A

and/or enrolled in Part B. The Inflation Reduction Act (IRA) of 2022 included several changes to the Medicare Part D prescription drug benefit that are being phased in over a two-year period (2024-2025). See here for our deep dive into the Part D redesign for 2025, and the implications for payors and biopharma.

Exhibit 47: US Health Insurance coverage by type



Source: Census Bureau, Goldman Sachs Global Investment Research

Inflation Reduction Act: Drug Pricing Policy

The Inflation Reduction Act passed in 2022 including legislation that requires price negotiation between CMS and manufacturers on certain drugs, which have been on market for a specific duration of time and are a significant component of the Medicare budget (selected from a list of 50 drugs with the highest spend), with additional drugs selected per year (on a cumulative basis). Drugs will be selected for negotiation from Part D until the 2028 negotiation cycle, which will include 20 drugs across Part B and Part D (at steady state). Other considerations for selection include:

- **Time on market.** Small molecule drugs are eligible for negotation nine years post initial approval, whereas biologic therapies are eligible following thirteen years on market. This has been a focus for the industry with respect to lobbying for potential modifications to the bill's implementation.
- **Type of drug.** Some drugs are expected to be exempt from negotiations (or subject to distinct implementations), including: orphan drugs, fixed dose combination drugs, plasma-derived therapy, and "small biotech" drugs, though there are additional nuances to these exemptions.
  - Orphan drugs are exempt provided their only indication(s) are for that condition.
  - Small biotech drugs are exempt beginning in 2028, and have a maximum discount in 2029/2030. A small biotech drug is classified as a drug which represents over 80% of a company's total part B or D spending and represents <1% of total Part B/D spending.
  - New formulations may be exempt provided the formulation comprises a fixed-dose combination of two "active ingredients/active moeities". It remains

to be seen how this will be implemented, and the full scope of these exemptions, where there has been specific focus on what characterizes a fixed-dose combination.

We have previously written extensively on implementation of this legislation, as guidance has been revised and products for negotiation have been identified. Most recently, focus related to this legislation has been on price negotiations which were released for the first set of selected drugs and broadly in-line with our expectations. These prices will go into effect beginning in January 2026.

Notably, pharmaceutical companies in the midst of price negotiations have commented on limited near-term impact to revenue/profitability, but most anticipate that the impact will be greater as additional drugs are added to the list for negotiation.

Center for Medicare and Medicaid Innovation

The Center for Medicare and Medicaid Innovation (CMMI) was founded to develop and test new healthcare payment and service delivery models. These alternative payment models (APMs) are intended to incentivize high-quality and cost-efficient care, and can apply to a specific health condition, care episode, provider type, community, and/or innovation within Medicare Advantage or Medicare Part D.

For example, in 2023 CMS announced three new payment models for testing:

1. **Medicare $2 Drug List:** allows Medicare Part D sponsors to offer plans with maximum co-payment of $2/drug for a defined set of ~150 generic drugs. The focus on Part D sponsors/generic classes limits the impact of this plan on the biopharma industry.
2. **Cell and Gene Therapy Access Model:** Medicaid focused model targeting cell and gene therapy access, wherein CMS would partner with biopharma/biotech companies and state Medicaid agencies to test outcomes-based agreements. CMS will announce specifics of this plan in 2024/2025, and test the model as early as 2026. We see potential for this model to expand access to cell and gene therapy, where 36% of the US pediatric population is covered by Medicaid (17% of the adult population).
3. **Accelerating Clinical Evidence Model:** This model would adjust Medicare Part B payment amounts for drugs approved via the Accelerated Approval pathway, in order to support timely completion of confirmatory trials. This suggests that payment rates will be lower for drugs approved under accelerated approval vs. standard regulatory approvals.

Beyond these models, additional areas of research recently highlighted focus on accelerating biosimilar adoption via shared savings arrangements and/or bundles for certain classes.

Since disclosing these models, CMMI has provided one update on their status. With respect to the Cell and Gene Therapy Model, the agency highlights the proliferation of new agents recently approved or expected to be approved shortly (e.g. sickle cell gene therapies), generating significant need for state Medicaid programs which forecast

significant near-term spend on cell and gene therapies, and intends to accelerate the adoption of this model in 2025 (vs. 2026 prior).

Exhibit 48: Clinical and commercial cell and gene therapies
*Not exhaustive

Company	Asset	Indication	Stage	Cell/Gene	Unadjusted US Peak Sales (GSe) (M)
ADAP	Tecelra	Synovial sarcoma	Commercial	Gene	N/A
AMGN	Imlygic	Melanoma	Commercial	Gene	N/A
Amlogenyx	TBD	Alzheimer's disease	Clinical	Gene	Private
BLUE	Zynteglo	Beta thalassemia	Commercial	Gene	
BLUE	Lyfgenia	Sickle cell disease	Commercial	Gene	
BLUE	Skysona	Cerebral adrenoleukodystrophy	Commercial	Gene	
BMRN	Roctavian	Hemophilia A	Commercial	Gene	$550M
BMY	Abecma	Relapsed, refractory multiple myeloma	Commercial	Cell	$1,200M
BMY	Breyanzi	Chronic lymphocytic leukemia, small lymphocytic lymphoma	Commercial	Cell	$1,500M
Cardinal Glennon Children's Medical Center	Allocord	Hematopoietic disorders	Commercial	Gene	Private
Cell Trans	Lantidra	Type 1 Diabetes	Commercial	Cell	Private
Cleveland Cord Blood Center	Clevecord	Hemotapoietic disorders	Commercial	Cell	Private
Duke University School of Medicine	Ducord	Hematopoietic disorders	Commercial	Cell	Private
FCSC	laViv	Nasolabial fold wrinkles	Commercial	Cell	N/A
FDMT	4D-150	Wet age-related macular degeneration	Clinical	Gene	$1,400M
FDMT	4D-150	Diabetic macular edema	Clinical	Gene	$1,100M
Ferring Pharmaceuticals	Adstiladrin	BCG-unresponsive NMIBC	Commercial	Gene	Private
Gamida Cell Inc.	Omisirge	Hematologic malignancy	Commercial	Cell	Private
GILD	Yescarta	Non-hodgkin lymphoma	Commercial	Cell	$1,200M
GILD	Tecartus	Mantle cell lymphoma, acute lymphoblastic leukemia	Commercial	Cell	$490M
GLPG	GLPG5301	Multiple myeloma	Clinical	Cell	N/A
GLPG	GLPG5101	Non-hodgkin lymphoma	Clinical	Cell	N/A
GLPG	GLPG5201	Chronic lymphocytic leukemia	Clinical	Cell	N/A
IOVA	Amtagvi	Melanoma	Commercial	Cell	$1,800M
JNJ	Carvykti	Multiple myeloma	Commercial	Cell	$2,900M
KRYS	Vyjuvek	Dystrophic epidermolysis bullosa	Commercial	Gene	$1,000M
KYKOF	Lenmeldy	Metachromatic leukodystrophy	Commercial	Gene	N/A
KYKOF	Strimvelis	ADA-SCID	Commercial	Gene	N/A
Mallinckrodt Pharmaceuticals	Stratagraft	Thermal burns	Commercial	Cell	N/A
New York Blood Center, Inc.	Hemacord	Hematopoietic disorders	Commercial	Cell	Private
NVS	Zolgensma	Spinal muscular atrophy	Commercial	Gene	$660M
NVS	Kymriah	ALL, DLBCL, FL	Commercial	Cell	$230M
ORGO	Gintuit	Mucogingival conditions	Commercial	Cell	N/A
PFE	Beqvez	Hemophilia B	Commercial	Gene	N/A
PTCT	Upstaza	AADC deficiency	Commercial	Gene	$40M**
QURE	Hemgenix	Hemophilia B	Commercial	Gene	$490M
RGNX	ABBV-RGX-314	Wet age-related macular degeneration	Clinical	Gene	$1,100M
RGNX	ABBV-RGX-314	Diabetic retinopathy	Clinical	Gene	$300M
RGNX	RGX-202	Duchenne muscular dystrophy	Clinical	Gene	$1,700M
RGNX	RGX-121	Hunter syndrome	Clinical	Gene	$170M
ROG	Luxturna	Inherited retinal disease	Commercial	Gene	$80M
Sanpower Group Co.	Provenge	Metastatic castrate resistant prostate cancer	Commercial	Cell	N/A
SRPT	Elevidys	Duchenne muscular dystrophy	Commercial	Gene	$3,700M
Sumitomo Pharma	Rethymic	Congenital athymia	Commercial	Cell	N/A
VCEL	Maci	Knee cartilage defects	Commercial	Cell	N/A
VRTX/CRSP	Casgevy	Sickle cell disease	Commercial	Gene	$1,200M
VRTX/CRSP	Casgevy	Beta thalassemia	Commercial	Gene	$130M

***Global*

Source: Data compiled by Goldman Sachs Global Investment Research

On the Accelerating Clinical Evidence Model, CMMI reinforced need for efficient confirmatory studies when accelerated approvals are granted. The agency continues to collect input on this model, and within the context of recently established FDA authorities (described above), will continue to monitor developments. CMMI has not provided a timeline for the implementation of this model, however, we note an average lag between accelerated approval and confirmatory data of ~3 years during which time a product might be subject to lower net reimbursement under this model.

Intellectual Property

To incentivize new drug development, governments issue intellectual property protection for agents as patents and/or market exclusivity. To qualify for a patent, the drug must be proven to be useful, novel, and non-obvious.

Generic agents:

There are multiple types of patents granted to new drugs, including:

- Composition of matter: patents on the molecule itself, considered the strongest form of patent protection.
- Method-of-Use: how the drug is used
- Formulation: dosage or administration device
- Process: steps formed to create the drug

One may also hear about method-of-treatment patents (similar to method-of-use), crystal structure patents, polymorph patents, and others, each with relative strengths and weaknesses.

The FDA maintains an electronic list of all approved small molecule drugs and their associated patents called the Orange Book (the Purple Book is the equivalent for biologic products).

Patents provide protection for 20 years after the initial filing of the patent, however, there are multiple potential extensions available to drug manufacturers:

- Regulatory exclusivity: all drugs are eligible for five years of protection following initial approval, though drugs initially approved for a rare disease are eligible for seven years of regulatory exclusivity.
- Pediatric extensions: by studying the drug in question within pediatric populations, a drug may be eligible for an additional six months exclusivity, applied to the patent of choice.
- Hatch-Waxman extension: given drug development eats up some (and in some cases, a meaningful portion) of the patent life, sponsors are eligible to apply a Hatch-Waxman extension to the patent of their choice (generally one viewed as particularly strong). This extension is based on one-half the time from IND filing to NDA submission, and cannot exceed 14 years.

Evaluating the strength of intellectual property surrounding each product is one of the most technically difficult aspects of biophama investing. However, a few rules of thumb apply: I) composition of matter patents are the strongest available, and are generally not challenged, ii) beyond the composition of matter patent, a patent thicket (multiple issued patents across multiple types of patents) provides reasonable protection vs. generic entry.

Paragraph IV Procedures

The Abbreviated New Drug Application (ANDA) is the regulatory filing required for approval of a new generic agent, which will contain significantly less information vs. an NDA given the underlying assertion that the generic drug filed via ANDA is comparable to a branded drug already approved and on market.

Under the legal framework introduced by the Hatch-Waxman act of 1984, a "Paragraph IV certification" is filed by a potential generic manufacturer. This certification asserts that, in the opinion and to the best knowledge of the filer, patents listed for the branded drug in the FDA's Orange Book are invalid, unenforcable, or will not be infringed by the generic drug in question.

Branded drugs are eligible for Paragraph IV challenge four years following the initial approval of the product. Once filed, the branded drug sponsor has 45 days to challenge this assertion. If challenged, a 30-month stay is instituted, during which time the generic and branded sponsors will litigate patent rights in court. The 30-month stay may be voided if the patent expires or is judged invalid during the 30-month period.

There are multiple potential outcomes for this patent litigation:

- The patent(s) may be voided, at which point the generic manufacturer has the right to enter the market.
- The patent(s) may be upheld, barring the generic drug from market till after it expires.
- The branded and generic manufacturers may reach a settlement for when the generic drug will enter the market.
  - The sponsors may agree to an "authorized generic" wherein the generic company or a subsidiary of the branded drug sponsor markets the exact same drug (including inactive ingredients), but without the brand label.

  If the litigation has not been concluded by the time the 30-month stay has ended, a generic manufacturer may enter the market "at-risk". However, if the litigation is decided against them, they will owe damages to the branded manufacturer in question.

Biosimilars: more complicated than generics

Biologic drugs are inherently more difficult to replicate vs. small molecules, thus there is a separate regulatory path for their approval. A biosimilar product is similar to, and has no clinically meaningful differences from, an FDA approved biologic (reference product). Unlike a generic product, which can be copied with relative simplicity, biologics cannot be copied because these products vary slightly from batch to batch.

Thus, in order for a biosimilar product to be approved, these biologic agents must undergo testing to verify that it is similar and has no clinically meaningful differences vs. the reference product with respect to safety, purity, and potency. While the approval is abbreviated vs. approval of the reference product, biosimilar sponsors are required to conduct additional studies, including analytical studies (proving structural/functional similarity between products), animal studies (providing toxicology and pharmacology data), and clinical studies (demonstrating similar pharmacokinetics and immungenecity, clinical differences). The FDA may exercise discretion regarding the exact requirements for a biosimilar applications.

Thoughts on interchangeability: An "interchangable biosimilar" must meet additional standards, including studies on switching between the reference product and biosimilar. This designation enables patients to switch from the reference product to an interchangable biosimilar without the express direction of a physician (i.e. at the pharmacy, similar to how branded and generic drugs are interchangable at the pharmacy). While interchangeability allows this switching from the reference product, these products do not act like generics (where switching is common) as utilization of an interchangeable biosimilar is also impacted by formulary placement. Payors/PBMs may require members to take a specific biosimilar product and could place a non-interchangeable biosimilar on a preferred formulary tier based on net price and/or rebate received from the manufacturer.

Biosimilar market disruption ahead

Biosimilar products have had a somewhat slow start in the US (EU adoption has, by contrast, been robust). However, recent biosimilar approvals on key biologic products are expected to have an increasing impact over the next decade - we estimate the coming wave of biosimilars will impact a >$55B addressable market of brand value by 2030E.

Exhibit 49: LOEs through 2030 represent a ~$56B addressable market

Reference drug	Generic name	'23 brand net sales	Biosimilar entry:
Simponi	golimumab	$1,124	2024E
Cimzia	certolizumab	$1,155	2024E
Stelara	ustekinumab	$6,966	2025E
Soliris	eculizumab	$1,734	2025E
Xolair	omalizumab	$1,955	2026E
Trulicity	dulaglutide	$5,433	2027E
Enbrel	etanercept	$3,650	2029E
Pharmacy benefit		**$22,018**	
Eylea	aflibercept	$5,720	2024
Prolia / Xgeva	denosumab	$4,048	2025E
Yervoy	ipilimumab	$1,338	2025E
Opdivo	nivolumab	$5,283	2028E
Keytruda	pembrolizumab	$15,114	2028E
Orencia	abatacept	$2,754	n/a
Medical benefit		**$34,257**	

Source: FDA, Company data, Goldman Sachs Global Investment Research

Exhibit 50: BIOSIMILAR REBATES: Incremental $13-$20B of rebates possible, with $0.1-$0.6B kept by PBMs
GS estimate of sales erosion post biosimilar competition, with 1-3% of rebates kept by PBMs

	Biosimilar	Competitors	US gross sales	US net sales		Erosion in net sales (%)		Net sales post competition		Chg. rebates/fees ($)		% retained by PBM		$ retained by PBM	
Reference drug	entry date	Approved	2021, $mn	2023, $mn	GTN %	More	Less	Low	High	Low	High	Low	High	Low	High
PHARMACY-BENEFIT BIOSIMILARS															
Humira	2023	10	$28,236	$12,160	-57%	-80%	-60%	$2,432	$4,864	$6,615	$9,047	1%	3%	$66	$271
Stelara	2023-2024E	2	$10,671	$6,966	-35%	-60%	-40%	$2,786	$4,180	2,647	4,040	1%	3%	26	121
Soliris	2025E	1	$1,228	$1,734	41%	-40%	-20%	$1,040	$1,387	321	668	1%	3%	3	20
Actemra	2022-2023E	2	$1,961	$1,099	-44%	-40%	-20%	$659	$879	203	423	1%	3%	2	13
Simponi	2024E	0	$1,611	$1,124	-30%	-40%	-20%	$674	$899	208	433	1%	3%	2	13
Enbrel	2029E	2	$8,081	$3,650	-55%	-40%	-20%	$2,190	$2,920	675	1,405	1%	3%	7	42
Cimzia	2024E	0	$1,891	$1,155	-39%	-40%	-20%	$693	$924	214	445	1%	3%	2	13
Xolair	2024E	0	$2,382	$1,955	-18%	-40%	-20%	$1,173	$1,564	362	753	1%	3%	4	23
Tysabri	2027E	1	$1,443	$998	-31%	-40%	-20%	$599	$798	185	384	1%	3%	2	12
Total (pharmacy-benefit)			**$57,504**	**$30,841**	**-46%**			**$12,248**	**$18,416**	**$11,429**	**$17,598**			**$114**	**$528**
DIABETES PRODUCTS															
Lantus	2021	2*	$6,497	$238	-96%	-40%	-20%	$143	$190	$37	$85	1%	3%	$0	$3
Novolog	2022E	0	$5,979	$677	-89%	-40%	-20%	$406	$542	105	240	1%	3%	1	7
Humalog	n/a	1*	$5,233	$863	-84%	-40%	-20%	$518	$691	121	293	1%	3%	1	9
Victoza	2024	1	$3,709	$527	-86%	-40%	-20%	$316	$421	82	187	1%	3%	1	6
Trulicity	2027E	0	$12,221	$5,433	-56%	-40%	-20%	$3,260	$4,346	940	2,027	1%	3%	9	61
Total (diabetes)			**$33,639**	**$7,738**	**-77%**			**$4,643**	**$6,191**	**$1,284**	**$2,832**			**$13**	**$85**
Total (pharmacy benefit + diabetes)			**$91,143**	**$38,580**	**-58%**			**$16,891**	**$24,606**	**$12,714**	**$20,430**			**$127**	**$613**

Source: FDA, IQVIA, Company data, Goldman Sachs Global Investment Research

Most notably, Humira biosimilars launched in 2023, representing the first significant Part D biosimilar to come to market in the US. Humira alone represents ~30% of biologic and diabetes product revenues losing patent protection through 2030; recall Humira US revenues of $18.6B in 2022 prior to biosimilar competition. Ten companies have launched a biosimilar (including AMGN's Amjevita, where we note a modest launch thus far but are monitoring uptake), with some including both branded and unbranded versions. The discount vs. Humira price depends on whether the product is branded (~5% discounts across branded biosimilars) or unbranded (55-86% discount across six unbranded biosimilars); three have been granted interchangability status, though only one for the high concentration.

In 2023, CVS launched Cordavis to work with manufacturers to commercialize or co-produce biosimilars, with initial partnerships with Sandoz and ABBV for a co-branded product. The company removed branded Humira from its formulary as of April 1, 2024, and has moved significant market share since then. Following CVS's changes, Cigna announced that low-list price versions of adalimumab would be available for $0 out-of-pocket, and UNH added unbranded adalimumab without prior authorization requirements effective 5/1/24.

Exhibit 51: Biosimilar Humira coverage by PBM
Biosimilar Humira coverage - September 2024

Drug/ Biosimilar	Interchangeability status	List price	Formulary coverage				
			OptumRx	Caremark	Express Scripts	Carelon	Humana
Amjevita (Amgen)	No	Branded - $6,576	1/1/2023				
		Unbranded - $3,115					
Cyltezo (Boehringer Ingelheim)	Yes	Branded - $6,507	09/01/23		09/01/23	12/01/23	
		Unbranded - $1,315					
Hyrimoz (Sandoz)	No	Branded - $6,576	09/01/23	04/01/24	09/01/23		
		Unbranded - $1,315					
		With Cordavis - $1384		2Q24			
Hadlima (Organon)	No	$1,038					
Abrilada (Pfizer)	Yes	$6,576/ $2,769					
Hulio (Biocon)	No	1. Branded - $6,576	09/01/23	04/01/24			
		2. Unbranded - $1,038					
Yusimry (Coherus)	No	$995					
Idacio (Fresenius Kabi)	No	$6,576					
Yuflyma (Celltrion)	No	$6,577					
adalimumab-abdm (Boehringer Ingleheim)	yes	with Quallent $0 OOP			06/01/24	12/01/23	
Simlandi (Teva/Alvotech)	yes	Branded- $1,042			06/01/24		
	yes	with Quallent $0 OOP			06/01/24		

Source: Company data, Reuters, Goldman Sachs Global Investment Research

Against this backdrop, Humira sales declined 32% in 2023, and management guidance projects another 33% decline in 2024 (US erosion of 36%). We view the cadence of Humira volume and price erosion as presenting a helpful precedent for future biosimilar launches. While initial biosimilar launches saw more gradual price erosion vs. generics, Humira potentially set a new precedent with certain manufacturers offering a list price that is ~85% below Humira at launch, driving price lower faster. While we expect that each market will be somewhat unique, reflecting differences in indication (acute vs. chronic), administration devices, number/manufacturing capacity of biosimilars, we believe that the pricing discounts established with Humira should caution pricing assumptions for future biosimilar launches.

Drug Manufacturing

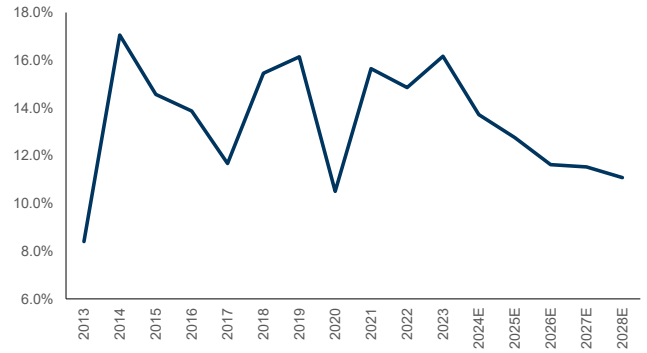
With the advent of biotechnology, specifically large molecule therapies, there has been a significant increase in the complexity of manufacturing drugs. We review the manufacturing process for these large molecules, which we estimate is a ~$12-17.5B market, within.

Bioprocessing Manufacturing Overview

Classic drug treatments have been small molecule, which are chemically synthesized. In contrast, a growing number of drugs are large molecule otherwise known as biologics. Large molecule drugs are organically grown in host cells that produce a backbone of complex proteins. These two types of drugs vary across a number of traits, from structure to mode of ingestion to clinical application. Small molecule drugs typically are comprised of 20 to 100 atoms per molecule while even the smallest of large molecule drugs typically has roughly 5,000 to 50,000 atoms per molecule. This difference in molecular scale means that large molecules are characterized by a highly complex, unstable structure. The smaller scale of small molecules lends itself to less complexity and more stability. The increased complexity of the biologic's structure means that the

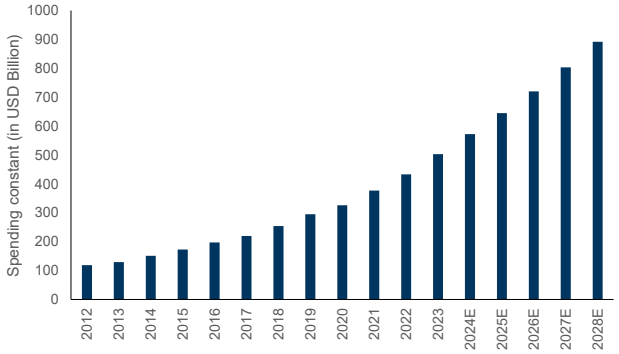
development and manufacturing process for large molecules is significantly more complicated than that of small molecules. Aspirin is an example of a small molecule treatment. Keytruda, Merck's highly successful cancer drug, is an example of a biologic.

Exhibit 52: Annual growth rate in biologic spend



Source: IQVIA

Exhibit 53: Global Biologic Drug Spend

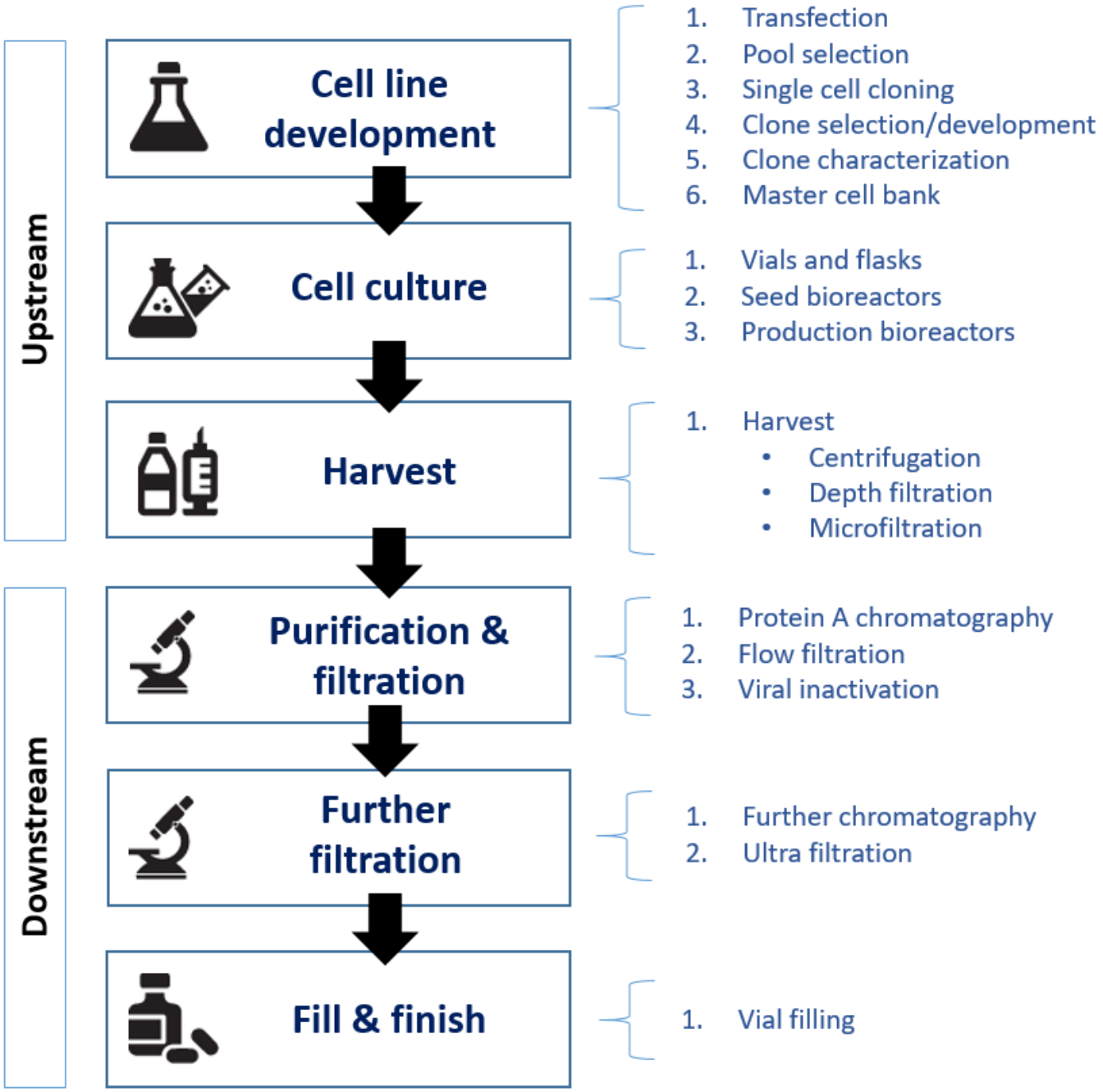


Source: IQVIA

Process

There are a significant number of steps in the process, requiring multiple types of machines with various consumables used at almost every step. There isn't a one-size fits all single step for purification and filtration, but rather multiple steps that utilize different properties to account for different types of potential contaminants. We have listed suppliers of various inputs at each stage of the process — this is not an exhaustive list of suppliers by input and also does not necessarily reflect market share.

Exhibit 54: mAb Manufacturing Steps
Stages can have even additional sub-steps, we have summarized the broad process



Source: Liu, Ma, Winter, Bayer, https://europepmc.org/article/PMC/2958570, BPI

Exhibit 55: Upstream stages serviced by vendor
No particular order, list is not exhaustive but rather illustrative

Source: Company data, Goldman Sachs Global Investment Research

Cell Line Development

Transfection is the process of introducing nucleic acids into cells to change the properties of those cells to study and modulate gene expression. Once cells are stably transfected in cell pools, they can be sorted into single cell lines which can then be assessed and selected as targets based on productivity, growth performance and other metrics of interest. Finally, the target cell lines are characterized in more detail. Inputs for this stage include custom cell lines, transfection reagents, well plates for pool selection, FACS for cell sorting and flasks and some cell culture media for scale-up for master cell bank generation.

Cell Culture

The goals of cell culture is the generation of the proper number of cells from the selected optimal single cell line for the usage of a production bioreactor for large volume scale-up. The cells are usually run through multiple growth systems which become larger with each run (such as: vials to shake flasks to small scale seed bioreactors and finally to larger production bioreactors). Bioreactors help grow cell volumes beyond the initial smaller volume that comes out of cell line development and smaller cell culture growth mediums. Bioreactors can range from less than 10 liters to up to 20,000 liters for stainless steel bioreactors (SSB) and up to 5,000 liters for a single-use bioreactor (SUB). Over the past few years, there has been a shift in the industry towards SUB, particularly in bioprocessing. There are multiple catalysts for this trend. Single use systems require less cleaning, low utility costs, more flexibility in facility design and batch application and typically less capex spend.

Suppliers of these inputs: for smaller cell culture media: (Cytiva, Thermo, Waters, Avantor, Millipore Sigma, Sartorius, Bio-Techne and many others) for bioreactors: Thermo, Sartorius, DHR (Cytiva & Pall).

Harvest

There are three primary methods of harvesting from bioreactors, which can be used individually, in tandem or in sequence. These are centrifugation, depth filtration and microfiltration. Broadly these all involve isolating target cells from the growth medium in the bioreactor, leaving harvested cell culture fluid (HCCF) that is then suitable for further filtration via chromatography. Centrifugation involves spinning samples, creating layers of particles based on density. This method is most useful for quantity maximization in short time periods but the danger of this process is potential cell damage and the ensuing purity contamination.

The second method is depth filtration which uses a filter media to trap particles of different densities in different areas, allowing for collection of the target cells. This process does not result in potential cell damage such as centrifugation but is not as efficient at high volume batches (typically 4000L is the cutoff wherein centrifugation is the preferred method).

Microfiltration is similar to depth filtration but on a more precise scale as the filter media utilizes smaller pores. The advantage of this is that batches can be harvested with more precision while the trade-off is volume, as microfiltration is useful only with smaller volumes.

Suppliers of these inputs: centrifugation (Thermo, Eppendorf, Ohaus (Mettler Toldeo), others), depth filtration (Pall (DHR), Millipore Sigma, Sartorius, 3M, others) and micro filtration (Pall (DHR), Sartorius, Bio-Rad, Thermo).

The cost of a manufacturing a single gram of antibody could be as high as $10,000, meaning a single kilogram of antibody could come with a price tag of $10,000,000. Of this, roughly 60% to 65% is in upstream. Of that ~60% in upstream, about half is in the fermentation stage. This is particularly true for singe-use bioreactors, which have significant consumable overhead costs.

Exhibit 56: Downstream stages serviced by vendor
No particular order, list is not exhaustive but rather illustrative

Source: Company data, Goldman Sachs Global Investment Research

Purification and filtration

The capture process occurs post harvesting and is a purification step typically involving protein A chromatography. Protein A chromatography is the most frequently used affinity chromatography method in biomanufacturing. This is a robust process for capturing a more purified product and removes most of the process-related impurities generated during cell culture and fermentation such as Host Cell Proteins, DNA and other unwanted components. Affinity resins tend to be one of the more expensive consumables in the manufacturing process, as a single 250mL bottle of affinity resin can cost more than $10,000. Suppliers of affinity resins include (Thermo, Bio-Rad, Cytiva, Repligen, Avantor, PerkinElmer and many others).

Further filtration steps such as tangential flow filtration could be undertaken at this stage. Tangential flow filtration passes the fluid of interest parallel to a filter, rather than perpendicularly as in normal filtering processes in order to reduce filter media clogging (Repligen, Pall, Sartorius). The next stage is viral inactivation, in which various techniques are utilized to ensure that viruses in a sample are prevented from causing contamination, either by rendering them non-infectious or removing them entirely from the sample. There are multiple methods for this process, from heat to artificial pH adjustment to detergent as well as others (Pall, Mettler, Millipore Sigma, Charles River and others).

Further filtration

In this stage, the product is further purified utilizing multiple methods. The first is more rounds of chromatography. Ion exchange chromatography is used to separate molecules based on charges. Anion exchange chromatography uses a positively charged ion exchange resin for molecules with net negative surface charges. Cation exchange

chromatography uses a negatively charged ion exchange resin for molecules with net positive surface charges. Once the target molecule is bound, unbound (and unwanted) material is washed out. This step may be repeated multiple times to gain even higher purification levels. To attain even higher levels of purification, additional steps can be taken. One of these includes ultra filtration, a pressure-driven process that separates unwanted particulate matter from compounds using an ultrafine membrane filter.

Suppliers include:

- **Ion exchange chromatography:** Bio-Rad, Waters, Cytiva, Millipore Sigma,
- **Ultrafiltration:** Pall, Sartorius, Millipore Sigma

Fill and finish

Fill-finish is the final stage in the biologic drug manufacturing process. It comes after upstream development and cell culture, harvest and downstream purification. While a less scientifically complex step in the process, fill and finish is a critical part of manufacturing as any mistakes at this stage can render a drug product useless, an incredibly expensive proposition given all the previously invested costs further upstream. Aseptic fill finish is the area where a sterile drug is transferred from a filling needle to a sterile container, usually a vial or prefilled syringe.

Fill and finish is a stage in the production cycle where automation plays a notable role, which is expected to grow over time. This stage is less reliant on complex science and more reliant on classic industrial manufacturing processes (albeit while maintaining strict quality standards), leaving greater potential for efficiency capture with increased automation options. This is a stage that is served by contract manufacturing organizations (CMOs) more than Tools names although some Tools companies do offer fill and finish capabilities.

Vendors at this stage include Catalent, Thermo and many others

Sizing the Bioprocessing Manufacturing Market

Sizing the bioprocessing market is challenging given the lack of wide-spread industry data. We consulted with multiple industry experts as well as did our own analysis to come up with a framework for sizing the market which we intend to be illustrative to readers of the relative scale of the industry.

The definition of even what exactly is included in the bioprocessing end market varies depending on who is asked. In our market sizing exercise below, we are focused on only manufacturing. We do not size the research and discovery costs pre-manufacturing although we do capture some costs that would be listed as R&D and not COGS for pharma companies such as pre-commercial manufacturing for clinical trials which would be R&D and not be COGS. What is coined more broadly as "bioprocessing" could also include significant upstream research costs and include other products such as PP&E that we did not explicitly consider.

We had two primary ways of estimating market size. The first method was using an estimate of weekly throughput for a large bioreactor (20,000 liter bioreactor), an

estimate of total global bioreactor capacity, and an estimate of annual uptime to get to a total annual throughput. We then used an estimate of cost per dose to get to a total annual production cost number. Our second method was a more simple COGS assumption on the total global dollar sales of biologics to derive an addressable market.

The first method is outlined here and all number assumptions were based on expert network calls as well as our own industry analysis: We used an estimated COGS for a single 20,000L bioreactor batch run of $3M. We assumed the number of doses that can be harvested from this run to be 100,000, giving a cost per dose of $30. Based on our conversations with industry participants we estimate total global capacity is 10 million doses/week. We estimated 40 weeks of usage per year given maintenance, facility upgrades and other downtime uses. With 40 weeks of annual runtime and 10 million doses per week, we estimate 400,000,000 total annual doses. 400,000,000 annual doses times $30/dose gives total annual COGS of $12B.

Exhibit 57: Biologics global batch volume analysis

Global output volume analysis	
COGS for single 20k L batch run	3,000,000
Number of doses	100,000
Cost/dose	30
Global liter capacity	2,000,000
Doses/week	10,000,000
Weeks of use/year	40
Total annual global dose capacity	400,000,000
Implied global COGS = cost/dose X global dose capacity =	**12,000,000,000**
grams/liter	1.0
liters/batch	20,000
grams/batch	20,000
cost/gram	150
kilograms/batch	20
kilograms/year	800

Source: Data compiled by Goldman Sachs Global Investment Research

We then sanity checked this first method with a more simple second method. We did this by taking total biologics sales multiplied by a COGS percentage estimate. Assuming 95% gross margins and thus 5% COGS on $350B in biologics sales, we get to an addressable market of $17.5B. All-in, we estimate the market to be between $12B to $17.5B, or roughly $15B at the mid-point. As we noted in the first paragraph of this section, this is the bioprocesssing manufacturing market, not total bioprocessing overall. Using the proportion of R&D costs to cost of goods sold for large biopharma companies, which is roughly two thirds using a set of large cap pharma companies such as PFE, MRK, ABBV, BMY, and LLY for the 5 year period pre-Covid (2016 to 2020), we can add 2/3 of the manufacturing cost as the R&D cost to the addressable market, which would be 2/3 X $15B = $10B, getting us to a total bioprocessing market of $15B + $10B = $25B. We note that an implicit assumption in this cost extrapolation is that vendors can capture the same percentage share of costs for R&D as COGS (i.e. some research costs such as paying the wages of scientists are not revenue streams that Tools companies can capture as easily as can be captured in manufacturing streams such as with fermentation costs). We do not mean for this analysis to be taken as a fully in-depth market sizing (given lack of all the data we would need for that) but rather as an illustrative example of the relative scale of the market.

Considerations: the volume of active product produced can vary widely depending on the drug in question. The efficiency of the production process can also vary widely. Pricing on a particular therapy often does not reflect the relative volume of product needed. The manufacturing cost per gram can vary by many degrees of magnitude depending on the drug in question.

GLP-1 Manufacturing Opportunity

Much has been written on the opportunity and potential of new obesity therapeutics — in a base case, GS analysts project that the worldwide obesity market could potentially grow to $130B by 2030; in a blue-sky scenario our options strategists highlight a market potential as large as $400B. Despite this, we believe the market size and opportunity set for the manufacturing of these therapies remains relatively opaque. While much of the manufacturing is currently done in-house by Novo Nordisk and Eli Lilly, our report aims to shed light on the manufacturing process, costs and outsourced opportunity for the Life Sciences sector.

We estimate the long term potential market size for GLP-1 manufacturing is ~$10B and the role of outsourcing will likely increase with volumes. We would note that GLP-1 manufacturing will likely result in slightly lower margins than monoclonal antibodies (mAbs) or complex gene therapies; however, the volume opportunity is significant and should help offset these potentially lower margins. Additionally, we expect the market to increasingly shift towards outsourcing as therapies currently being developed by companies other than Eli Lilly and Novo Nordisk move towards the commercial stage. This dynamic represents a significant opportunity for those companies in our coverage who are serving the upstream and downstream portions of GLP-1 manufacturing.

We see the total GLP-1 manufacturing opportunity reaching ~$10B in 2030 (more details in our Sizing the GLP-1 Manufacturing Opportunity report), but the true opportunity for companies in the Life Sciences tools and manufacturing space lies in the portion of that spend that is outsourced. While the obesity market is currently dominated by Eli Lilly and Novo Nordisk, who have strong backgrounds in metabolic disease and a preference for keeping production in house, we believe that increasing volumes along with new entrants into the space will lead to ~50% outsourcing and a ~$5B opportunity for outsourced providers in 2030.

We believe there is upside to this opportunity from higher GLP-1 volumes or outsourcing rates closer to the broader pharmaceutical industry average at ~66%, and also believe that certain companies may see outsized benefits depending on future production and administration methods of GLP-1 drugs.

Cell therapy supply chain

Even more complex manufacturing processes are necessary to support the development and commercialization of cell- and gene-therapy products, which have proliferated since the first approval of Kymriah in 2017; there are now more than twenty such approved products and even more in development.

Autologous cell therapy, which continues to dominate this landscape, requires

patient-specific manufacturing processes which require numerous steps and carry elongated timelines (2-4 weeks is common); during this time, patients may worsen (~10%) and/or manufacturing failures can arise, such that a significant portion of patients will never receive drug. Steps include:

- **Cell isolation.** In the case of autologous cell therapy, the process begins with cell extraction (from patient bone marrow or blood samples). This heterogeneous set of cells is then isolated for the cell subsets that are desired, based on type of cell (phenotype), viability, and for purity.
- **Cell activation and expansion.** This step requires growth media and equipment to expand the relatively small number of harvested cells to the scale necessary for clinical products. This requires a balance to achieve the necessary cell proliferation/activation without driving cell overactivation or exhaustion.
- **Cell engineering.** Cell therapies are designed and optimized for properties that will be useful in the context of clinical effectiveness (e.g. proliferation, persistence), typically using engineering techniques that can include CRIPSR/Cas9, viral transduction, and non-viral methods. Allogeneic CAR T cells are generated from healthy donor samples, and specifically engineered to avoid an immune response.
- **Cell characterization.** Quality control is necessary to ensure the efficacy and safety of cell therapy products, which will be administered to patients. There are multiple steps throughout the process to ensure that the product meets pre-specified critical quality attributes, and multiple tests should be performed to evaluate the product.

Beyond autologous cell therapies, which are primarily used for the treatment of blood cancer, the recent approval of IOVA's Amtagvi showcases another complicated manufacturing process with respect to Tumor Infiltrating Lymphocytes (TILSs). Similar to CAR T cell therapy, these products are developed from extracted cells, manufactured on a patient-by-patient basis, and require significant optimization and quality controls; IOVA has described a 22-day manufacturing process following significant optimization.

Gene therapy manufacturing is also complex, with two common processes depending on whether the target product is adenoviral (AAV) or lentiviral (LV) based. For AAV gene production, the steps include: i) plasmid (small, circular, double-stranded DNA molecule) production and purification (three plasmids required), ii) transfection to AAV producing cell line, iii) expansion, and iv) purification. LV manufacturing also includes LV-producer cell culture and expansion, followed by transfection of 3-4 plasmids. Across both processes, purification is a major challenge impacting manufacturing efficiency, cost, and quality of the vector production.

Given this complexity, cell and gene therapy manufacturing capacity and know-how have been bottlenecks to development and commercialization of such products, and companies often opt to control manufacturing in-house. However, as demand for these products continues to rise, we anticipate an increase in external manufacturing capacity.

Potential Implications of the BioSecure Act

Our colleague Ziyi Chen has written extensively about the potential impact of the

BioSecure Act on the global supply chain for drug development and manufacturing as detailed here and here. The bill recently passed through the House with a vote in the Senate expected to similarly garner bipartisan support.

As the bill stands now, there is a grandfathering clause included in the latest version: 1) for companies currently identified in the bill, such as WuXi Apptec and WuXi Biologics, a prohibition would take effect 60 days after issuance of the bill but would not apply to contracts entered into before the effective date, including currently negotiated contract option years, prior to Jan 1, 2032; 2) for newly identified names, a prohibition would take effect 180 days after issuance and would not apply to contracts that were entered into before the effective date, prior to five years after identification.

While we see this latest version including the eight year grandfather clause as an incremental improvement to the potential negative impact to supply chains, we would note that drug development and manufacturing programs can last longer than the eight year period which may affect future decisions around new and existing programs and how decisions by the pharma and biotech firms are made in terms of selecting partners. However, our recent conversations with industry group BIO (world's largest biotechnology advocacy organization) suggest that eight years is sufficient to rework supply chains, based on a survey of 124 biotechnology companies within the organization.

Appendix A: Events Calendar

These conferences are held annually, at approximately the same date but often at a rotating location.

Exhibit 58: Key 2024 medical conference (non-exhaustive) and dates

Conference	Title	Dates
ASCO GI	ASCO Gastrointestinal Cancers Symposium	1/18-1/20/2024
ECCO	European Crohn's and Colitis Organisation	2/21-2/24/2024
AAAAI	American Academy of Allergy, Asthma and Immunology	2/23-2/26/2024
ASCO GU	ASCO Genitourinary Cancers Symposium	2/25-2/27/2024
CROI	Conference on Retroviral And Opportunistic Infections	3/3-3/6/2024
AD/PD	Alzheimer's and Parkinson's Disease	3/5-3/9/2024
AAD	American Academy of Dermatology	3/8-3/12/2024
WADC	World ADC Europe	3/12-3/15/2024
ACMG	American College of Medical Genetics	3/12-3/16/2024
AACR	American Association for Cancer Research	4/5-4/10/2024
ACC	American College of Cardiology	4/6-4/8/2024
AAN	American Academy Of Neurology	4/13-4/18/2024
ELCC	European Lung Cancer Conference	4/20-4/23/2024
AUA	American Urological Association	5/3-5/6/2024
APA	American Psychiatric Association	5/4-5/8/2024
ARVO	Association for Research in Vision and Ophthalmology	5/5-5/9/2024
ASGCT	American Society of Gene and Cell Therapy	5/7-5/11/2024
AACE	American Association of Clinical Endocrinology	5/9-5/11/2024
NKF	National Kidney Foundation	5/14-5/18/2024
EADV	European Academy of Dermatology and Venerology	5/16-5/18/2024
ATS	American Thoracic Society	5/17-5/22/2024
DDW	Digestive Disease Week	5/18-5/21/2024
EAS	European Atherosclerosis Society	5/26-5/29/2024
ASCO	American Society of Clinical Oncology	5/31-6/4/2024
SLEEP	SLEEP 2024	6/1-6/5/2024
ENDO	The Endocrine Society	6/1-6/4/2024
ESHG	European Society of Human Genetics	6/1-6/4/2024
ATC	American Transplant Congress	6/1-6/5/2024
EASL	European Association for the Study of the Liver	6/5-6/8/2024
ECFS	European Cystic Fibrosis Society	6/5-6/8/2024
GS HCC	GS Healthcare Conference	6/10-6/13/2024
EULAR	European League Against Rheumatism	6/12-6/15/2024
EHA	European Hematology Association	6/13-6/16/2024
ASM	American Society for Microbiology	6/13-6/17/2024
ICML	International Conference on Malignant Lymphoma	6/19-6/22/2024
ADA	American Diabetes Association	6/21-6/24/2024
EAN	European Academy of Neurology	6/29-7/2/2024
ASRS	American Society of Retina Specialists	7/17-7/20/2024
IAS	International AIDS Society	7/22-7/26/2024
AAIC	Alzheimer's Association International Conference	7/28-8/1/2024
IPF	IPF Summit 2024	8/-/2024
DDS	Obesity & NASH Drug Development Summit	9/-/2024
WSS	World Sleep Society	9/5-9/10/2025
IASLC	International Association for the Study of Lung Cancer	9/7-9/10/2024
ERS	European Respiratory Society	9/7-9/11/2024
EASD	European Association for the Study of Diabetes	9/9-9/13/2024
ESMO	European Society for Medical Oncology	9/13-9/17/2024
ANA	American Neurological Association	9/14-9/17/2024
MDS	International Congress of Parkinson's and Movement Disord	9/27-10/1/2024
CHEST	American College of Chest Physicians	10/6-10/9/2024
Muscle	World Muscle Society	10/8-10/12/2024
ECTRIMS	European Committee for Treatment and Research in MS	10/18-10/20/2024
ENA/Triple	EORTC/NCI/AACR Meeting	10/23-10/25/2024
ASN	American Society of Nephrology Kidney Week 2023	10/23-10/27/2024
CTAD	Clinical Trial on Alzheimer's Disease	10/29-11/1/2024
NACFC	North American Cystic Fibrosis Conference	11/-/2024
AASLD	American Association for the Study of Liver Diseases	11/-/2024
TOS	Obesity Week	11/3-11/6/2024
WADC	World ADC USA	11/4-11/7/2024
SITC	Society for Immunotherapy of Cancer	11/6-11/10/2024
ACR Convergence	American College of Rheumatology	11/14-11/19/2024
AHA	American Heart Association	11/16-11/18/2024
ASH	American Society of Hematology	12/7-12/10/2024
SUO	Society of Urologic Oncology	12/4-6/2024
SABCS	San Antonio Breast Cancer Symposium	12/10-12/14/2024
ESMO IO	ESMO Immuno-Oncology	12/11-12/13/2024

Source: Goldman Sachs Global Investment Research

Appendix B: Key Therapeutic Areas

We detail key therapeutic areas of considerable focus for the biotech industry today, highlighting also key players in the respective indications. Note that this not exhaustive, but rather a focus on disease areas that are currently in focus because of the size of the potential market opportunity and/or the intensity of competitive clinical development within the disease.

Oncology

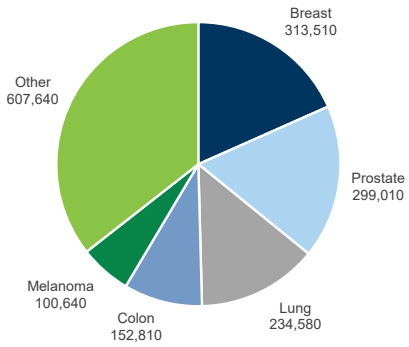
Solid tumors

Per the National Cancer Institute (NCI), solid tumors are abnormal masses of tissue that usually do not contain cysts or liquid areas, caused by uncontrolled cell growth. The distinct types of solid tumors are named after the location within the body where they originate and the type of cells involved, though they can often consist of multiple and varied cell types. We know some biological causes of cancer, though these vary across tumor types and are not always well-established. Finally, solid tumors may be malignant (cancer) or benign.

Breast, prostate, lung, colon, and skin (melanoma) cancers represent the most commonly observed (<5%) types of malignant solid tumors in the US (Exhibit 59). Beyond these, the NCI's Surveillance, Epidemiology, and End Results (SEER) program recognizes solid tumors in 18 other anatomical locations including the pancreas, central nervous system, and liver to name a few (represented by the "Other" category within our exhibits).

Mortality (rate of death), based on the number of expected 2024 deaths for a particular tumor type, varies considerably across tumors (Exhibit 60, Exhibit 61). This is partially due to the emergence of diagnostics capable of detecting cancer (or precancerous cells) ahead of symptom onset. Additionally, new drugs have prolonged survival for patients with these conditions. Among remaining areas of unmet need, pancreatic and lung cancers stand out the most among solid tumor for their high degrees of mortality (Exhibit 62).

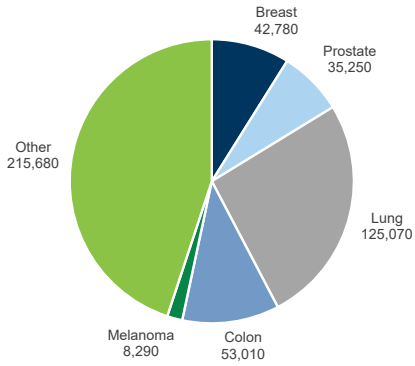
Exhibit 59: Estimated 2024 incidence of solid tumors



The "Other" category makes up tumors that are <5% of the total cases

Source: SEER

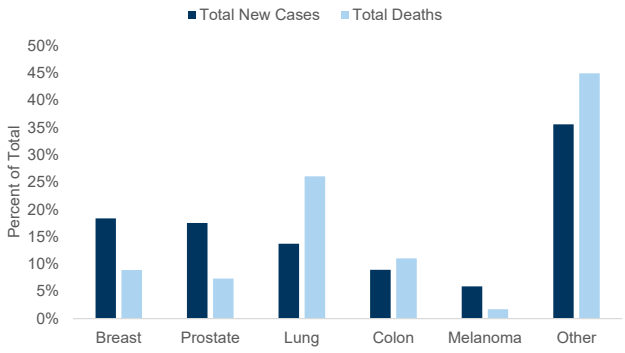
Exhibit 60: Estimated 2024 deaths due to solid tumors



The "Other" category makes up tumors that are <5% of the total cases

Source: SEER

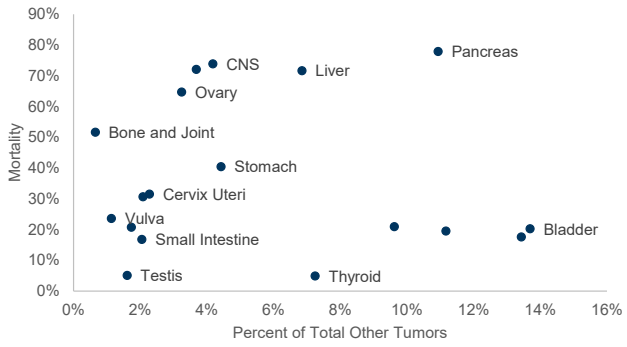
Exhibit 61: Incidences vs. mortality of solid tumors



The "Other" category makes up tumors that are <5% of the total cases

Source: SEER

Exhibit 62: Incidence vs. mortality of less common (<5% of total) solid tumors



Source: SEER

Immuno-oncology vs. precision medicine

Two of the most common types of treatments in oncology are immunotherapies and precision medicines. Immunotherapies harness the body's immune system to fight disease and are often called by the moniker of Immuno-Oncology (I/O) when applied to cancer. I/O approaches have seen considerable success across multiple tumor types, most notably melanoma and select lung cancer populations. By contrast, precision approaches, characterized as precision oncology, refer to drugs that target specific proteins that are mutated in the context of cancer cells, causing the disease. Patients will be characterized based on the presence of these mutations, and administered drugs tailored for their specific tumor type.

I/O approaches have seen meaningful success

The hallmark class of I/O agents is checkpoint inhibitors, which got their name because they block so-called "checkpoints" that would otherwise turn off the immune system, enabling the tumor to evade an attack. The emergence of these therapies has improved outcomes across multiple indications. For example, the 5-year relative survival rates of

metastatic melanoma increased from 18% for patients diagnosed in 2009 to 38% in 2015, following the advent of early immuno-oncology drugs: Opdivo and Yervoy.

The first approved checkpoint inhibitor was Yervoy (BMY; 2011), which targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). Later, in 2014, the FDA approved drugs targeting programmed death 1 (BMY's Opdivo and MRK's Keytruda). Currently, several companies (MRK, GILD/RCUS, ROG, BMY) are evaluating new drugs against additional targets (e.g., TIGIT, LAG3). Unlike other oncology agents, checkpoint inhibitors are approved for relatively broad use, with Keytruda approved to treat 19 distinct indications as of March 2024. These agents continue to be key revenue drivers for pharmaceutical companies, with Visible Alpha estimates of $32.9B for 2028 Keytruda sales alone.

Beyond checkpoint inhibitors, several additional therapies fall within the I/O umbrella including cancer vaccines and tumor infiltrating lymphocytes (TILs). Vaccines aim to train the body to generate a specific immune response against the patient's tumor, with both personalized and off-the-shelf approaches in development. So far, cancer vaccines have shown success in tumors likely to trigger a strong immune response like melanoma (hot), and limited efficacy in ones that are not, like colorectal cancer (cold). They are not expected to work well in patients that have very advanced cancer, as these patients do not have robust immune systems able to mount a response to the cancer.

Tumor infiltrating lymphocytes (TILs) similarly aim to generate an immune response to attack the patient's specific tumor. In this case, tumor tissue is first extracted and manipulated such that immune cells (called lymphocytes) can be grown in the presence of these tumor cells. Once generated, the tumor-specific immune cells are reintroduced to the patient, where they are able to mount an educated immune response against the tumor. That said, TILs as a drug class has only recently emerged as a viable strategy within oncology, with the first TIL drug, Amtagvi (lifileucel), being approved via the accelerated approval pathway on February 16, 2024 for advanced or metastatic melanoma. Beyond Amtagvi, there are several other TIL therapies in clinical development for solid tumors, including Obsidian's OBX-115 in advanced or metastatic melanoma and KSQ Therapeutics KSQ-001EX eTIL in solid tumors.

Precision oncology may provide greater benefit to a focused patient population

The primary aims of precision oncology companies are to identify genetic drivers of cancer (oncogenes), identify the patients with these genetic mutations, and develop drugs to treat them. There are dozens of known oncogenes, though some are more common than others. Tumors in different tissues (i.e. breast vs. lung cancer) will have different oncogenes, though there are some that overlap across multiple cancer types.

There are well-established oncogenes for which there are several approved therapies already on the market (e.g., EGFR, ALK), however, patients are not cured with these drugs. In fact, over time, cancer cells will develop resistance mechanisms to the targeted therapy. Often, new drugs will be developed that overcome or address these resistance mechanisms (i.e. AZN's Tagrisso was developed to address resistance to early EGFR inhibitors; it achieved $5.8B in 2023 sales).

Some oncogenes are more difficult than others to drug, even though they are known to

be common in certain cancer settings. For example, KRAS is a well-known mutation present at high rates in lung cancer, pancreatic cancer, and colon cancer, where we have only recently made breakthroughs with new drug approvals (AMGN's Lumakras, BMY's Krazati).

Given the nature of this approach, precision oncology drugs are likely to have a more narrow drug label. Patient identification for clinical study and commercial use of these drugs requires that patients be screened for specific genetic mutations, which is more and less common for certain cancer types or in specific treatment settings. In order for these drugs to realize their full potential, increases in the rate and quality of genetic tests are required.

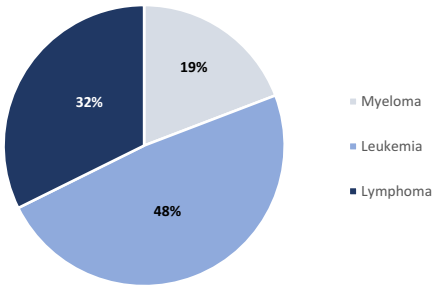
Hematology (blood cancer)

Hematologic malignancies. Hematologic malignancies are a family of cancers affecting the blood and consistent of three primary categories: leukemia, myeloma, and lymphoma, the latter of which is further categorized into non-Hodgkin or Hodgkin lymphoma. Leukemia affects blood cells (typically white blood cells) within the bone marrow, lymphoma affects lymphocytes (a type of white blood cell), and myeloma affects plasma cells (a type of white blood cell). Per the Leukemia & Lymphoma Society, there were ~185K new cases of blood cancer in 2023 (~9.4% of new cancer cases; Exhibit 63).

There are multiple subtypes of leukemia and lymphoma related to what type of blood cell(s) it affects. Common types of leukemia include acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). Common types of non-Hodgkin lymphoma (NHL) include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. The two main types of Hodgkin lymphoma are classical and nodular lymphocyte predominant.

The treatment paradigm for hematologic malignancies can include chemotherapy, a stem cell transplant, wherein a patient's stem cells are replaced with new, healthy stem cells, and immunotherapies, which use a patient's own immune system to attack and kill cancerous cells. Despite existing treatment options, some patients do not respond to the first line of therapy and require additional treatment. In recent years, there have been significant advancements in the field, which have led to the development and approval of several new treatment options such as BMY's CAR-T (see below for an overview on CAR-Ts) Breyanzi, which was approved in relapsed/refractory LBCL on 2023 and has since been approved in CLL and follicular lymphoma, and LEGN/JNJ's CAR T Carvykti, which was approved in 2022 for relapsed/refractory multiple myeloma. However, despite recent advancements, there is still significant unmet need for more effective treatment options, particularly in leukemia and myeloma, where according to Cancer Research UK, the five-year survival rate was ~56% in 2021. In leukemia, there is particularly high unmet need in AML, where the five-year survival rate was 30.5% overall from 2012 to 2018, according to the Leukemia & Lymphoma Society.

Exhibit 63: Relative distribution of hematologic malignancies



Source: Leukemia & Lymphoma Society

Non-malignant blood disorders. In addition to hematologic malignancies, there remains unmet need in non-malignant blood disorders, including hemoglobinopathies (a group of blood disorders that affect one's hemoglobin, a protein in red blood cells that carries oxygen throughout the body) such as sickle cell disease and thalassemia, thalassemia can be further categorized into non-transfusion dependent thalassemia (those who do not require regular blood transfusions) and transfusion-dependent thalassemia (those who require regular blood transfusions), as well as alpha and beta thalassemia depending on whether there is a mutation in the alpha or beta globin gene. In the US, there are ~100K individuals with the sickle cell disease, ~2K adults with transfusion-dependent thalassemia, and ~4K adults with non-transfusion dependent thalassemia. Both thalassemia and sickle cell disease are often characterized by anemia, which can cause fatigue, weakness, and shortness of breath. Sickle cell disease is also often characterized by pain crises, which are periods of extreme pain caused by the blockage of blood flow. Depending on the severity of disease, treatment options can include blood transfusions and bone marrow transplants. In sickle cell disease, hydroxyurea is also commonly used, which inhibits ribonucleotide reductase to prevent sickling and reduce the frequency of pain crises.

In recent years, there have been significant advancements in the field, which have led to the development and approval of several new treatment options. These novel therapies include PFE's Oxbryta, which was approved for sickle cell disease in 2023 and works by increasing hemoglobin's binding affinity for oxygen, BMY's Reblozyl, which was approved for transfusion-dependent thalassemia in 2019, CRSP/VRTX's CRISPR gene-edited therapy Casgevy, which was approved in 2023 and 2024 for sickle cell disease and beta thalassemia, respectively, and BLUE's gene therapies Zynteglo and Lyfgenia, which were approved in 2022 and 2023 for thalassemia and sickle cell disease, respectively.

Despite these recent advancements, there remains unmet need in both sickle cell disease and thalassemia for more effective treatment options, particularly for patients not eligible for gene therapy. Additionally, there are currently no approved therapies for alpha thalassemia or non-transfusion dependent thalassemia.

Cell therapy

Drug developers have sought to harness T cells' ability to target cells expressing foreign proteins while leaving neighboring healthy cells unperturbed to treat multiple cancers. Companies achieve this aim by engineering T cells to have chimeric antigen receptors or CARs. CARs are proteins that enable T cells to respond to a predetermined protein as if it were foreign and thereby eliminate cells expressing it. Engineered T cell containing CARs have emerged in recent years as a novel drug class, regarded as CAR-Ts.

Currently, the FDA has approved six CAR-T products to treat multiple hematologic malignancies (Exhibit 64). These therapies are autologous, meaning that therapies are made from cells drawn from each patient. Designing autologous CAR-Ts involves (1) collecting T cells from the cancer patient through a blood draw, (2) engineering the patient's T cells to express the CAR targeting a highly expressed protein on the tumor cells, and (3) re-infusing them back into the patient.

Although CAR-Ts cells have supported the treatment of hematologic malignancies, they have been markedly less successful in solid tumors for several possible reasons. Such reasons include the CAR-Ts inability to penetrate solid tumors and the immunosuppressive impacts of the solid tumor's microenvironment. Numerous CAR-T companies (LYEL, ALLO, and CRSP to name a few) are developing next-generation agents to overcome these hurdles and treat solid tumors.

Exhibit 64: 2023 sales of approved CAR-Ts

Drug	Target	Company	2023 Sales ($M)	Indication
Yescarta	CD19	GILD	1,499	large B-cell lymphoma (LBCL), diffuse LBCL (DLBCL), primary mediastinal LBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma (FL), and relapsed or refractory FL
Kymriah	CD19	NVS	508	relapsed or refractory acute lymphoblastic leukemia (ALL), DLBCL, FL
Carvykti	BCMA	JNJ/LEGN	500	relapsed or refractory multiple myeloma (MM)
Abecma	BCMA	BMY/TVST	472	relpased or refractory MM
Tecartus	CD19	GILD	371	relapsed or refractory mantle cell lymphoma (MCL) and relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Breyanzi	CD19	BMY	364	relapsed or refractory LBCL, DLBCL, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and FL.

Source: FDA, Company 10-K filings

Cardiometabolic disease

Obesity

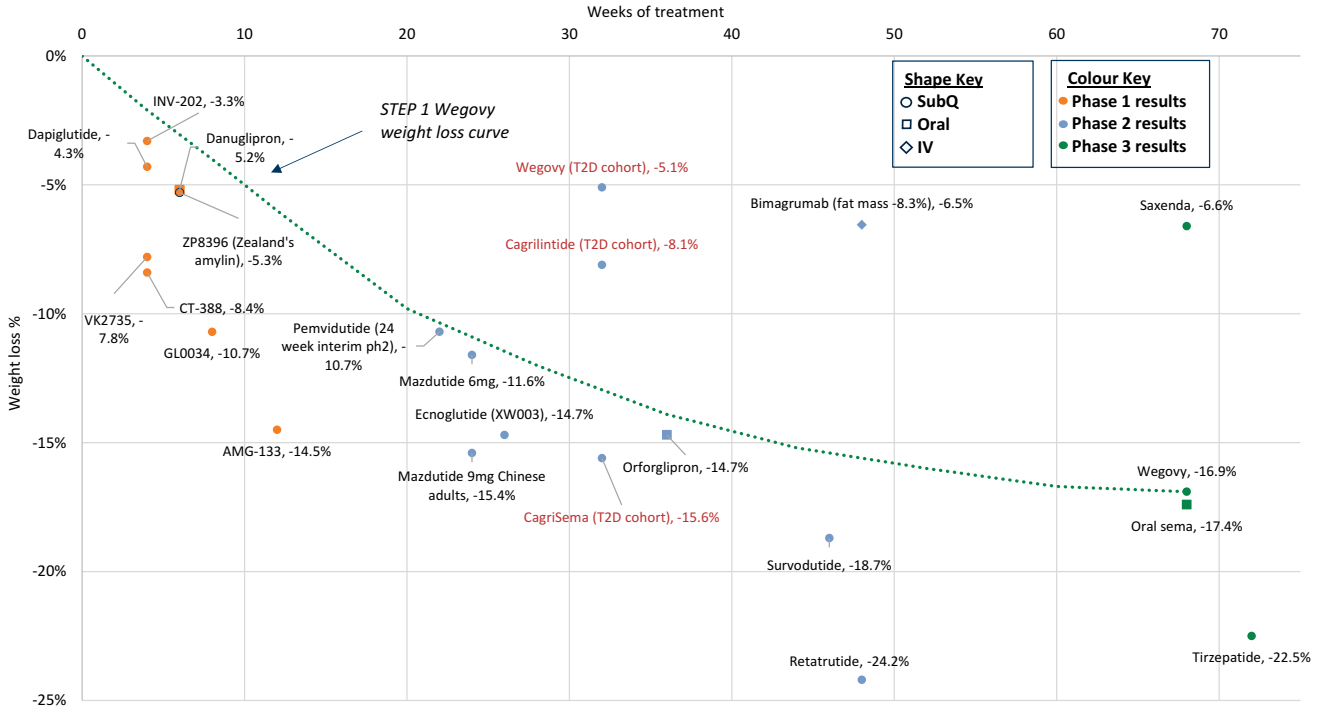
Obesity is a complex disease characterized by excessive weight due to too much body fat. The disease increases the risk of developing several other health conditions, including diabetes, arthritis, cardiovascular disease, and liver disease. There is an estimated prevalence of 105M obese adults in the US and 1B people worldwide. The global commercial opportunity for obesity therapies could potentially grow to $130B in 2030, based on GS estimates. See detail here and here.

This market opportunity has captivated significant interest among healthcare and generalist investors, driving the $570B/$320B increase in LLY and NOVO market caps since their GLP-1 receptor agonist products were first identified as a potentially safe and effective anti-obesity medications in pivotal trials. There are many other products currently in development, including next-generation GLP-1 receptor agonists and others

employing different mechanisms of action, each with the aim to carve out a role within the large and growing obesity market.

Exhibit 65: Weight loss efficacy of late stage assets (weight loss % in obese patients vs weeks of treatment) with STEP 1 weight loss curve for reference

Non placebo adjusted numbers, on treatment data, Red text indicates T2D cohort



Source: Company data, Goldman Sachs Global Investment Research

Despite the recent success, there are many approaches currently in development which seek to improve on the weight loss provided by these GLP-1 receptor agonist programs. These seek to provide greater weight loss, convenience (oral or less frequent dosing), better tolerability (fewer discontinuations), maintenance strategies, and approaches to enhance lean muscle mass relative to fat loss.

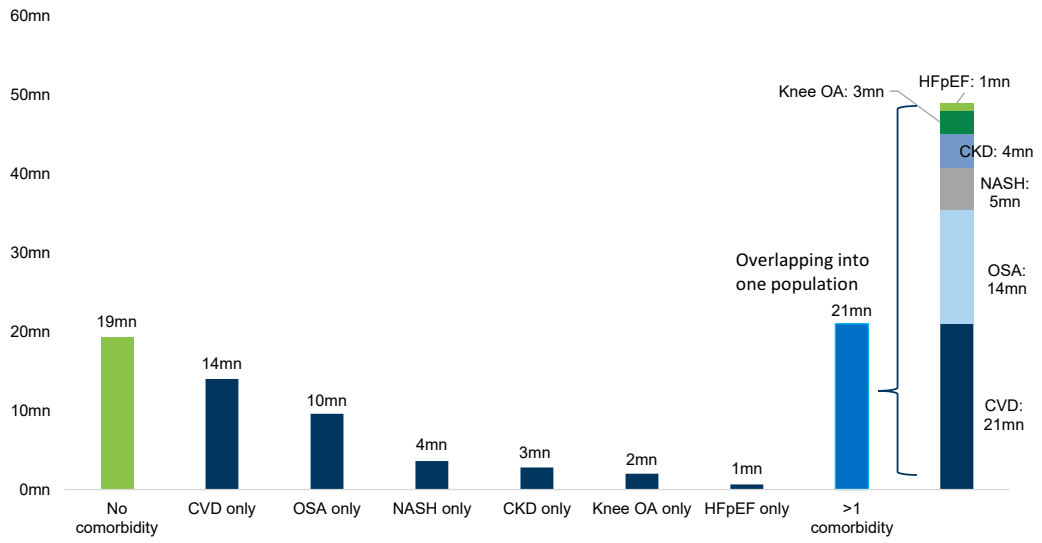
Beyond weight loss, these drugs have also demonstrated benefit on associated diseases. For example, NOVO's semaglutide demonstrated a statistically significant reduction in cardiovascular risk with the SELECT results, and we have also seen benefit on sleep apnea, MASH (more details below), with additional outcome studies planned or ongoing in knee osteoarthritis, chronic kidney disease, heart failure, and even Alzheimer's disease. We expect positive results across these populations could unlock new market opportunities for anti-obesity medication of up to 73M obese and non-diabetic patients in the US.

Exhibit 66: Increasing degrees of weight loss are associated with relative improvements in associated health benefits

Weight loss bracket	Associated health improvements
0-5% weight loss	- Hypertension - Hyperglycaemia
5-10% weight loss	- Dislipidaemia - Prevention of type 2 diabetes - NAFLD (Non-Alcoholic Fatty Liver Disease)
10-15% weight loss	- Kidney disease - NASH (Non-Alcoholic Steatopepatitis) - GERD (Gastroesophageal Reflux Disease, or acid reflux) - OSAS (Obstructive Sleep Apnea
>15% weight loss	- Cardiovascular disease - CV mortality - Heart Failure - T2D remission

Source: Novo Nordisk company data

Exhibit 67: Based on our analysis we see the 73 million obese non T2D US individuals potentially being broken down into the following mutually exclusive groups



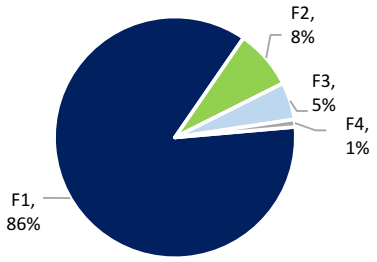
Source: Goldman Sachs Global Investment Research

MASH (Metabolic dysfunction-associated steatohepatitis)

Metabolic dysfunction-associated steatohepatitis (MASH, previously known as nonalcoholic steatohepatitis [NASH]) is a type of fatty liver disease often associated with other conditions like obesity, type 2 diabetes, and high blood fat content. The biological drivers of the disease are complex, as its presentation may be the result of numerous conditions acting in parallel.

While approximately 5% of the general population has MASH, a much smaller portion of patients are diagnosed due to the asymptomatic nature of the disease in its earlier stages. The disease can be divided based on the degree of liver scarring (fibrosis stage: F1-F4), with the least severe stage of disease (F1) presenting with generally few to no symptoms, while the most severe stage (F4) characterized by significant scarring (cirrhosis). F1 MASH accounts for the greatest portion of MASH patients (86%; 6.8M), followed by F2/F3 MASH (8%/5%; 630K/400K), and finally F4 MASH (1%; <100K).

Exhibit 68: 8 million MASH patients split based on stage of fibrosis



Source: Goldman Sachs Global Investment Research

The FDA approved the first agent to treat MASH, MDGL's Rezdiffra, on March 14, 2024. Beyond the launch which commenced in 2Q24, GS estimates subscribe $6.6B in peak sales to the company in 2033 in MASH. Additional therapies featuring distinct mechanisms of action are also in development. Most promising among these agents are the fibroblast growth factor analogs, which have shown strong health benefit in proof-of-concept studies. We also highlight the GLP-1 receptor agonists, which have demonstrated benefit on liver fat reduction, MASH resolution, and fibrosis, albeit the magnitude of effect and appropriate patient population within MASH for this class of therapy remain debated.

Exhibit 69: Approved and emerging therapuetics in MASH

Drug	Mechanism of Action	Timing	Event	Company	GSe unadjusted peak sales ($M)
denifanstat	FASN inhibitor	YE24	Phase 3 trial initiation	SGMT	3,000
efruxifermin	FGF-21 analog	TBD	Phase 3 SYNCHRONY data	AKRO	
pegozafermin	FGF-21 analog	2025	Topline Phase 3 data	ETNB	
pemvidutide	GLP1-RA/GCG-RA	1Q25	Phase 2 IMPACT data	ALT	2,000
Rezdiffra	THR-β agonist	2024	Initial launch cadence	MDGL	6,600
semaglutide	GLP1-RA	2H24	Phase 3 ESSENCE data	NVO	2,900
survodutide	GLP1-RA/GCG-RA	1H26E	Phase 3 trial completion	ZEAL	450
tirzepatide	GLP1-RA/GIP-RA	TBD	Phase 3 trial initiation	LLY	
VK2809	THR-β agonist	2024	Phase 2b data	VKTX	

Source: Company reports

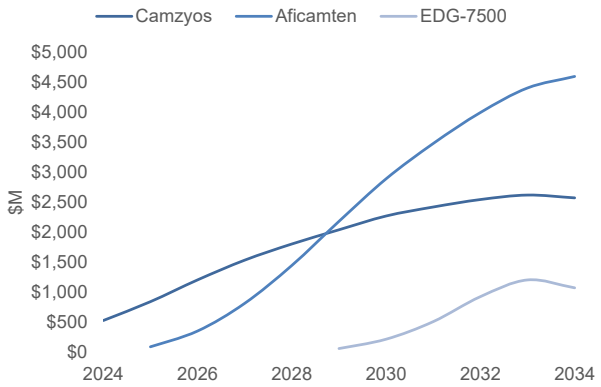
Obstructive Hypertrophic Cardiomyopathy (HCM)

Obstructive hypertrophic cardiomyopathy (oHCM) is a type of progressive HCM characterized by enlargement of the left chamber wall of the heart resulting in obstruction of left chamber outflow of blood flow. This disease can cause sudden death,

heart failure, or abnormal heartbeats in otherwise healthy individuals. Regarding prevalence, HCM impacts roughly 700K individuals in the US with an estimated 60% of those patients having oHCM.

In terms of disease management, oHCM patients with mild symptoms typically make lifestyle adjustments to avoid undue strain on the heart, such as avoiding heavy weightlifting. Beyond lifestyle management, physicians may prescribe prescription drugs to treat oHCM symptoms, including a beta-blocker such as Lopressor for initial treatment. Recently, cardiac myosin inhibitors have emerged as a new class of medicine for oHCM patients. BMY's Camzyos, which was approved in 2022, and CYTK's aficamten, which is in clinical development, are the two primary cardiac myosin inhibitor medicines. Camzyos is projected to generate peak revenue in excess of $2B in oHCM per VisibleAlpha consensus estimates (Exhibit 70). Also, EWTX recently announced its cardiac sacromere modulator EDG-7500 is being evaluated in the Ph2 CIRRUS-HCM trial for oHCM.

Exhibit 70: Projected revenue opportunity for cardiac myosin inhibitor agents in HCM



Source: Goldman Sachs Global Investment Research

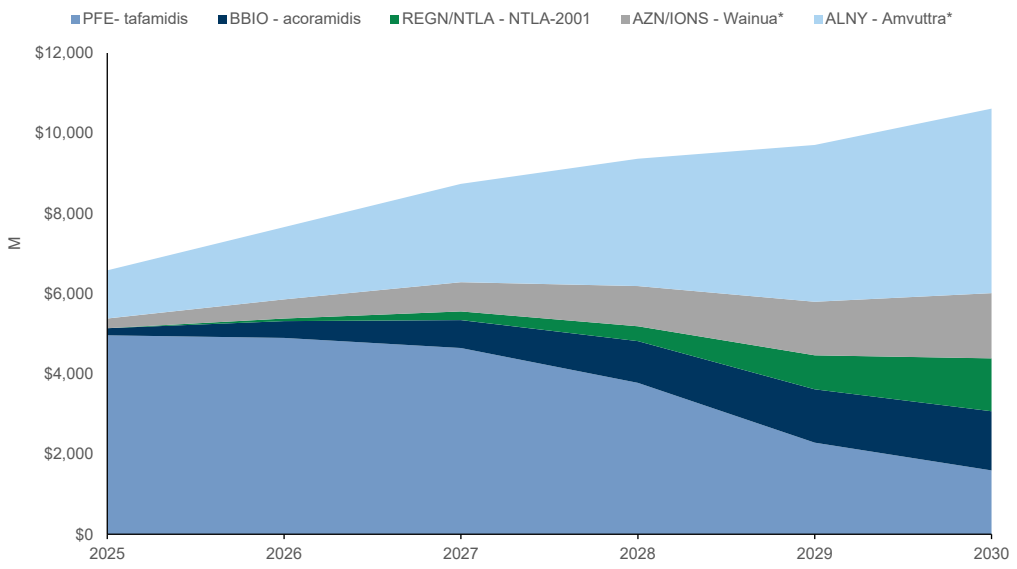
ATTR Amyloidosis

Transthyretin amyloidosis (ATTR) is a rare, progressive disease caused by misfolded transthyretin (TTR) protein that accumulates as amyloid deposits in multiple tissues, including in the nerves (impacting motor function) in hereditary ATTR amyloidosis polyneuropathy (hATTR-PN; ~50K patients worldwide) and in the heart resulting in heart failure with ATTR-cardiomyopathy (CM; ~200-300K patients worldwide). In hATTR-PN, ALNY's TTR-silencing RNA interference (RNAi) therapies Onpattro and Amvuttra are the standard-of-care (generating FY23 sales of $912M), and AZN/IONS' antisense oligonucleotide (ASO) Wainua received FDA approval in late-23. In ATTR-CM, currently only PFE's stabilizer Vyndaqel/Vyndamax (tafamidis; FY23 revenue of $3.3B) is approved and BBIO's stabilizer acoramidis faces a regulatory decision per the November 29, 2024 PDUFA.

ATTR-CM is the key market given the large population, where we note increasing competition across players, notably PFE, BBIO, ALNY, AZN/IONS, REGN/NTLA, and AZN/Neurimmune, with multiple modalities including stabilizers, RNAi, ASO, gene editing, and antibodies. ALNY's positive Ph3 HELIOS-B study of Amvuttra was a key

event as it relates to validating the silencer mechanism (thus providing read-through to AZN/IONS and REGN/NTLA), albeit we anticipate further data and commercial experience may be necessary to fully understand the prescribing, infrastructure and reimbursement dynamics associated with the entry of novel treatments, particularly in the context of tafamidis' potential 2028 loss-of-exclusivity (which could be extended). We model for unadjusted 2030 GSe sales of $3.4B, $3.3B, $2.6B and $1.4B for ALNY's, BBIO's, IONS' and REGN/NTLA's CM assets, respectively, noting that VisibleAlpha consensus indicate expectations that market share will shift to silencer therapies over time (Exhibit 71).

Exhibit 71: Consensus sales estimates across ATTR-CM agents



ALNY and AZN/IONS estimates include all indications to capture sales for the treatment of patients with mixed phenotype.

Source: Visible Alpha Consensus Data

Central Nervous System

Neurodegenerative disorders

There are many neurodegenerative disorders, which can present at different ages and via distinct behavioral and/or functional abnormalities. While Alzheimer's disease is probably the best known, others include Parkinson's disease, Friedreich's Ataxia, ALS, among others. These diseases have been historically difficult to treat, due to considerable heterogeneity across patients and the pace of progression. Further complicating matters, diagnosis often occurs after considerable, irreversible disease progression.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive dementia that leads to a slow and gradual decline (over the course of 7-10 years) in memory, cognition, and ability to perform daily activities. It is characterized by the gradual accumulation of toxic amyloid beta (Aß) plaques and elevated brain inflammation leading to significant cognitive decline.

AD accounts for ~60-80% of all dementias, and affects >47M people worldwide. According to the Alzheimer's Association: (1) over 6.2M individuals over the age of 65 in the US have AD, a number that the foundation expects to nearly double by 2050; and (2) costs for all individuals with AD and other dementias are estimated to be $355B in 2021, including ~$76B in out-of-pocket spending. Based on these numbers, we believe that an effective and safe treatment for AD has significant commercial potential.

In 1996, Aricept (Donepezil) was the first FDA approved drug for the treatment of AD and reached peak worldwide revenues of nearly $4B. Prior to the June 7th, 2021, approval of Aduhelm, only five drugs had been approved in AD and have since dominated the AD symptomatic treatment market despite their limited duration of efficacy and unfavorable safety profile. Since then, additional amyloid targeting therapies have emerged including BIIB's Leqembi which was approved in January, 6th, 2023, and LLY's Kinsula was approved on July, 2nd, 2024. Both agents are approved to treat patients in the mild cognitive impairment of mild dementia stage of the disease. We note that BIIB is evaluating Leqembi in earlier stage patients, specifically AD patients with brain plaques but no signs of dementia. Current GS estimates subscribe $11.4B/$6.2B in unadjusted sales to these programs in 2035 (Exhibit 72). The primary hurdles to realizing this potential include:

- **Diagnostic infrastructure**. The gold standard modes of AD diagnosis are amyloid PET, which measures the build-up of abnormal beta-amyloid proteins in the brain, and cerebrospinal fluid (CSF) biomarker testing. On the former, access to PET clinics is limited and costly ($5,000-$8,000 per scan). On the latter, CSF testing relies on unscallable invasive spinal tap procedures. Thus, these challenges pose significant barriers to AD diagnosis.

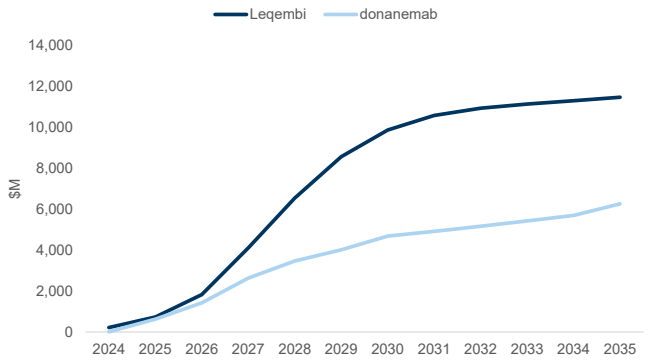
  In recent years, there has been rapid developments around the use of blood-based biomarkers (BBMs). The Alzheimer's Association expects BBMs to revolutionize AD clinical care and sees potential for them to replace PET/CSF.

  Among key pioneers developing BBMs, we highlight QTRX (covered by Matt Sykes). QTRX is poised to become first-to-market with a BBM with an overall accuracy of 90.7% vs. CSF biomarkers and PET imaging. From a cost perspective, QTRX assay costs $300 compared to a $5,000-$8,000 PET scan and a $1,500 CSF spinal tap. The company plans to submit for traditional FDA approval by YE24 suggesting full-approval by late 2025 or early 2026.

- **Payer coverage:** The primary expected impact of the upcoming approvals and subsequent uptake in AD will be to MCOs, especially those with Medicare exposure as ~80% of AD patients would fall under Medicare. Recall that Medicare Advantage (MA) MCOs follow CMS guidelines, and hence any reconsideration of the Medicare & Medicaid Services (CMS)' National Coverage Determination (NCD), will be a key driver of the impact. If the drug is deemed a material cost (exceeds 0.1% of CMS' budget, a low bar in our view for a drug of this size), CMS will cover the cost until it can be incorporated into pricing. As an example, Leqembi received this broader Medicare coverage after the FDA granted traditional approval. The extent of utilization in the coming years will remain a risk factor, particularly for MA-exposed names, and companies could look to manage utilization through coverage policies

and payment mechanisms tied to outcomes. The impact and potential coverage in commercial would be distinct from MA, where MCOs would need to review the trial data to determine how it should be covered for commercial clients.

Exhibit 72: GSe unadjusted sales for anti-amyloid therapies in Alzheimer's disease



Source: Goldman Sachs Global Investment Research

Beyond the amyloid-directed agents, we highlight novel approaches in development to treat AD. These include ALEC's TREM2 targeting antibody AL002 or its sortilin inhibitor AL101, ATHA's small molecule HGF-MET modulator fosgonimeton, BIIB's tau-targeting programs, namely BIIB080 (tau targeting ASO) and BIIB113 (oral small molecule targeting tau accumulation), and DNLI's tau targeting ASO (OTV:MAPT), utilizing the company's novel blood-brain-barrier (BBB) technology. We further note that ALNY is utilizing an upstream strategy, targeting amyloid precursor protein (APP) via RNA interference (vs. clearing amyloid plaques post-formation, per the approved antibodies), which may reduce both intracellular and extracellular Aß as well as all APP cleavage products (all Aß isoforms) to enable natural clearance mechanisms. We highlight the stage of development, mechanisms of action, rationale from these approaches in the table below (Exhibit 73).

Exhibit 73: Emerging therapies in AD

Drug	Company	Mechanism of action	Development Stage	Update	Timing
AL002	ALEC	TREM2 agonist	Ph2	Topline data	4Q24
AL101	ALEC	Sortilin inhibitor	Ph2 (PROGRESS-AD)	Topline data	TBD
mivelsiran	ALNY	APP-targeting siRNA	Ph1	Topline data	Late 2024
fosgonimeton	ATHA	HGF-MET modulator	Ph3 (LIFT-AD)	Topline data	3Q24
BIIB080	BIIB	Tau-targeting ASO	Ph3 (CELIA)	Topline data	TBD
BIIB113	BIIB	Small molecule targeting tau accumulation	Ph1	Topline data	TBD
OTV:MAPT	DNLI	Tau-targeting ASO	IND-enabling studies	Ph1 initiation	TBD

Source: Company data

A majority of AD patients suffer from agitation and/or psychosis, to that extent companies are developing agents for these sub-indications. Agitation is a behavioral syndrome characterized by exaggerated motor activity and verbal and/or physical aggressiveness, and emotional distress. Psychosis, on the other hand, presents as patients experiencing hallucinations, delusions and/or paranoia. Above symptoms lead to increased likelihood of nursing home placement, more severe dementia and increased mortality risk.

There are no approved treatments for AD psychosis yet, and doctors generally prescribe atypical antipsychotics and/or anti-depressants. Subsequently, several companies are progressing their assets through clinical trials including ACAD and KRTX (acquired by BMY) to treat these symptoms. With respect to agitation related to AD, Rexulti (brexpiprazole), an atypical antipsychotic, was recently approved by the FDA and several other drugs are being evaluated within this sub-indication, including from AXSM, BTAI, and ITCI.

Exhibit 74: Key drugs in development in Alzheimer's disease agitation and psychosis

Indication	Company	Asset	Mechanism of action	Stage of development
Alzheimer's agitation	Axsome	AXS-05	NMDA receptor antagonist and sigma-1 agonist	Phase 3
	Bioxcel Therapeutics	Igalmi	dexmedetomidine (sublingual film)	Phase 3
	Intracellular Therapies	ITI-1284	deuterated form of lumateperone	Phase 2
	Lundbeck / Otsuka Pharma	Rexulti	serotonin-dopamine activity modulator	Approved
Alzheimer's psychosis	Acadia Pharmaceuticals	ACP-204	$5HT_{2A}$ blocker	Phase 2/3
	Cerevel Therapeutics	emraclidine	M4 positive allosteric modulator	Phase 1
	Intracellular Therapies	ITI-1284	deuterated form of lumateperone	Phase 2
	Karuna Theraputics	KarXT	M1-M4 muscarinic agonist	Phase 3

Source: Data compiled by Goldman Sachs Global Investment Research

Amytrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease caused by the deterioration and death of motor neurons. These motor neurons extend from the brain, through spinal cord and peripheral central nervous system and direct muscle movements like walking, talking, and even breathing. Patients with ALS are categorized from possible ALS to definite ALS by the number of regions presenting with lower and/or upper motor neuron signs such as weakness, loss of reflexes and muscle tone (based on the revised El Escorial classification, Exhibit 75). Patients are typically diagnosed within 9-12 months of symptom onset, and the diagnosis is one of exclusion (i.e., other conditions are ruled out). The average survival from ALS symptom onset is three years, though the rate of progression can vary considerably by patient with an estimated ~20% of patients surviving for five years, ~10% for ten years, and ~5% that may survive for >20 years. The most common cause of death for patients with ALS is respiratory failure.

Exhibit 75: El Escorial criteria is used to categorize ALS patients

Definite ALS	Probable ALS	Probable ALS, laboratory results supported	Possible ALS
Presence of upper motor neuron and lower motor neuron signs in three anatomical regions	Presence of upper motor neuron and lower motor neuron signs in at least two regions with upper motor neuron sign rostral to lower motor neuron signs	Presence of upper motor neuron and lower motor neuron signs in one region with evidence by EMG of lower motor neuron involvement in another region	Presence of upper motor neuron and lower motor neuron signs in one region or upper motor neuron signs in two or three regions, such as monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis

Source: National Institutes of Health

Current standard of care: There are no curative therapies approved for ALS, though two drug products have demonstrated modest benefit on ALS symptoms. These are riluzole (Rilutek) and edaravone (Radicava), which were approved in 1995 and 2017, respectively. Despite their approval, we think the efficacy of these two therapies is underwhelming at best, as evidenced by the respective labels and secondary clinical analyses evaluating these drugs. Apart from these, BIIB's Qalsody is also approved (via the accelerated

approval pathway) to treat a sub-type of ALS (SOD1 mutation). While AMX0035 (Relyvrio) was briefly approved for ALS, the drug was pulled from the market following an unsuccessful Phase 3 trial, reinforcing the difficulties of drug development within the indication. However, there remain a number of therapies in development, wherein we summarize those in Phase 2 and 3 studies and beyond (Exhibit 76).

Exhibit 76: Late-stage drugs in ALS

Company	Asset	Mechanism of action	Phase
AB Science	masitinib	tyrosine kinase inhibitor	Phase 3
Abbvie	ABBV-CLS-7262	eIF2B activator	Phase 2/3
BrainStorm Cell Therapeutics	NurOwn	autologous mesenchymal stem cell neurotrophic factor cell therapy	Phase 3b
Clene	CNM-Au8	targets mitochondrial function and NAD pathway	Regulatory
Denali Therapeutics	DNL343	eIF2B activator	Phase 2/3 (HEALEY)
Ionis Pharmaceuticals	ulefnersen	FUS-inhibitor antisense agent	Phase 3
MediciNova	ibudilast	glial attenuator; suppresses pro-inflammatory cytokines	Phase 2b/3
NeuroSense Therapeutics	PrimeC	combination of Ciprofloxacin and Celecoxib	Phase 2b/3

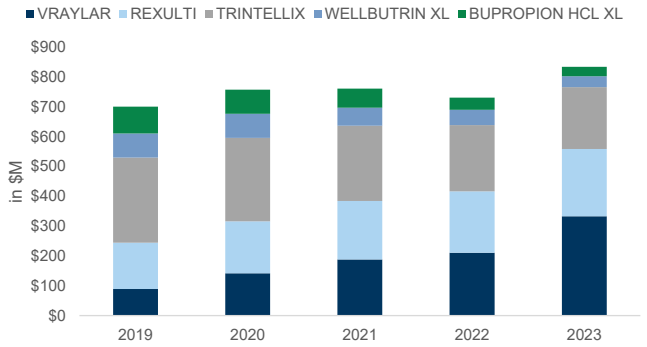
Source: Data compiled by Goldman Sachs Global Investment Research, Biomedtracker

Neuropsychiatry

Neuropsychiatric conditions are those characterized by disturbances in the nervous system, which cause mental disorders, and can include disordered perceptions, memory, attention, motivation, and others.

Major depressive disorder. MDD is a chronic mental health disease characterized by intense feelings of sadness for extended periods of time. Nearly 7% (or an estimated 16-17M) of US adults experience major depressive episodes on an annual basis. MDD is typically treated with selective serotonin re-uptake inhibitors (SSRIs) such as Prozac (fluoxetine) and Celexa (citalopram). While SSRIs are effective in treating depression, 1/3 of MDD patients remit after adequate antidepressant therapy. In 2007, Abilify (aripiprazole) was the first of the second-generation antipsychotic approved as an adjunctive treatment to antidepressant for MDD. Later, Rexulti (brexpiprazole), Seroquel (quetiapine), Symbyax (olanzapine/fluoxetine) and most recently, ABBV's Vraylar were granted approval in the same setting. Beyond commercial drugs, numerous companies are developing agents to treat MDD including CTNM, ITCI, NBIX, NMRA and XENE, with varied and novel mechanisms of action.

Exhibit 77: Top 5 drugs within MDD based on revenues

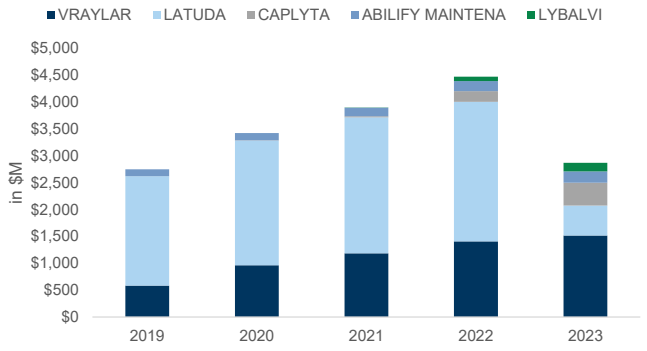


Ranked based on 2023 revenues

Source: IQVIA

Bipolar disorder (previously referred to as manic-depressive or manic depression) is a chronic mental illness causing extreme mood swings from emotional highs (mania or hypomania) to extreme lows (depression). It affects ~6M adults in the US every year, with a median age of onset ~25 years. Bipolar 1 is characterized by having experienced one or more manic (increased energy, with hyperactivity and a decreased need for sleep, racing thoughts, inflated self-image, substance abuse) episodes. Unlike bipolar 1, bipolar 2 patients experience mood shifts between depression and hypomanic episodes, but never full manic episodes (hypomanic episodes are less severe). The split between bipolar 1 and bipolar 2 is roughly 50:50. The first-line treatment includes mood stabilizers such as valproic acid and lithium, although they are more beneficial in preventing manic episodes than depressive episodes. Thus, for depressive episodes, a combination therapy (valproic + lithium) is superior; however, ~50% of the patients do not respond to this combination. This is when antipsychotics (e.g. Abilify, Vraylar, Latuda), and/or antidepressants are added to the treatment paradigm (e.g. Citalopram, Fluoxetine, Sertraline). Several other mechanisms are also being evaluated within bipolar disorder, such as 5-HT2A antagonists + N-methyl-D-aspartate (NMDA) antagonists.

Exhibit 78: Top 5 drugs within BPD based on revenues



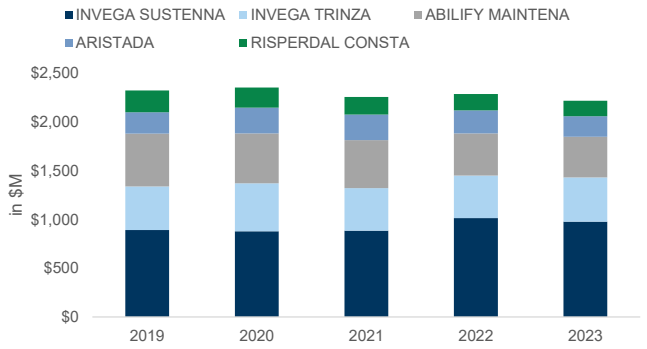
Ranked based on 2023 revenues

Source: IQVIA

Schizophrenia is a long-term and heritable neuropsychiatric disorder characterized by

psychosis (disturbed perception of reality) that affects nearly 2.4M people in the US. Symptoms include delusions, hallucinations, and agitation with affected individuals usually unaware of their behavior. The treatment is typically lifelong and includes a combination of antipsychotics, anti-tremor, and behavioral therapy. The treatment landscape in schizophrenia is crowded with over a dozen antipsychotics (including both first- and second-generation) approved and many having already gone generic. However, significant treatment-related adverse effects such as rapid weight gain, dyslipidemia, other metabolic abnormalities, and motor dysfunction such as tardive dyskinesia result in 74% of all schizophrenia patients on antipsychotics discontinuing treatment within 18 months. Similar to bipolar disorder, several novel mechanisms of action are being explored in the space, including KarXT (oral modulator of muscarinic receptors), and 5-HT2A inverse agonists, among others.

Exhibit 79: Top 5 drugs within Schizophrenia based on revenues



Ranked based on 2023 revenues

Source: IQVIA

Looking to novel mechanisms of action in the space

As patients go through antidepressants, anti-psychotics, mood stabilizers and other classes of therapy, there continues to be an unmet need for disease modification, and improved symptom management with better safety profiles. That said, there are numerous novel mechanisms in development within neuropsychiatry. Specifically, we highlight KarXT, tavapadon and emraclidine, and navacaprant. For instance, KarXT is a combination of xanomeline (muscarinic receptor M1/M4 agonist) from LLY and trospium chloride (muscarinic antagonist) designed to improve the adverse events observed with xanomeline alone (such as nausea, diarrhea, vomiting) while maintaining its efficacy. Emraclidine, on the other hand, is a *positive allosteric modulator* M4 muscarinic receptor, wherein M4 is viewed as a primary driver of therapeutic activity within schizophrenia.

Inflammation & Immunology

Inflammatory/immunology disorders are diseases where the body's immune system mistakes its own healthy cells as foreign and attacks them (autoimmune disease). These diseases typically cause patients to experience inflammation. Each is characterized by the body site of the inflammation and the secondary symptoms. The onset of

symptoms waxes and wanes, and their impact on quality of life can range from mild to severe.

Physicians frequently attempt to treat these disorders by shutting down inflammatory pathways driving the disease's symptoms. There are two general targeted pathways, those involving Type 1 Helper (T_H1) T cells and those involving Type 2 Helper (T_H2) T cells. These cells draw other cells to body sites, which are responsible for initiating inflammation. We may cluster diseases based on whether they respond to therapies that halt T_H1 or T_H2 activation like ABBV's Humira or REGN's Dupixent, respectively. Below, we outline the diseases the FDA has approved each drug to treat and the estimated number of US patients for each (Exhibit 80).

Beyond T_H cells, B cells are also responsible the for initiation of autoimmunity. Under healthy circumstances, these cells play a prominent role within the immune system by creating a suite of molecules known as antibodies. Antibodies are designed to recognize known pathogens and alert the immune system of their presence. Several autoimmune diseases are driven by the formation of antibodies that target healthy cells including myasthenia gravis and Graves' disease to name a few. There are several approved and developmental agents designed to halt B cell activity by either targeting B cells (e.g., Rituxan) or their antibodies (e.g., Vyvgart).

Exhibit 80: Indications treated by Humira/Dupixent

Drug	Disease	US patient number (K)
Humira	Rheumatoid Arthritis	1,500
	Juvenile Idiopathic Arthritis	300
	Psoriatic Arthritis	800
	Ankylosing Spondylitis	500
	Crohn's Disease	1,000
	Ulcerative Colitis	1,250
	Plaque Psoriasis	6,400
	Hidradenitis Suppurativa	320
	Uveitis	390
Dupixent	Atopic Dermatitis	15,700
	Asthma	24,600
	Chronic Rhinosinusitis with Nasal Polyposis	4,800
	Eosinophilic Esophagitis	180
	Prurigo Nodularis	130

Source: FDA, Goldman Sachs Global Investment Research

Common mechanisms of action of drugs used to treat autoimmune diseases

Cytokines are proteins secreted by cells meant to alert and activate the immune system. There are >100 cytokines, but 33 of these molecules known as interleukins (IL) are of special interest to drug hunters due to their well-established roles in autoimmunity. Several drugs to treat autoimmune diseases are designed to alter the function of specific ILs. Such agents include antibodies targeting IL-1 (anakinra), IL-6 (tocilizumab), IL-17 (secukinumab), and IL-23 (risankizumab) to name a few. These drugs are approved to treat a wide variety of indications where clinical evidence has implicated the specific IL in disease biology.

Beyond cytokine targeting agents, there are several other classes of drugs to treat autoimmune diseases including JAK inhibitors, S1P modulators, and anti-integrin therapies. The former group, JAK inhibitors, consists of small molecules that disrupt the ability of cells to respond to cytokines. While there are various different marketed JAK

inhibitors (e.i., Rinvoq, Xeljanz, Sotyktu), these agents vary in their ability to target distinct JAK proteins including JAK1, JAK2, JAK3, and TYK2. Those targeting JAK1-3 have come under scrutiny recently, as their FDA labels of these drugs feature a class-wide black box safety warning regarding the potential of rare heart related safety risks. The latter classes of agents, S1P modulators and anti-integrin therapies, both work by limiting the ability of immune cells to reach the site of inflammation, though each targets a distinct biological pathway.

Orals vs. biologics

Convenience is a priority for the treatment of autoimmune disorders, as drug developers consider designing agents that improve patient access and convenience vs. prior generations. Consider the TNF-alpha targeting class. The first approved agent was Remicade, which is administered via intravenous infusion. The following generation of drugs were all designed to be administered through at-home self-injections. Over time, manufacturers of these agents further improved their formulations to reduce the pain of administration. Currently, emergent therapies seek to establish differentiation from at-home injectables via oral delivery. Companies have suggested that patients would be willing to try safe oral drugs ahead of more potent injectable therapies due to the convenience benefits, even if it comes at a haircut to efficacy. Thus, we expect the use of orals will rise ahead in the treatment paradigm of more potent injectable therapies over time (though this will likely be disease and drug dependent).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a term describing chronic inflammatory diseases of the gastrointestinal (GI) tract, Crohn's disease (CD) and ulcerative colitis (UC). ~900K-1.2M and ~700K-1M Americans have UC and CD, respectively (see here, here, and here). UC patients experience symptoms of rectal bleeding, bloody diarrhea, and abdominal pain. In addition to these symptoms, CD patients also experience scarring across their intestines. Among the total patients in each disease population, physicians we spoke to suggests 30-40% experience severe disease and require treatment with advanced therapies.

There are several advanced therapies approved to treat IBD and more in the clinic (Exhibit 81). Among the approved agents, there are multiple classes distinguished by safety, efficacy, and rout of administration. Some classes, like that of antibodies blocking TNF-alpha or small molecule inhibitors of the JAK proteins, feature more than one branded drug. Among the clinical assets, we highlight the TL1A inhibiting class, consisting of MRK's PRA023 and ROG's RVT-3101. These agents were acquired from biotechs RXDX and ROIV/PFE for a combined takeout value of ~$18.1B in 2023.

Exhibit 81: Late-stage and commercial drugs in IBD

Company	Ticker	Asset	Target	Administration	CD Stage	UC Stage
AbbVie	ABBV	Humira	TNF-alpha	injection	Marketed	Marketed
AbbVie	ABBV	Rinvoq	JAK	oral	Marketed	Marketed
AbbVie	ABBV	Skyrizi	□IL-23A	injection	Marketed	Marketed
Bristol-Myers Squibb	BMY	Zeposia	S1P	oral	Phase 2	Marketed
Eli Lilly & Company	LLY	Omvoh	□IL-23p19 subunit	injection	Phase 3	Marketed
Janssen Biotech	JNJ	Remicade	TNF-alpha	injection	Marketed	Marketed
Janssen Biotech	JNJ	Stelara	IL-12/IL-23	injection	Marketed	Marketed
Janssen Biotech	JNJ	Tremfya	□IL-23p19 subunit	injection	Regulatory	Regulatory
Merck	MRK	PRA023	TL1A	injection	Phase 2	Phase 3
Pfizer	PFE	Xeljanz	JAK	oral	Marketed	Marketed
Pfizer	PFE	Velsipity	S1P	oral	Phase 3	Marketed
Roche	ROG	RVT-3101	TL1A	injection	Phase 2	Phase 3
Sanofi/Teva	SNY/TEVA	TEV'574	TL1A	injection	Phase 2	Phase 2
Takeda Pharma	TAK	Entyvio	α4β7 integrin	oral	Phase 3	Marketed
UCB	UCB	Cimzia	TNF-alpha	injection	Marketed	Marketed

Source: Data compiled by Goldman Sachs Global Investment Research

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a debilitating chronic inflammatory skin disorder associated with the formation of painful lesions and inflamed skin lumps known as nodules within skin folds. HS patients can experience severe pain from the disease's symptoms, which can lead to professional impairment and reduced quality of life. Beyond the direct impacts of the disease, patients also experience systemic inflammation, which drives a higher incidence of hearth disease, IBD, and arthritis. There are an estimated ~300K Americans living with HS, ~1/3 of treated patients achieve remission, ~1/3 report gradual improvement of clinical symptoms with regular treatment with Humira, and the remainder fail to respond to treatment.

IL-17 inhibiting antibody Cosentyx (approved on October 31, 2023) was the first advanced therapy approved by the FDA to treat HS since September 2015. Several additional IL-17 antibodies are in the pipeline including UCB's bimekizumab currently under regulatory review in the US (approved in Europe) and MLTX's/SLRN's sonelokimab/izokibep both currently in Ph3 studies. ABBV is also evaluating its inhibitor of JAK in a Phase 3 study, where it may become the first-in-class product, though several others are quickly following behind.

Exhibit 82: Late-stage and commercial drugs in HS

Company	Ticker	Asset	Target	Administration	Stage
Aristea Therapeutics	private	RIST4721	CXCR2	oral	Phase 3
Eli Lilly and Company	LLY	eltrekibart	CXCR1/CXCR2	oral	Phase 2
Incyte Corporation	INCY	povorcitinib	JAK	oral	Phase 3
MoonLake Immunotherapeutics	MLTX	sonelokimab	IL-17A/IL-17F	injection	Phase 2
Novartis Pharmaceuticals	NVS	iscalimab	CD40	injection	Phase 2
UCB Biopharma	UCB	Bimzelx	□IL-17A/IL-17F	injection	Marketed
AbbVie	ABBV	Humira	TNF-alpha	Injection	Marketed
Novartis Pharmaceuticals	NVS	Cosentyx	IL-17A	injection	Marketed

Source: Data compiled by Goldman Sachs Global Investment Research

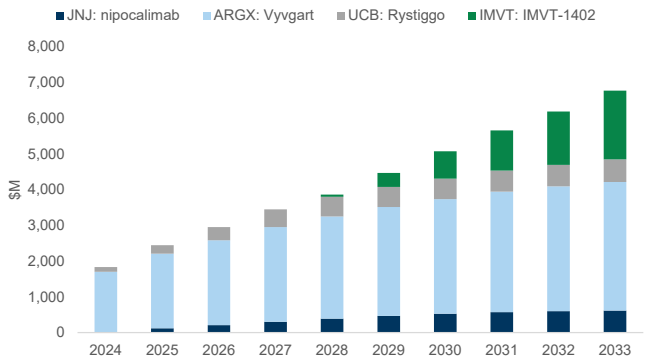
Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by discord between nerve and muscle cells caused by the formation of pathogenic antibodies that target healthy cells and tissues. The disease causes patients to experience weakness of specific muscles in the face, neck, and limbs. There is an estimated prevalence of MG of

36K-60K patients in the US today, with patients classified by age of onset, severity, and the presence of specific pathogenic drivers. The commercial opportunity for new therapies in the space is primarily in patients with severe or refractory (treatment-resistant) disease estimated to represent ~15% of patients. Visible Alpha estimates ascribes peak sales estimates >$7B across the neonatal fragment crystallizable receptor (FcRn) binding antibody class (Exhibit 83). There are several approved (ARGX's Vyvgart and UCB's Rystiggo) and clinical-stage (IMVT's batoclimab/IMVT-1402 and JNJ's nipocalimab) FcRn antibodies for MG. ARGX's Vyvgart sets the standard for FcRn antibodies given its safety profile, route of administration optionality, and time-to-market advantage. Thus, we expect development-stage FcRn's to be measured against Vyvgart. We watch for follow-on programs to compete for differentiation based on potential improvements to long-term tolerability, efficacy, clinical trial design, and convenience (at-home subcutaneous).

Beyond these agents, another class of therapies approved to treat MG is the complement inhibitors. These agents work by blocking complement, a component of the immune system over activated in MG patients. The first complement inhibitor approved to treat the disease was AZN's Soliris in 2017, following approvals to treat Paroxysmal Nocturnal Hemoglobinuria and atypical hemolytic uremic syndrome in 2007 and 2011. On the heels of Soliris, AZN received approval for its next generation complement inhibitor Ultomiris, designed to improve upon the dosing of its predecessor, in 2022. Recent commentary from ARGX management teams suggests that these agents are being used to treat patients progressing beyond FcRn inhibitors. Several other complement inhibitors are in clinical development (Exhibit 84).

Exhibit 83: Unadjusted sales estimates for leading FcRn antibodies in MG



Source: Visible Alpha Consensus Data

Exhibit 84: Complement inhibitors in myasthenia gravis

Drug	Target	Modality	Stage	Regimen
Soliris	Complement protein C5	antibody	Marketed	IV; 900mg weekly for 4 weeks followed by 1200mg biweekly
Ultomiris	Complement proteins C5 and C5b	antibody	Marketed	SC; 0.3 mg/kg daily
pozelimab	Complement proteins C5	antibody	Phase 3	30 mg/kg IV for first dose followed by 10mg/kg SC weekly
cemdisiran	Liver complement protein C5	siRNA	Phase 3	SC; 600 mg every 4 weeks
gefurulimab	Complement proteins C5	antibody	Phase 3	SC; weekly weight-based dosing
danicopan	Complement factor D protein	small molecule	Phase 2	120 mg or 180 mg twice daily

Source: Company reports

Opthamology

Ophthalmology disorders are diseases that can significantly impact vision and quality of life. Individuals with ocular diseases could be at risk of reversible or irreversible vision loss, inflammation of the eye, and an altered appearance of the eye, amongst other risks. Ophthalmologists often employ a wide range of treatment options to either manage symptoms or delay disease progression. These treatments encompass biologics, protein-based molecules, and surgical intervention. Physicians frequently attempt to treat these disorders by shutting down inflammatory pathways driving the disease's symptoms.

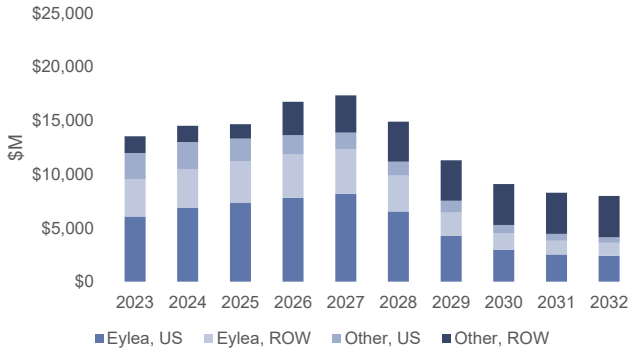
Despite the availability of such treatment options, many individuals still face the risk of irreversible vision loss. A distinct challenge in addressing ocular disease is that the eye is an immune-privileged, small, and compartmentalized. As such, local delivery of therapies is often required to show clinical benefit and reduces the risk associated with systemic administration. Based on precedent, local administration of therapies come with its own set of risks, including pain, bleeding, retinal tear/detachment, retinal vasculitis, and vision loss. Below, we outline key ocular diseases the FDA has approved drugs to treat and the market size associated with each.

Wet AMD

Wet age-related macular degeneration (AMD) is a disease that causes central vision impairment and blindness primarily amongst the elderly. The disease has a prevalence of about 1M patients in the US and 5M globally. REGN/BAYG's, NVS/ROG's, and ROG's anti-VEGF drugs Eylea, Lucentis, and Vabysmo, respectively, are the three primary therapies prescribed to wAMD patients. As of 2023, these therapies have generated revenue of $9.2B/$1.5B/$2.6B globally, respectively. That said, Eylea is facing genericization in the US due to its recent loss exclusivity. GS estimates peak sales for these branded agents in 2027 with the emergence of generic Eylea (Exhibit 85).

Looking ahead, REGN appears set to extend its wAMD franchise with the approval Eylea HD on August 18, 2023 (also indicated for diabetic macular edema and diabetic retinopathy), which generated $166M in sales for 2023. The company disclosed that Eylea and Eylea HD together have secured 45% of the anti-VEGF category share, compared to 49% in 4Q23. Beyond Eylea HD, there are several other agents in clinical development to treat wAMD, including KOD's anti-VEGF antibody biopolymer conjugate, tarcocimab tedromer, and gene therapies RGX-314, an AAV-based gene therapy that expresses anti-VEGF-A antigen-binding fragment, from Regenxbio's and Ixo-vec, an AAV-based gene therapy that expresses aflibercept, from Adverum Biotechnologies.

Exhibit 85: Eylea HD extends REGN's wAMD franchise with genercization of Eylea (low-dose) shrinking branded market TAM



Source: Goldman Sachs Global Investment Research

Geographic Atrophy

Geographic atrophy (GA) is a form of AMD of that generally causes irreversible loss of vision, leading to blindness mostly among elderly individuals. GA has an estimated prevalence of 1M patients in the US with a global prevalence of roughly 5M. The commercial opportunity in GA is comparable to that of wAMD (discussed above) as the disease also impacts approximately 1M patients in the US and 5M globally.

There are currently only two drugs approved for individuals with GA, which are APLS' Syfovre and Astellas Pharma's Izervay. Syfovre is on track to generate peak sales of $3B in the US, per VisibleAlpha estimates. Conversely, Izervay is estimated to generate peak sales of $290M in the US. This significant difference may be attributed to Izervay being limited to 12 months of use. These drugs are not expected to reverse vision loss; however, they may slow disease progression by preserving vision for longer. Beyond these approved drugs, there are a growing number of potential treatments for GA that could grow the market opportunity for the treatment landscape.

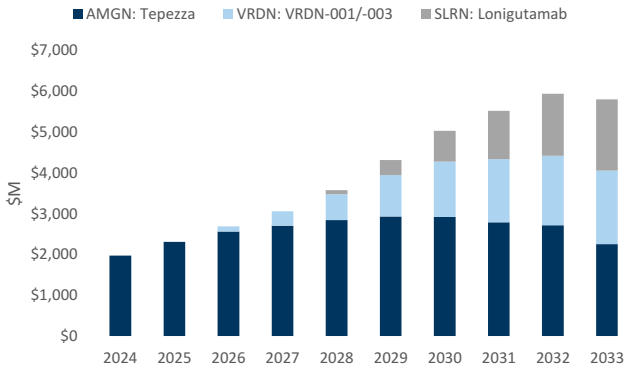
Thyroid Eye Disease

Thyroid eye disease (TED) is an autoimmune disease caused by inflammation of muscles, connective, and fatty tissue around the eye. The disease may be classified as being in either the active or chronic phase, depending on the severity of inflammation. Active disease may be thought as having more inflammatory activity than the chronic phase. Generally, symptoms include eye redness, eye swelling, bulging eyes, and double vision. The annual incidence of TED is estimated to be around 16 per 100k in women and 2.9 per 100k in men.

AMGN's Tepezza (teprotumumab), an IGF-1R antibody, is the first and only approved treatment in the US for TED, generating revenue of about $1.8B in 2023 (-11% Y/Y growth). Smaller than expected market opportunity and low penetration in chronic patients has been a key debate amongst investors and is one potential explanation for stagnating Tepezza sales. Also, most payers restrict use of Tepezza to 8 doses per lifetime, so some believe the opportunity in chronic patients could diminish over time as the market becomes primarily incidence driven. Novel SC formulated products may offer

enhanced benefits/conveniences to patients, and many physicians believe that SC therapies for TED could eventually render IV formulated products obsolete. To this end, notable SC formulated IGF-1R therapies in development include VRDN's VRDN-003 and SLRN's lonigutamab, as well as SC formulated versions of teprotumumab in development by AMGN. Sling Therapeutics (private) is also developing an orally administered small molecule IGF-1R inhibitor and multiple other targets are being explored in TED including FcRn (ARGX, IMVT), IL-6/-6R (ROG, TRML), 1L-11R (Lassen Therapeutics), and TSH (CRNX).

Exhibit 86: Unadjusted sales estimates for leading IGF-1R therapies in TED



Source: Visible Alpha Consensus Data

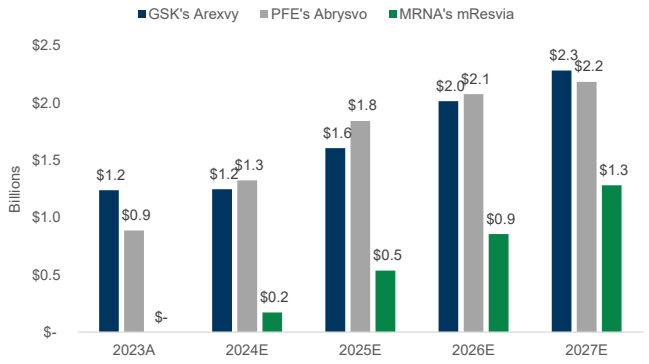
Virology - RSV

RSV (Respiratory syncytial virus) is a common respiratory virus that typically causes mild, cold-like symptoms, but can cause more severe infections (including pneumonia) and warrant hospitalization, particularly in infants and older adults. The CDC currently estimates that RSV leads to 60,000 to 160,000 hospitalizations amongst adults aged 65 years and older, and 58,000 to 80,000 hospitalizations amongst children aged 5 years and below in the U.S. each year, highlighting a significant clinical burden.

Treatment for RSV is typically supportive, with hospital treatment for severe infections including intravenous fluids, humidified oxygen, and mechanical ventilation in rare cases. For prevention and mitigation, the CDC recommends a single dose of RSV vaccine for all adults aged 75 and older, as well as for adults aged 65 and up with increased risk of severe RSV infections- this includes those with certain chronic medical conditions, such as chronic lung or heart disease, and immunocompromised individuals. There are currently 3 approved vaccines for adults, including GSK's Arexvy, PFE's Abrysvo, and MRNA's mResvia. The current recommendation, adopted at the June 2024 Advisory Committee on Immunization Practices (ACIP) meeting, updated the language from the prior "shared clinical decision making" recommendation for RSV vaccines, and notably does not include the 50 to 59 years of age group, where GSK's Arexvy is approved. For infants, nirsevimab (a monoclonal antibody made by AZN/SNY) is recommended by the CDC to protect infants under 8 months and children up to 19 months who are at higher risk for severe RSV, while PFE's Abrysvo is the only vaccine approved in the maternal setting.

Current market size estimates from commercial players in RSV include MRNA's estimate of a >$10B opportunity (with ~$6B-$8B in the older adult settings), GSK's estimate that market will reach ~£6B in sales by 2028, and SNY's estimate that it will reach €8B in sales by 2030 (split 60:40 adults:infants/toddlers). For the approved vaccines from GSK, PFE and MRNA, visible alpha consensus estimates (Exhibit 87) show the market reaching close to ~$6B by 2027.

Exhibit 87: Projected near-term sales across emerging RSV agents



Source: Visible Alpha Consensus Data

Rare/orphan disease

Rare/orphan diseases are those that affect less than 200K people within the US, encompassing a broad range of disease pathologies. While the addressable market is small, drugs treating such diseases often carry a high price points and require relatively limited commercial infrastructure to support launches. Orphan drugs are also attractive because they will not be subject to IRA negotiations in the future.

Pulmonary Arterial Hypertension (PAH)

Pulmonary hypertension (PH) represents a class of diseases characterized by high blood pressure in the blood vessels of the lungs. These diseases may be classified into the following groups defined by the World Health Organization (WHO) based on their specific cause (Exhibit 88). Within these sub-types, development has primarily been focused on PAH (WHO-FC 1), which is estimated to affect as many as ~40-45K individuals in the US. Pulmonary arterial hypertension is a progressive, life-threatening disease that is caused by the thickening and narrowing of arteries in the lung, which obstructs the flow of blood into the lungs resulting in increases in blood pressure that can lead to right heart failure. PAH symptoms can include chest pain, shortness of breath, and dizziness, and patients have a median survival time of approximately seven years.

Exhibit 88: World Health Organization classification of functional status of patients with pulmonary hypertension

Class	Name	Description
WHO-FC I	Pulmonary Arterial Hypertension	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC II	Pulmonary Arterial Hypertension due to Left Heart Disease	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC III	Pulmonary Arterial Hypertension due to Lung Disease and/or hypoxia	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC IV	Chronic Thromboembolic Pulmonary Hypertension	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right HF, Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

Source: World Health Organization (WHO)

Standard of care: There are currently multiple approved drugs with distinct mechanisms of action (endothelin, NO-sGC-cGMP, and prostacyclin pathways) available to PAH patients, many of which are available as generics. These include calcium channel blockers, endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5i) and guanylate cyclase simulators, prostacyclin analogues and prostacyclin receptor agonists.

Most recently, MRK's Winrevair (sotatercept) gained FDA approval, and is expected to be a landmark product within PAH, per our expert survey. Beyond these product-specific generics and class competitors, the clinical development space is also becoming increasingly crowded with agents such as GOSS's seralutinib and INSM's treprostinil palmitil inhalation powder, and KROS' KER-012.

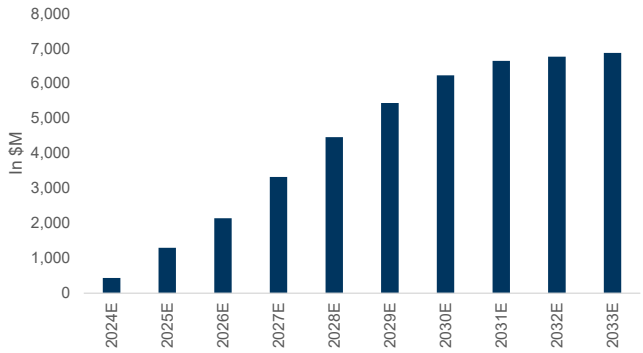
Patients will typically start on one or two drugs (double therapy), of the ERA and PDE5i class. As their disease worsens, they will layer on additional drugs such as prostacyclin analogues (called therapeutic escalation). Per physicians, 5%/35%/55% of patients are on single, double, and triple therapy regimens, and we expect new agents to similarly be added to the treatment protocol (vs. used as a replacement). For instance, physicians view Winrevair as appropriate across the majority of patients, regardless of whether they are currently on monotherapy/double therapy/triple therapy. Per GS estimates, Winrevair has a peak sales potential of $5B+.

Exhibit 89: Clinical development landscape in PAH

Company	Ticker	Asset	Mechanism of action	Route of administration	Phase	Update	Timing
Gossamer Bio	GOSS	seralutinib	PDGFR, CSF1R and c-KIT inhibitor	Inhalation	III	TBD	TBD
Insmed	INSM	treprostinil palmitil inhalation powder	dry powder formulation of a prostacyclin analogue	Inhalation	II	Topline data	2H25
Keros Therapeutics	KROS	KER-012	TGF-beta mAb	Subcutaneous	II	Topline data	2Q25
Merck & Co.	MRK	MK-5475	Guanlyte cyclase	Inhalation	II/III	TBD	TBD
Reviva	RVPH	brilaroxazine	Serotonin/dopamine modulator	Subcutaneous	II	TBD	TBD
United Therapeutics	UTHR	ralinepag	Prostacyclin receptor inhibitor	Oral	III	TBD	TBD

Source: PubMed, NEJM, Company data, Data compiled by Goldman Sachs Global Investment Research

Exhibit 90: Visible Alpha estimates suggest ~$7B global peak sales potential for Winrevair in PAH



Source: Visible Alpha Consensus Data

Muscular dystrophies

Muscular dystrophies are a group of genetic diseases that cause progressive muscle weakness and muscle degeneration, which hinders movement. Most common muscular dystrophies are Ducehnne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), facioscapulohumeral dystrophy (FSHD), and myotonic dystrophy type 1 (DM1). Currently, there are no curative therapies for muscular dystrophy but novel genetic approaches such as exon skippers, gene therapies, and RNA therapeutics, have emerged to modify disease and restore muscle function to patients.

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD/Duchenne) is a rare muscular disorder that is caused by a genetic mutation that causes a lack of functional dystrophin, a protein responsible for repairing damaged muscle fibers. The condition leads to a progressive weakening and degeneration of the muscles and accompanying complications such as cardiopulmonary issues, ultimately resulting in death, with the life expectancy for most DMD patients being roughly 25 years. Duchenne affects males exclusively and about 1.5 per 10K live male births in the US, according to the American Academy of Neurology (AAN), with a total US prevalence of about 14K patients. There is a high unmet medical need in the disease, particularly in maintaining motor function and ambulation, and the treatment landscape has evolved in recent years.

AAN guidelines call for the use of oral corticosteroids to address survival, quality of life (QoL), motor function, scoliosis, pulmonary function, and cardiac function in DMD patients, and several are approved in the US (Exhibit 91). In recent years, therapies with genetic approaches have been approved to treat specific subpopulations in DMD. Exon-skipping therapies, of which 4 are approved in the US (SRPT's Amondys 45, Exondys 51, and Vyondys 53 and NS Pharma's Viltepso), aim to offset the lack of functional dystrophin in DMD patients by selectively "skipping" specific exons in the patients' genes that are thought to be disease-causing. Most recently, SRPT's Elevidys gene therapy was fully approved for all DMD patients aged 4 and older who are amenable to receiving the treatment. Separately, PTCT's Translarna is not approved in

the US but remains conditionally authorized by the EMA in the EU, in a rare departure from the opinion of the CHMP which highlights the unmet medical need among DMD patients.

The treatment landscape has evolved meaningfully in recent years, and ahead, we look to RGNX's gene therapy for DMD, currently in the clinic, as well as EWTX's sevasemten program, a small molecule that seeks to treat gene therapy experienced DMD patients and preserve ambulation and motor function by protecting muscles from over-contracting.

The treatment landscape has evolved meaningfully in recent years, and ahead, we look to clinical trials from RNA and DYN on the development of antibody oligonucleotide conjugates for exon 44 and 51 skipping, respectively. Also within the DMD treatment landscape, we highlight RGNX's gene therapy asset, currently in the clinic, as well as EWTX's sevasemten program, a small molecule that seeks to treat gene therapy experienced DMD patients and preserve ambulation and motor function by protecting muscles from over-contracting.

Exhibit 91: Approved agents to treat DMD

Company	Brand Name	Molecule name	MOA	Patient Population	Dosing
Approved nonsteroidal treatment for DMD					
Italfarmaco S.p.A	Duvyzat	givinostat	histone deacetylase inhibitor	Age 6+	Oral 8.86 mg/mL 2x daily
Approved glucosteroids for DMD					
Multiple	Rayos / Predinsone Intens	prednisone	corticosteroid	Nearly all early-stage DMD patie	Oral 0.75 mg/kg QD
PTC Therapeutics	Emflaza	deflazaort	corticosteroid	Nearly all early-stage DMD patie	Oral 0.9 mg/kg QD
Santhera Pharmaceutic	Agamree	vamorolone	corticosteroid	Nearly all early-stage DMD patie	Oral 6 mg/kg QD
Approved genetic therapies for DMD					
NPS Pharma	Viltepso	viltolarsen	antisense oligonucleotide	Exon 53 nonsense variants	80 mg/kg infused QW
PTC Therapeutics	Translarna*	ataluren*	premature codon stop read-thro	Age 2+ with nonsense varoiant	10/10/20 mg oral TID
Sarepta Therapeutics	Vydondys 53	golodirsen	antisense oligonucleotide	Exon 53	30 mg/kg infused QW
Sarepta Therapeutics	Exondys 51	eteplirsen	antisense oligonucleotide	Exon 51	30 mg/kg infused QW
Sarepta Therapeutics	Amondys 45	casimersen	antisense oligonucleotide	Exon 45	30 mg/kg infused QW
Sarepta Therapeutics	Elevidys	delandistrogene moxeparvovec	AAV microdystrophin transgene	Amenable DMD patients aged 4	1.33 x 10^14 infused once

* conditional marketing authorization in the EU. Not approved in the US.

Source: Data compiled by Goldman Sachs Global Investment Research, FDA

Myotonic dystrophy type 1 (DM1)

Myotonic dystrophy type 1 (DM1) is a genetic, multi-system neuromuscular disease affecting approximately 40K people in the US. DM1 is characterized by muscle contractions and weakness, and secondary pulmonary or cardiovascular issues. There are currently no approved therapies for the condition. Emerging players in the space, like Avidity Biosciences (RNA) and Dyne Therapeutics (DYN), are utilizing RNA therapeutics to target the underlying cause of disease (mutant mRNA), to attempt to reverse disease progression. RNA is currently projected to have a first-to-market advantage vs. DYN, as it is assessing its agent, del-desiran, in a phase 3 study in DM1.

Facioscapulohumeral dystrophy (FSHD)

Facioscapulohumeral dystrophy (FSHD) is a hereditary, progressive muscular dystrophy affecting approximately 40K people in the US. The disease is characterized by asymmetric skeletal muscle loss that causes weakness in the face, shoulder, arms, and trunk, and eventually progresses to muscle weakness in the lower body. Around 20% of patients have the terminal form of the disease, causing them to become wheelchair

bound by the age of 50. There are no FDA approved therapies for FSHD, but several companies are developing clinical candidates to fill this void. Leading the clinical race, FULC will report topline data from its ongoing phase 3 REACH study of small molecule losmapimod in 2H24. Several other companies are trailing behind (Exhibit 92), where we note that RNA may be the second to begin a registrational trial study (expected 2H24).

Exhibit 92: Upcoming catalysts in FSHD development landscape

Company	Asset	Stage	Target	Modality	Upcoming catalyst	Timing
ARWR	ARO-DUX4	Phase 1	DUX4	siRNA linked to integrin peptide	Phase 1 data	2025
DYN	DYNE-302	Preclinical	DUX4	siRNA antibody conjugate	Phase 1 study initiation	TBD
FULC	losmapimod	Phase 3	p38 alpha/beta	small molecule	Phase 3 REACH data	4Q24
RNA	del-brax	Phase 1/2	DUX4	siRNA antibody conjugate	registrational trial initiation	2H24
ROG	RO7204239	Phase 2	myostatin	antibody	Phase 2 trial completion	mid-2025E

Source: Company reports

Disclosure Appendix

Reg AC

We, Corinne Johnson, Salveen Richter, CFA, Nathan Rich, Matthew Sykes, Rajan Sharma, Chris Shibutani, M.D., James Quigley, Andrea Tan, Ph.D., Paul Choi, Richard Law, Ph.D., Craig McLean, Ph.D., Tommie Reerink, Omari Baruti, Ph.D. and Sarah Conrad, hereby certify that all of the views expressed in this report accurately reflect our personal views about the subject company or companies and its or their securities. We also certify that no part of our compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

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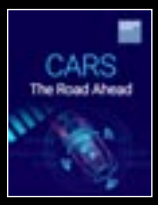

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