CFRA

Industry Surveys

Biotechnology

JUNE 2023

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CHARTS & FIGURES

NEW THEMES

What's Changed: The commercialization of Covid-19 vaccines, which is expected to occur sometime this year, is expected to bring a vital change to the biopharmaceutical space in the near future. Check out page 9 for more information.

What's Changed: We updated the chart for the top 10 biosimilars' sales forecast for the 2026-2028 period. See page 14.

EXECUTIVE SUMMARY

CFRA has a neutral outlook on the Biotechnology industry. Here are the current trends and key themes that we see for the future.

The Market for Covid-19 Vaccines and Treatments Is Shifting Towards Commercialization

Since late 2019 and the first outbreak of Covid-19, many biopharmaceutical companies have put forth efforts to develop and commercialize therapies for Covid-19. Successful companies quickly experienced the positive effects of Covid-19 treatments on their sales and profitability. In February 2023, the U.S. government announced the commercialization of Covid-19 vaccines, treatments, and tests, in line with the end of the public health emergency declaration in May 2023. The range of commercial price per dose is expected to quadruple between $110 and $130, more than the weighted average price per dose paid by the federal government at $28.90 for Moderna and Pfizer bivalent doses. This will bring a vital change to the biopharmaceutical market in the near future, but many other factors that will influence the future commercial market and the exact price of Covid-19 vaccine doses are still difficult to predict at this point, in our view.

Inflation Reduction Act Puts Drug Prices in the Crosshairs

The surprise August 2022 passage of the Inflation Reduction Act sets the stage for a novel change in drug pricing that could be significant in a few years. While the Act does not have any teeth to it until 2026 (when pricing changes go into effect), and while it only starts with 10 drugs (yet to be named), we believe that the important part is the structure. A list of 10 drugs will subsequently become 20 drugs and raises the possibility that it could be expanded further. The bottom line, in our view, is that highly successful drugs could see their upside potential muted, to a degree, by a new pricing mechanism that brings down prices before generic competition actually begins.

M&A Activity Continues to be Robust

Mega M&A deals continued despite the pandemic, as major drugmakers remained eager as ever to find new avenues of growth to make up for sales of blockbuster drugs lost to patent expirations. This is aided by the industry’s debt level, which remains low relative to historical levels. In addition, the pandemic has seemingly brought industry collaboration to an all-time high, leading us to believe that the M&A environment is favorable. In the past few years, we’ve seen significant M&A activity in immunology and oncology, which Evaluate forecasts to be two of the fastest growing therapeutic areas through 2028. The top 10 largest biopharmaceutical M&A deals in the last 12 months as of end May 2023 reached approximately $86 billion, primarily contributed by oncology, rare disease, and immunology/inflammation fields. Going forward, we expect interest in these therapeutic areas to remain high.

How Friendly is the FDA?

Lately, the Food and Drug Administration (FDA) appears to be quite cooperative with the biopharmaceutical market, as evidenced by lower times to approval and robust approval activity. The controversial June 2021 approval of aducanumab for Alzheimer’s disease certainly convinced investors of the FDA’s friendly stance as biotech stocks appreciated substantially across the board; however, there was significant public pushback against the approval that has led to congressional investigations. There has also been evidence of a tougher FDA as the agency required new and updated safety warnings and restricted the usage of JAK inhibitors, such as Pfizer’s Xeljanz, AbbVie’s Rinvoq, and Eli Lilly’s Olumiant, due to increased risk of heart-related issues.

BIOTECHNOLOGY

Outlook: Neutral

MARKET CAP BREAKDOWN*

RANK NO.	COMPANY NAME	MARKET CAP ($ billion)
1	AbbVie	243.4
2	Amgen	117.9
3	Gilead Sciences	96.0
4	Vertex	83.3
5	Regeneron	78.8
	Others†	92.1

Source: CFRA, S&P Global Market Intelligence.
**Data as of May 31, 2023.*
†Refer to the "Comparative Company Analysis" section of this survey for the list of companies.

ETF FOCUS

ETF	AUM ($M)	Expense Ratio
IBB iShares Biotechnology	7,624.7	0.44
XBI SPDR S&P Biotech	6,707.7	0.35
BBH VanEck Biotech	482.3	0.35

BY THE NUMBERS

$110-$130
Expected range of vaccines commercial price per dose

46
Number of drugs approved by the FDA in 2022, close to prior 10-year average of 49

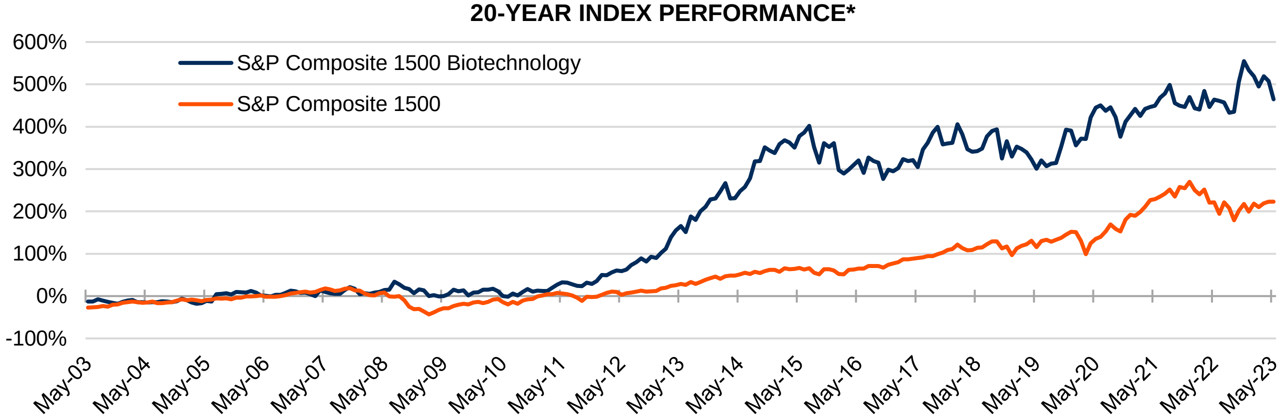
3.3%
2022-2028 CAGR for global R&D spending

8.9%
2023-2028 CAGR for worldwide biosimilars market

$3.2 billion
Total global biopharma VC investments as of Q2 2023

4.9%
Average drug price increase in 2022 vs. 4.8% in 2021

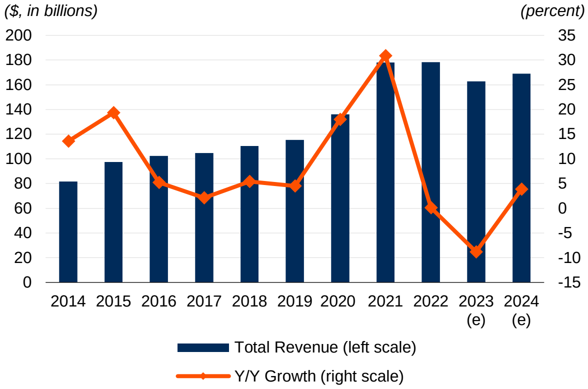
20-YEAR INDEX PERFORMANCE*



*Data as of May 31, 2023.
Source: S&P Global Market Intelligence.

FINANCIAL METRICS

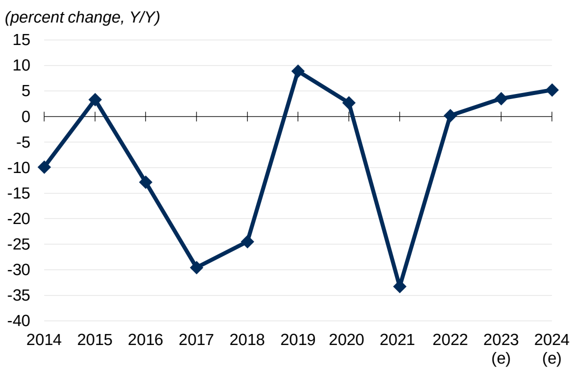
Revenue Growth



e-Estimate.
Source: S&P Global Market Intelligence, S&P Capital IQ Consensus Estimates.

- The high revenue growth in 2021 was attributed to the rapid growth of drugs approved in the last several years and sales boost from Covid-19 vaccines and treatments.
- We project revenue for the Biotechnology industry to drop 8.8% in 2023, down from the 0.1% growth in 2022, and to recover by 3.8% growth in 2024.
- The potential weak revenue growth in 2023 is primarily attributed to the drop in sales of Covid-19 vaccines amid the shift to commercialization and a number of expected patent expirations in the same year.

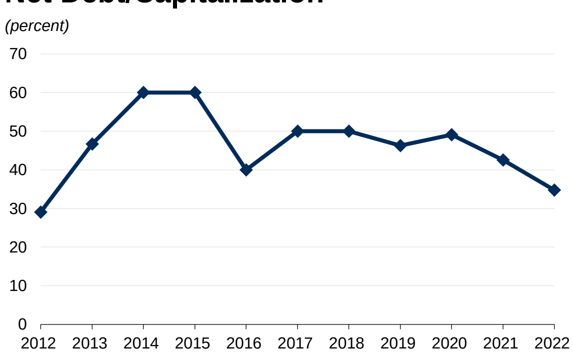
Median EPS Growth



e-Estimate.
Source: S&P Global Market Intelligence, S&P Capital IQ Consensus Estimates.

- We anticipate the industry's median EPS growth rate to increase by 3.5% in 2023 from a flat growth of 0.2% in 2022.
- We forecast median EPS to grow 5.2% in 2024, as the companies in the industry gradually return to profitability.
- The industry's earnings will be affected by the introduction of new drugs, the ramp-up in sales of said drugs (sales tend to peak 5 to 7 years after launch), the strength of pricing pressures, and the decline in sales of mature drugs (typically due to the loss of marketing exclusivity), in our view.

Net Debt/Capitalization

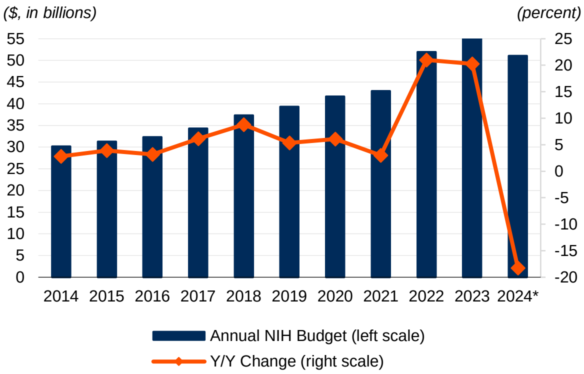


Source: S&P Global Market Intelligence.

- The industry's net debt-to-capital ratio stood at 35% in 2022, slightly lower than the historical average of 50%, reflecting strong M&A activity in the past few years.
- Looking forward, we foresee a potential cutback in M&A activity for the industry due to rising interest rates and weakening economic conditions.
- Many large-cap drug companies continue to seek new sources of long-term revenue growth as their blockbuster drugs face growing competition.

KEY INDUSTRY DRIVERS

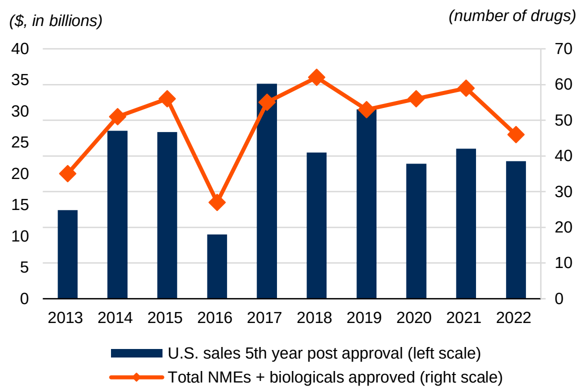
Annual NIH Budget



*Pending budget approval.
Source: National Institute of Heatlh.

- Spending by the National Institutes of Health (NIH) is key to biotech funding and innovation.
- In March 2023, President Biden submitted to Congress a proposed budget of $51.1 billion for the NIH, which includes discretionary budget authority of $48.9 billion, of which $407 million is associated with 21st Century Cures Act allocations and $83 million is for Superfund research activity (the U.S. fiscal year runs from October 1 to September 30).

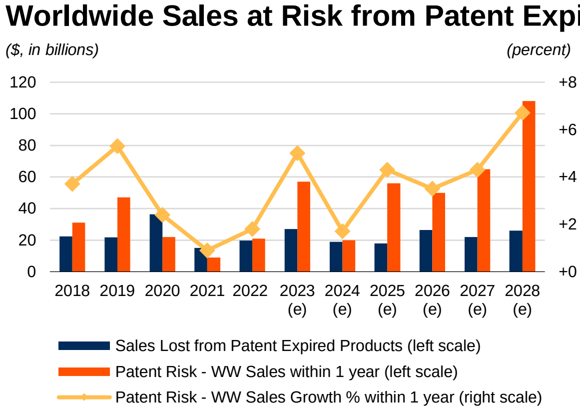
Drug Approvals in the U.S.



Source: Evaluate.

- In 2022, the FDA approved 46 new molecular entities (NMEs), down from 59 approved in 2021. Year-to-date as of end May 2023, 14 drugs have been approved.
- Although a number of drug applications encountered some decision delays in 2022, the total number of drugs approved was close to the 10-year average of 49.
- The 5th year sales expectations for drugs approved in recent years are encouraging for the long-term growth of the biopharmaceutical space.

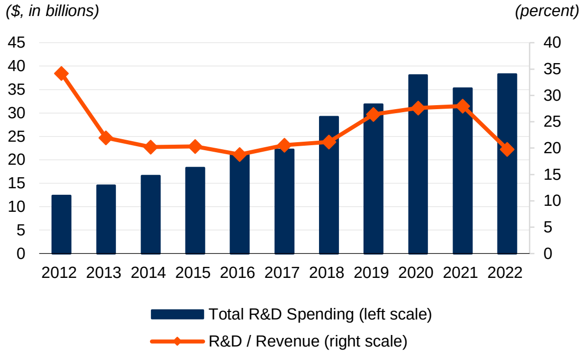
Worldwide Sales at Risk from Patent Expiration



e-Estimated.
Source: Evaluate.

- In 2023, we expect to see a marked increase in sales at risk. However, it is likely that the market has long anticipated the potential for lost sales.
- It is not uncommon for expectations around patent expirations to change due to patent litigation or patent extensions.

Aggregate R&D Spending*



*Constituents in the S&P Composite 1500 Biotechnology index.
Source: S&P Global Market Intelligence.

- R&D spending by biotech companies has grown recently, boosted by significant acquisition activities.
- Looking ahead, Evaluate expects global R&D spending to grow at a CAGR of 3.3% from 2022 to 2028 – slower than revenue growth of 6.0% – as companies direct less of their revenue toward R&D (or achieve higher R&D efficiency).

INDUSTRY TRENDS

Competitive Environment

Commercialization of Covid-19 Vaccines Expected to Revolutionize Biopharmaceutical Market
In February 2023, the U.S. government announced the commercialization of Covid-19 vaccines, treatments, and tests, in line with the end of the public health emergency declaration in May 2023. Since the beginning of the pandemic, the federal government has spent billions of dollars on emergency funds to supply Covid-19 vaccines, boosters, treatments, and tests to the public. Nevertheless, it is widely anticipated that these products will shift to the commercial market for their manufacturing, procurement, and pricing once the federal-purchased supply has depleted.

In late 2022, Pfizer and Moderna stated that they have been preparing for this transition going into 2023, where the market will be more fragmented compared to during the pandemic when the U.S. government was the sole purchaser of vaccines. Moderna also highlighted that the company has begun liaising with commercial players, distributors, and key pharmacies regarding the transition. In addition, both companies indicated that their range of commercial price per dose is expected to be between $110 and $130, which is 4 to 5 times more than the weighted average price per dose paid by the federal government at $28.90 for Moderna and Pfizer bivalent doses.

The transition to private market is expected to occur over the summer or early fall of 2023. Kaiser Family Foundation illustrated potential Covid-19 vaccine cost scenarios that may occur once the commercialization takes into effect, as per table below:

POTENTIAL TOTAL COVID-19 VACCINE COST SCENARIOS
For One Dose of a Covid-19 Vaccine/Booster per Adult

TYPE OF PURCHASE	PRICE/DOSE ($)	SCENARIO 1 100% of U.S. Adults (258 million doses)	SCENARIO 2 50% of U.S. Adults (129 million doses)	SCENARIO 3 25% of U.S. Adults (65 million doses)
Federal (Bivalent)	$29	$7.5 billion	$3.7 billion	$1.9 billion
Commercial (Low)	$110	$28.4 billion	$14.2 billion	$7.1 billion
Commercial (High)	$130	$33.5 billion	$16.8 billion	$8.4 billion

Source: Kaiser Family Foundation.

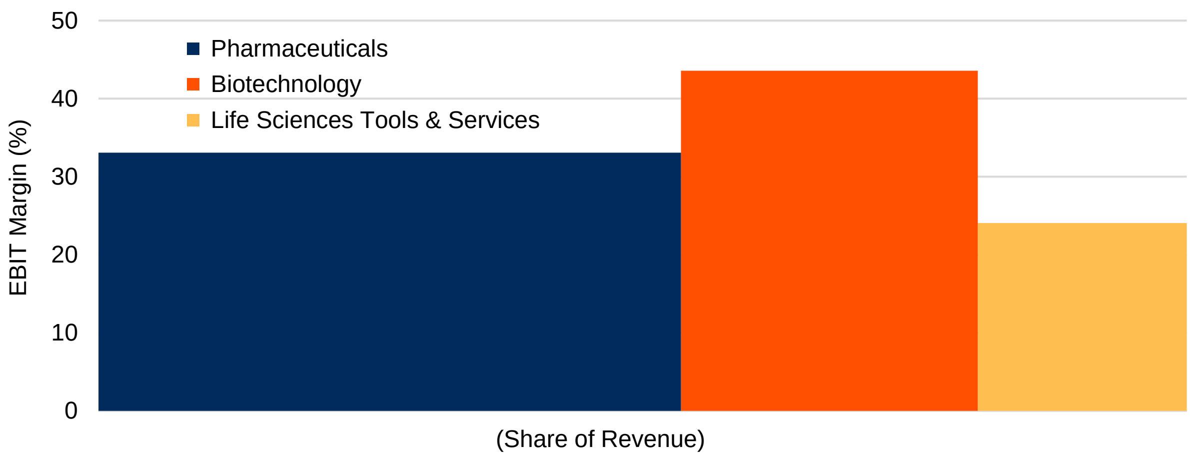
We expect this will bring a vital change to the biopharmaceutical space in the near future, but we think many other factors that will influence the future commercial market and the exact price of Covid-19 vaccine doses are still difficult to predict at this point.

Biosimilar Progress Remains Slow in the U.S.
Biosimilars are near copies of branded biologic drugs that have shown no clinically meaningful difference from their reference products. U.S. legislators originally hoped that biosimilars could alleviate drug costs in the same way that generic drugs have lowered costs for traditional pharmaceuticals.

However, makers of branded biologic drugs have often retained significant market share despite the approval of biosimilars or alternative therapies because sizable development, manufacturing, and commercialization costs deter potential entrants. Biosimilar manufacturers may not be able to aggressively offer discounts because of their need to recoup costs that are much higher on average than those required to successfully bring a generic drug to market. Other reasons holding back the uptake of biosimilars include the slow regulatory process, defensive strategies of drug innovator companies (*e.g.*, extensive patent litigation), lack of an interchangeability designation in the U.S., and insufficient patient and physician education about the safety and efficacy of biosimilars.

As demonstrated in the profit share map below, established biotech companies have high operating margins; however, the chart does not reflect the upfront development costs that are required for many years before any revenue is generated, nor the many failed therapies and companies.

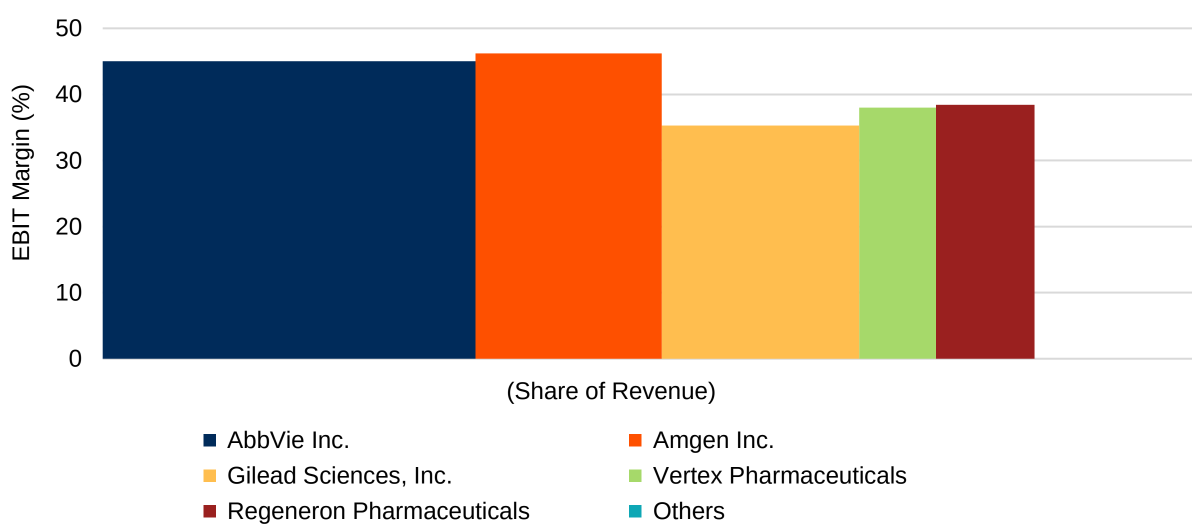
PROFIT SHARE MAP OF THE PHARMACEUTICALS, BIOTECHNOLOGY & LIFE SCIENCES INDUSTRIES
(5-year average)



Source: S&P Global Market Intelligence.

Within the Biotechnology industry, AbbVie contributed the most in terms of revenue (34.6%) with an operating margin of 45.0%.

PROFIT SHARE MAP OF THE BIOTECHNOLOGY INDUSTRY
(as of first quarter of 2023)



Source: S&P Global Market Intelligence.

PORTER'S FIVE FORCES

Although the Biotechnology industry has fierce competition, immense barriers to entry, and a constant threat of substitution, firms are still enticed to compete in the industry because of the alluring potential for extremely high profits. As a result, the Biotechnology industry has become notorious for the many companies that go bankrupt and the few companies that reach astronomical valuations without having sold anything. Companies that have a commercially successful first product are often able to use the cash flows from that first product to support new and existing R&D efforts, eventually leading to the establishment of multiple, diverse revenue streams.

Power of Buyers (Moderate) – In the Biotechnology industry, end consumers have little to no negotiating power. Negotiating power typically lies somewhere in the supply chain, either with third-party payers (typically health insurers and government programs), pharmacy benefit managers (PBMs, who manage drug lists available to patients), or pharmacies. Third-party payers typically determine how much, if any, reimbursement is supplied for dispensed drugs. If a drug is too expensive, private third-party payers can typically deny reimbursement. Medicare, a government health program, has limited to no negotiating power for certain classes of drugs that have been designated as protected. Meanwhile, PBMs design formularies, which are official lists of medicines that may be prescribed by health care providers or services. For drugs with limited or no competition (*e.g.*, still under exclusivity period or no other therapies are available), power of buyers is typically weak.

Power of Suppliers (Unique) – The raw materials and equipment used in biotechnology can often come from multiple suppliers. Much of the equipment and materials used by biotech companies may be easily sourced, meaning suppliers hold little power. However, the power of suppliers may be moderate to high in situations where biotech firms require the latest life science tools, equipment, or manufacturing processes. Many tools and equipment may require significant training before researchers can use them proficiently. This training and integration make it harder for biotech firms to switch to a different instrument supplier. Many biotech firms, especially less mature ones, rely on third parties to manufacture their drugs because it is more expensive to manufacture the drugs themselves. These third-party manufacturers can have significant negotiating power.

Barriers to Entry (High) – It is extremely difficult to enter the biotech market for a plethora of reasons. It is a highly regulated market in which it is difficult for new entrants to gain a thorough understanding of the regulatory processes and requirements. Biotech companies typically require significant upfront investment and may not achieve commercial success for many years. Companies often spend many years developing drug candidates that do not have commercial applications. In addition, established firms aggressively defend their intellectual property with patent litigation and other strategies. Established firms also negotiate contracts with distributors, PBMs, and third-party payers in ways that make it nearly impossible for new entrants to compete.

Threat of Substitutes (Unique) – A newly approved drug typically has patent protection and exclusivity rights for years, meaning that substitutes often have little to no power. However, biotech companies can face many substitutes, primarily in the form of small molecule traditional drugs, non-biopharmaceutical technologies, and biosimilar products. Small molecule drugs are drugs that have traditionally comprised a substantial proportion of the sales of pharmaceutical manufacturers. Non-biopharmaceutical technologies include medical devices and other technologies that can treat or alleviate health issues. Biosimilars are biologic products that are almost identical copies of branded biologic products (often, a drug). Biotech companies also face substitution in the form of other biotechnologies. We have seen the rise of new biotechnologies in recent years, such as gene therapy and mRNA therapeutics, and expect to continue to see the discovery and development of innovative technologies. As humans develop and harness more powerful biotechnologies, such as CRISPR-cas9, we expect other biotechnologies will become obsolete.

Rivalry Among Existing Competitors (High) – Because successful biotech therapies can be wildly profitable for companies that own the relevant intellectual property, industry competition is often fierce. For example, let's consider the world's most commercially successful drug, Humira (owned by AbbVie), which had sales of $21.2 billion in 2022. Many well-funded competitors, such as Amgen and Mylan, have tried to launch sales of their own biosimilar to Humira. AbbVie has aggressively defended its sales of Humira by obtaining many patents and litigating to protect those patents, particularly in the U.S., which is the largest market for most biotech companies. When the key patents for Humira inevitably expire, AbbVie is bound to face a deluge of competition.

In the Biotechnology industry, competition must typically wait for a patent exclusivity period to end. The Biologics Price Competition and Innovation Act (BCPIA) provides new biologics with 12 years of marketing exclusivity, during which rivals may not launch biosimilars. Another form of exclusivity is for orphan drugs. The first sponsor of an orphan drug for a designated rare disease or condition receives seven years of marketing exclusivity. Companies will try to effectively extend the exclusivity period for their drugs as far out as possible by applying for more patents. If the added patents are weak, competitors might contest them.

OTHER COMPETITIVE FACTORS

Biosimilar Competition

Biosimilars can typically be marketed once the original branded drug loses FDA-granted exclusivity and patent protection. The firm that manufactures the original biologic drug is typically referred to as the innovator. Biosimilar development in the U.S. has been hindered by branded biologic drug manufacturers who use tactics such as patent thickets, rebates, and bundled pricing to exacerbate the costs and challenges of biosimilar manufacturers. Some tactics are much less effective internationally because health care systems outside the U.S. are often more centralized. In addition, since biosimilars are typically slightly different from the original biologic, the FDA has set guidelines that make it expensive and difficult for biosimilar manufacturers to prove that their biosimilars are interchangeable with the innovator's drug. To this day, none of the FDA-approved biosimilars are considered interchangeable, which deters physicians from prescribing them. In Europe, biosimilars are much more readily substituted than in the U.S.

Due to the challenges in the U.S., biosimilars have not affected the biologic drug market as much as initially hoped. Biosimilars have helped lower prices where they are available, but not to the same extent that simple molecule pharmaceuticals face when a generic drug hits the market. Biosimilars are typically priced at about a 30% discount, while generic drugs are typically priced at an 85% discount to the originator's compound. We expect biosimilar discounts to increase over time as biosimilars become more common in the U.S. and the FDA provides a clearer pathway to achieving interchangeability. At the end of 2019, the CREATES Act was signed into law, a small step towards increasing the viability of biosimilars. The CREATES Act prevents branded drug makers from refusing to sell drug samples to biosimilar and generic manufacturers. We expect to see more proposals in the future to support the growth of biosimilars in the U.S.

Biosimilars have significantly reduced medical costs in Europe, as the European Union (EU) had approximately 81 approved biosimilars for 20 reference products as of end May 2023, the vast majority of which are marketed. The first EU biosimilar was approved in 2006. Meanwhile, the U.S. approved its first biosimilar in 2015 and has since approved approximately 38 biosimilars for 14 reference products, excluding insulin biosimilars, as of end May 2023. Only 23 of the approved biosimilars are marketed in the U.S. because of barriers to entry. Barriers in the U.S. to biosimilars tend to be much more difficult to overcome because the U.S. market is the largest and most important regional market for almost all drug manufacturers.

New Patent Issuances Detract From Biosimilar Cost Savings

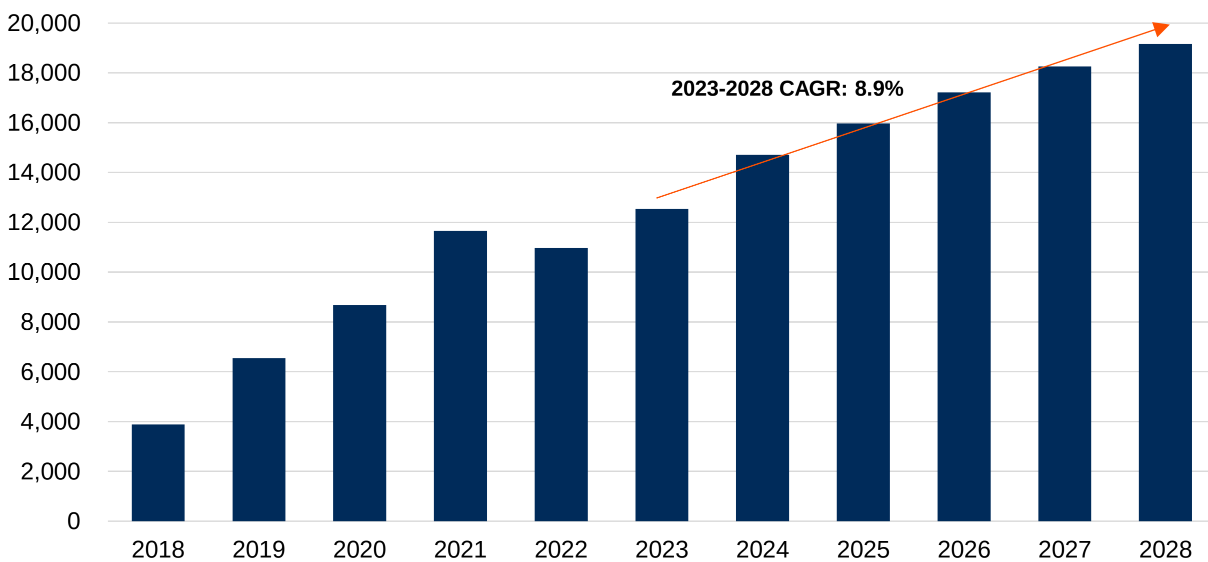
Despite the promise of biosimilars to replace older medicines with cheaper alternatives, several legacy biologic drugs have been issued new patents that extend product lifecycles and are likely to keep biosimilar competition off the market indefinitely.

For example, Biogen's original patent for Avonex (a drug for multiple sclerosis) was set to expire in 2013, but the company was granted a new patent in 2009, which effectively extended patent protection for the drug until 2026. Another example is Humira, a drug that has a composition of matter patent, which expired in December 2016. However, AbbVie (manufacturer of Humira) filed at least 70 other patents related to Humira's formulation and manufacturing, deterring aspiring biosimilar competitors. As a result, the company is not expected to face significant biosimilar competition to Humira in the U.S. until 2023, despite the December 2016 patent expiration.

These extensions make it difficult for biosimilar manufacturers to enter the market.

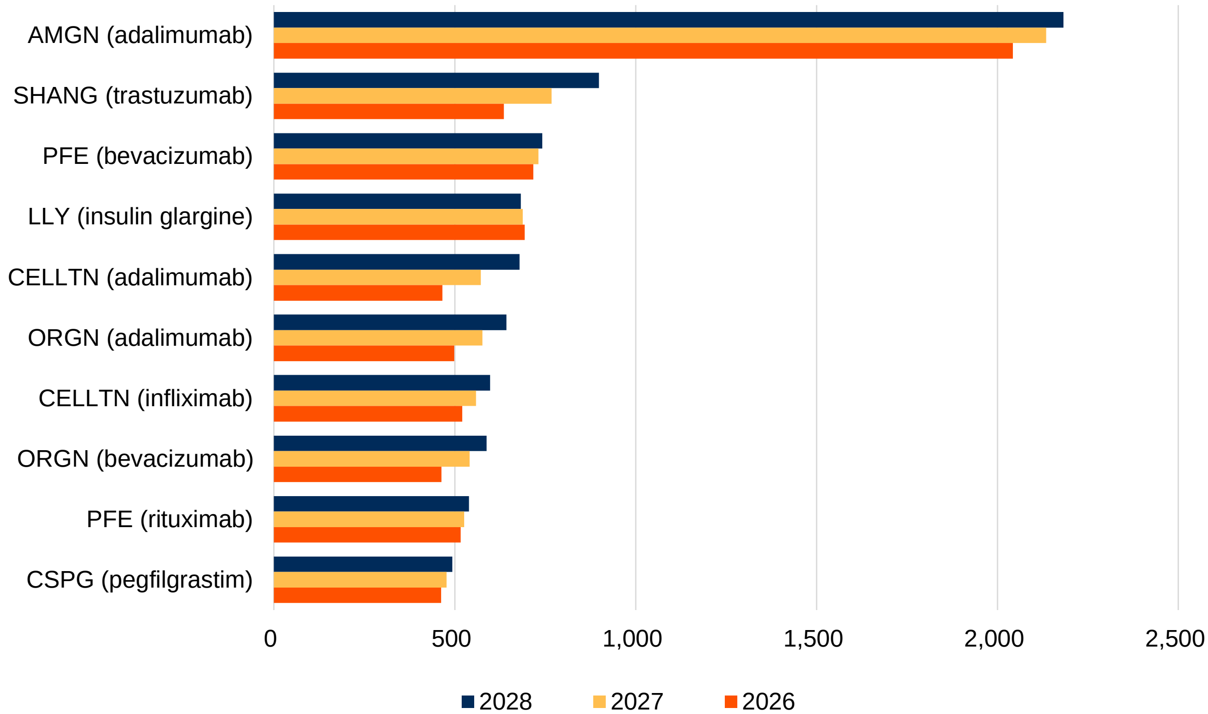
The 2012 introduction of the Inter Partes Review (IPR), a trial proceeding conducted by the Patent Trial and Appeal Board (PTAB) to challenge the validity of a patent, has slowed down the trend of patent extensions. Compared to litigation, the IPR is faster, cheaper, and has a higher chance of success.

WORLDWIDE BIOSIMILARS MARKET OUTLOOK
($, in billions)



Source: Evaluate.

TOP 10 BIOSIMILARS
($, in millions, ranked by 2028 forecast global sales)



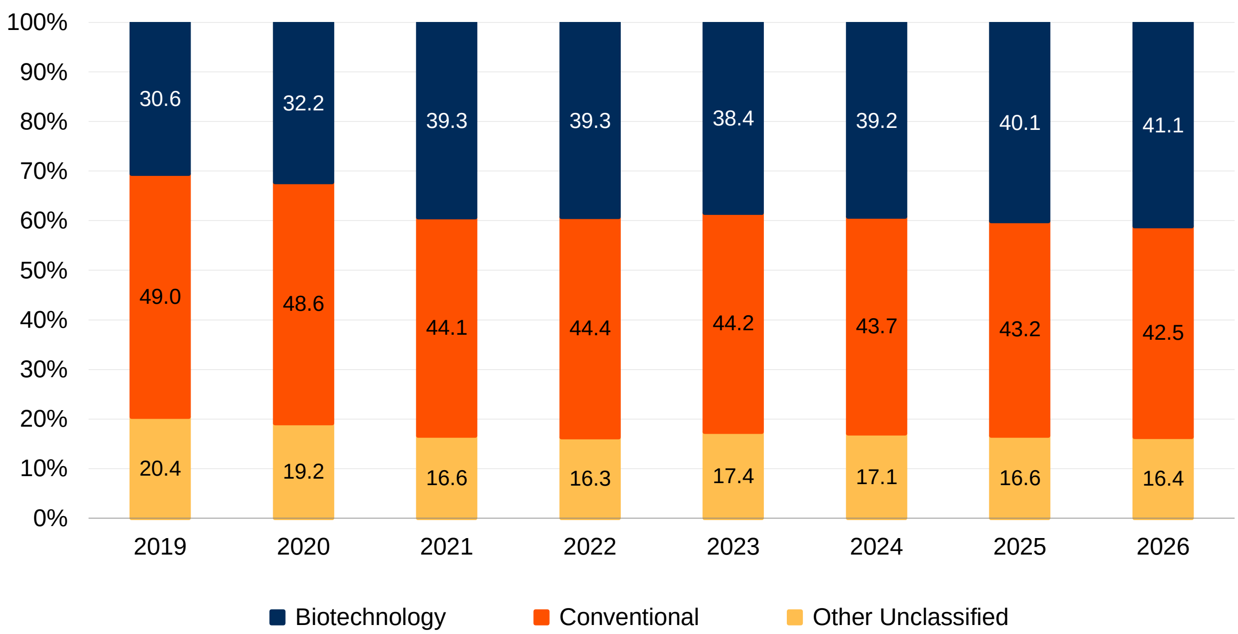
Source: Evaluate.

Operating and Regulatory Environment

Biotech's Presence Grows, Along with Its Ties to Big Pharma

In the last several years, the U.S. Biotechnology industry has experienced a strong pick-up in initial public offerings (IPO), mergers, and acquisitions. Many major pharmaceutical manufacturers have turned their focus to biotechnology. The trend has blurred the distinction between pharma and biotech companies.

GLOBAL SHARE OF PRESCRIPTION DRUG & OTC PHARMA SALES



Note: Biotechnology refers to modern techniques that use newer applications of biotechnology, such as genetic engineering and cell fusion. Conventional refers to traditional techniques of using living organisms to yield new products or modify foods for human use.
Source: Evaluate. Data as of May 22, 2023.

Sales from biotech products increased to $451 billion in 2022 from $166 billion in 2012, reflecting a compound annual growth rate (CAGR) of 10.5%. According to data provider Evaluate, 52% of worldwide prescription drug sales from the top 100 products in 2020 (latest available) came from biologics versus 38% in 2012. Evaluate forecasts that this figure will increase to 57% by 2026.

TOP 10 BIOTECHNOLOGY DRUGS
(ranked by 2022 global sales, in $, millions)

RANK	PRODUCT	COMPANY	MECHANISM OF ACTION	SALES 2019	2020	2021	2022
1	Humira	AbbVie	Tumor necrosis factor alpha (TNFa) antibody	19,735	20,409	20,694	21,237
2	Keytruda	Merck & Co	Programmed cell death protein 1 (PD1) antibody	11,121	14,380	17,186	20,937
3	Revlimid	Celgene	Interleukin-6 (IL-6) antagonist; Natural killer (NK) cell stimulant; NK T-cell (NKT) stimulant; TNFa inhibitor; Vascular endothelial growth factor (VEGF) inhibitor	11,161	12,154	12,821	9,978
4	Eliquis	Bristol-Myers Squibb	Coagulation factor Xa inhibitor	7,929	9,168	10,762	11,789
5	Eylea	Regeneron	Vascular endothelial growth factor receptor (VEGFR) antagonist	7,989	7,909	9,385	9,647
6	Stelara	Johnson & Johnson	Interleukin-12 (IL-12) antibody; Interleukin-23 (IL-23) antibody	6,600	7,707	9,134	9,723
7	Opdivo	Bristol-Myers Squibb	Programmed cell death protein 1 (PD1) antibody	7,989	7,917	7,523	8,249
8	Biktarvy	Gilead Sciences	HIV-1 integrase inhibitor; HIV-1 nucleoside reverse transcriptase inhibitor (NRTI)	4,738	7,259	8,624	21,237
9	Xarelto	Johnson & Johnson	Coagulation factor Xa inhibitor	2,313	2,345	2,438	2,473
10	Imbruvica	AbbVie	Bruton's tyrosine kinase (BTK) inhibitor	5,686	6,612	5,408	4,568
			Total Top 10	**85,260**	**95,861**	**103,975**	**119,838**

Source: Company reports, Evaluate.

Inflation Reduction Act 2022 Enacted to Reduce Drug Prices

On August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, which consists of an extensive package of health, tax, and climate change provisions. The law includes some provisions to reduce prescription drug costs for Medicare beneficiaries and lower drug spending by the federal government.

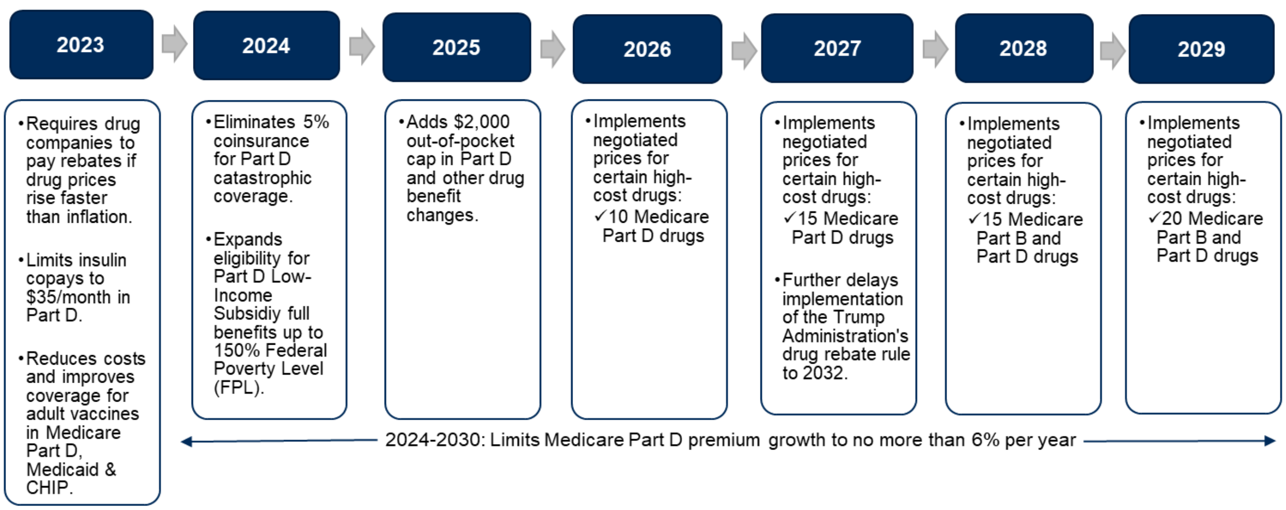
The law also includes two policies that would directly impact overall drug prices. One of the policies requires the federal government to negotiate prices for some high-cost drugs covered under Medicare. This would affect the Medicare Part D and B drug spending, where the spending is highly concentrated among a relatively small share of covered drugs, primarily those without generic or biosimilar competitors. Under the Inflation Reduction Act, negotiation is eligible for brand-name and biologic drugs without generic or biosimilar equivalents covered under Medicare Part D (retail prescription drugs) or Part B (administered by physicians), which are among the highest-spending Medicare-covered drugs. In order to be eligible for negotiation, the drugs should also be nine or more years (small-molecule drugs) or 13 or more years (biologicals) from FDA approval, according to the law. Another policy covered under the Inflation Reduction Act requires drug manufacturers to pay rebates to Medicare if they raise prices faster than inflation for drugs used by Medicare beneficiaries. According to Kaiser Family Foundation, half of all drugs covered by Medicare saw price hikes above the inflation rate of 1% over the period from 2019 to 2020. On top of that, one-third of these drugs also had price increases of 7.5% or more than the annual inflation rate in early

2022. The inflation rebate provision will be executed in 2020, where 2021 will be used as the base year for establishing price changes relative to inflation.

In addition, the Inflation Reduction Act also includes some provisions that will help to lessen out-of-pocket spending for Medicare beneficiaries. One of the provisions consists of a cap on Medicare beneficiaries' out-of-pocket spending under the Medicare Part D benefit, where coinsurance above the catastrophic threshold will be eliminated in 2024 and a $2,000 cap on spending will be added in 2025. Furthermore, the law also limits cost-sharing for insulin to $35 per month for Medicare beneficiaries starting in 2023, including covered insulin products in Medicare Part D and for insulin furnished though durable medical equipment under Medicare Part B. As of 2023, the law discards cost sharing for adult vaccines covered under Medicare Part D and enhances access to adult vaccines under Medicaid and Children's Health Insurance Program (CHIP). In 2024, the eligibility for full Part D Low-Income Subsidies (LIS) will be expended to low-income beneficiaries, with incomes up to 150% of poverty and modest assets and the partial LIS benefit currently in place for individuals with incomes between 135% and 150% of poverty will also be revoked.

The Inflation Reduction Act also encompasses a provision to further postpone the implementation of the Trump administration's drug rebate rule until 2023 instead of taking effect in 2027. The rebate rule would eradicate the anti-kickback safe harbor protections for prescription drug rebates negotiated between drug manufacturers and PBMs or health plan sponsors in Medicare Part D.

IMPLEMENTATION TIMELINE OF DRUG PROVISIONS IN THE INFLATION REDUCTION ACT



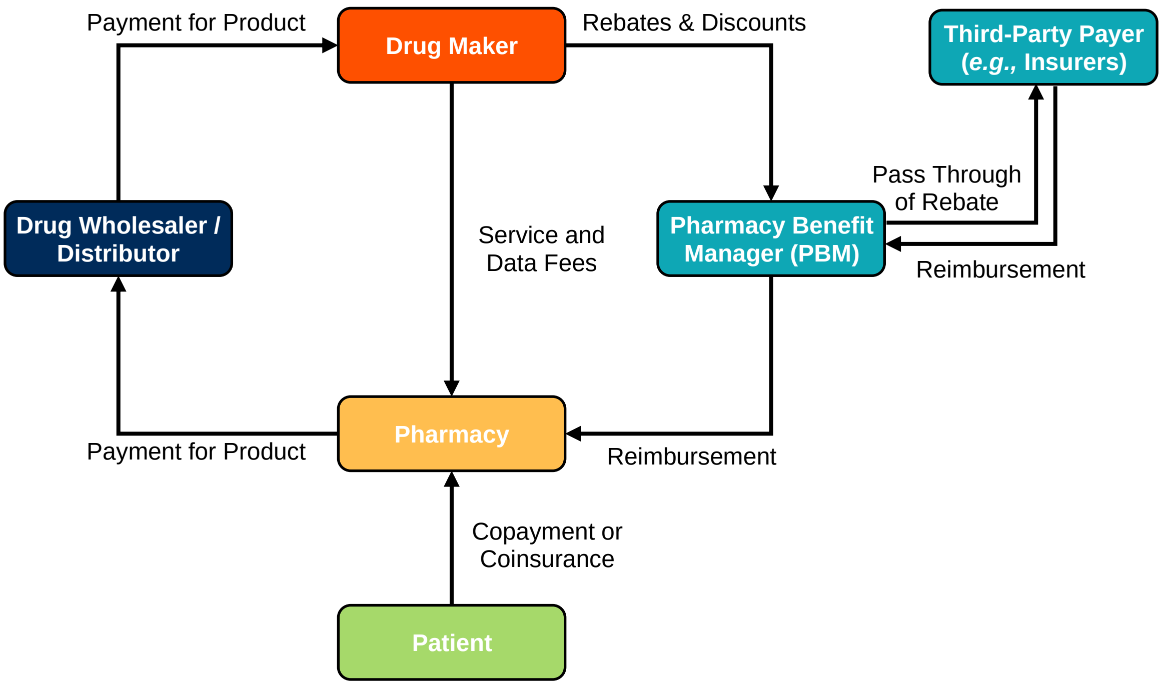
Source: KFF.

Drug Pricing Picture Is Complicated and Opaque

Constructive options to address drug prices appear limited because of the opaqueness around the true cost of drugs (*i.e.,* after rebates and discounts) that industry participants deliberately perpetrate. For example, in a study by IQVIA, the average list price of branded drugs is estimated to grow at a CAGR of 2.5%-5.5% from 2023 to 2027, whereas the average net price (*i.e.*, the price after discounts and rebates) is forecasted to grow at a CAGR of -1% to 2% over the same period, down from 4% CAGR for the past five years including projected effects of the Inflation Reduction Act. In addition, the way that payments flow in the U.S. health care system makes it difficult to point out the key actors or areas of the supply chain that are driving cost trends (see illustration on the next page). Typically, a drug maker sells to a wholesaler, which in turn sells the drugs to a pharmacy, where the patient gets prescription drugs. Other consumer products often go through a similar process; however, in the health care system, the third-party payers (*e.g.*, health insurers and Medicare) negotiate lower prices on behalf of patients (*e.g.*, rebates and discounts) and may provide reimbursements to patients for costs incurred.

The prices that patients pay vary by insurer and health plan. One way that insurers can lower costs for patients is by negotiating rebates with drug manufacturers. Insurers can pass the rebates on to consumers by reducing insurance premiums or drug prices at point of sale; however, it is extremely difficult to determine how various rebates and discounts are being allocated and reflected in health care costs, especially since negotiated savings are not publicly disclosed.

ILLUSTRATIVE FINANCIAL FLOW OF THE U.S. HEALTH CARE SYSTEM



Note: This diagram is not meant to be comprehensive or reflective of all financial relations in the industry.
Source: CFRA.

Drug manufacturers have blamed PBMs for the significant rise in drug prices because of the increased rebates that PBMs demand. PBMs, on the other hand, have blamed drug manufacturers, saying that they need higher rebates and discounts because of the rising list prices of drugs. In August 2018, CVS, one of the largest PBMs in the U.S., commented that it had historically only kept 2% of rebates. The company went a step further in December 2018 with the launch of its “guaranteed net cost” pricing model, which returns 100% of drug rebates to its clients. It seems that rebates may not have been the biggest driver of drug prices, as some believe.

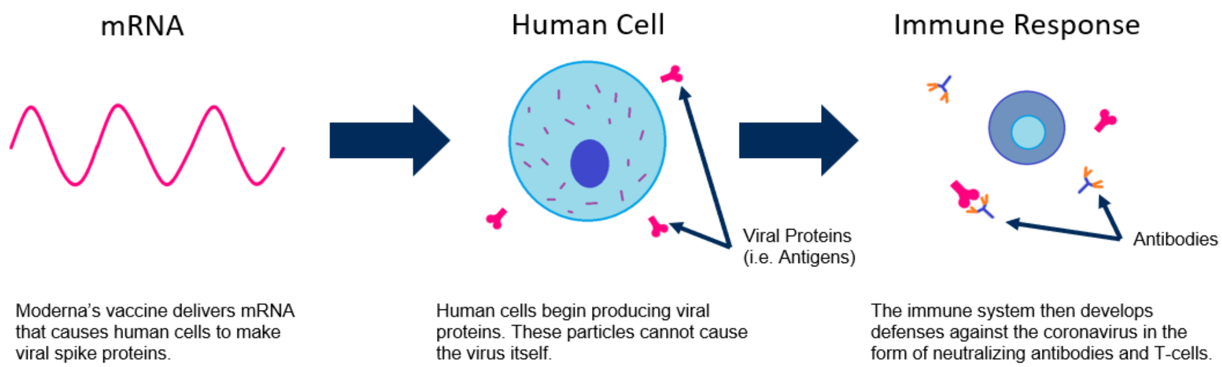
The Covid-19 pandemic highlighted the importance of pharmaceutical innovation and appropriate R&D spending to develop fast and effective cures to diseases. The major argument against lowering drug prices has been the potential negative impact on revenues, which would result in lower research costs and limited future innovation. To counter negative attention over high drug prices, some drug companies have become more vocal. Companies have launched marketing campaigns that focus on the drug industry’s substantial R&D spending and the many medical advancements that have been made. Due to the necessity to find a balance between more affordable drug prices and not harm innovation, there are disagreements about specific policy actions to be taken and their implementation. In our opinion, it may take some time to resolve these issues.

The Pandemic Was a Breakout Moment for mRNA-Based Therapies

At the beginning of the pandemic, Moderna, a leading developer of mRNA-based therapies, had no commercialized products and was widely expected to be earnings negative through 2022. In addition, no mRNA-based vaccine had ever been approved before by the FDA. Now, the leading Covid-19 vaccines are both mRNA-based, and Moderna's vaccine net sales were over $18.4 billion in 2022.

We think that mRNA-based therapeutics are primed to revolutionize the biopharmaceutical space. mRNA is critical to the body's production of all proteins required for life because mRNA carries the instructions for protein production. Another way to think of mRNA is as software code that tells your body what types of proteins to produce. In the graphic below, we illustrate how Moderna's vaccine works. A key benefit to mRNA therapies over most commercially available biotechnology-based therapies is that mRNA therapies use the recipient's body to produce the desired proteins, whereas many of the most commercially successful therapies are based on proteins that are synthesized outside of the human body. In addition, the manufacturing process for conventional vaccines, in particular, is typically complex and lengthy because such vaccines are made from finicky cell cultures that must grow in a certain way. mRNA therapies promise to significantly reduce production costs and time since the process for manufacturing mRNA vaccines is cell-free. In our opinion, mRNA therapies could become the next big driver of value creation for the biopharmaceutical market.

How Moderna's mRNA-Based Vaccine Works



BioNTech, a biotechnology company headquartered in the German city of Mainz, made its mark by developing Covid-19 vaccines with Pfizer. BioNTech, which is a cancer company, was able to shift its focus from fighting cancer to creating a Covid-19 vaccine. The company's significant achievement in developing the Comirnaty vaccine managed to save millions of lives and, at the same time, contribute unprecedented windfall of cash to the company. It has managed to earn a total amount of €19 billion in cash, a part of its assets, which equates to "a lifetime of funding" from the vaccine development. As a result, the company aims to resume pursuing its plan in oncology, with ambition to be able to tailor drugs to each patient's cancer.

According to Financial Times, the company utilized the messenger RNA (mRNA) technology in the development of Covid-19 vaccine and targets to use the same technology to tackle cancer in combination with other therapies. The company also believes that the consolidation of various treatments, including cell therapies, antibodies, and other ways of modulating the immune system, would be the best hope of developing a cure for cancer. In April 2022, it revealed the results of a study that combined mRNA with CAR T-cell therapy to reprogramme a patient's immune system. CAR T is a complex treatment that involves collecting and modifying a patient's immune cells to fight their cancer and has so far only worked in blood cancers. However, BioNTech scientists went the extra mile in developing an mRNA booster with the intention to make it useful in a larger range of cancers. The study also disclosed that the booster managed to expand the number of immune cells and boost their capability to eradicate a solid tumor.

In addition, the company's most advanced clinical oncology program is for cancer vaccines. As opposed to regular vaccines, they do not prevent the recipient from developing cancer, but are used as treatments to alert the immune system to kill mutated cells. Even though the concept of cancer vaccines has been around for decades, it has unfortunately been a non-success. Experts think that the failure could be attributed to the delay of therapies deployment, where new therapies are typically attempted in patients who have not responded to previous drugs and are normally at the later stage of cancer. However, experts believe that cancer vaccines might have the potential to work better at an earlier stage of cancer when the patient's immune system is more vigorous. BioNTech countered the experts' claim and emphasized that its early data suggested that its mRNA cancer vaccines are evoking immune responses several hundred times stronger than were previously reported for conventional cancer vaccines. On top of that, the company is also performing trials in earlier stage cancers and intends to provide the vaccines shortly after patients' surgery to remove the primary tumor has been completed. In a phase 1 trial conducted in June 2021, the company saw positive results in treating pancreatic cancer patients momentarily after surgery.

Nonetheless, BioNTech foresees challenges in convincing "conservative" regulators to adapt to individualized therapies that break the mold of conventional clinical trials. Although these challenges, coupled with scientific success uncertainty, could create a long journey ahead for the company, its latest scientific discoveries and implementation of advanced technologies could give new hope to cancer patients.

Specialty Drugs Outpace Inflation

Specialty drugs – which are often biologics – are a recent designation for therapeutics that are considered high cost, high complexity, or high touch. The cost of specialty drugs is increasing at a far higher rate than inflation. According to IQVIA, specialty drugs will account for 43% of total global drug spending, driven by growth in oncology and immunology, according to IQVIA.

In 2020, list prices for specialty brand medications climbed 36% from 2016, based on Evernorth Prescription Price Index for 2020 (latest available). In contrast, prices of specialty generic medications plummeted 42.3% in the same period. It is hard to tell how prices of brand-name drugs have changed for end consumers because of all the rebates and discounts used in the industry.

HOW THE INDUSTRY OPERATES

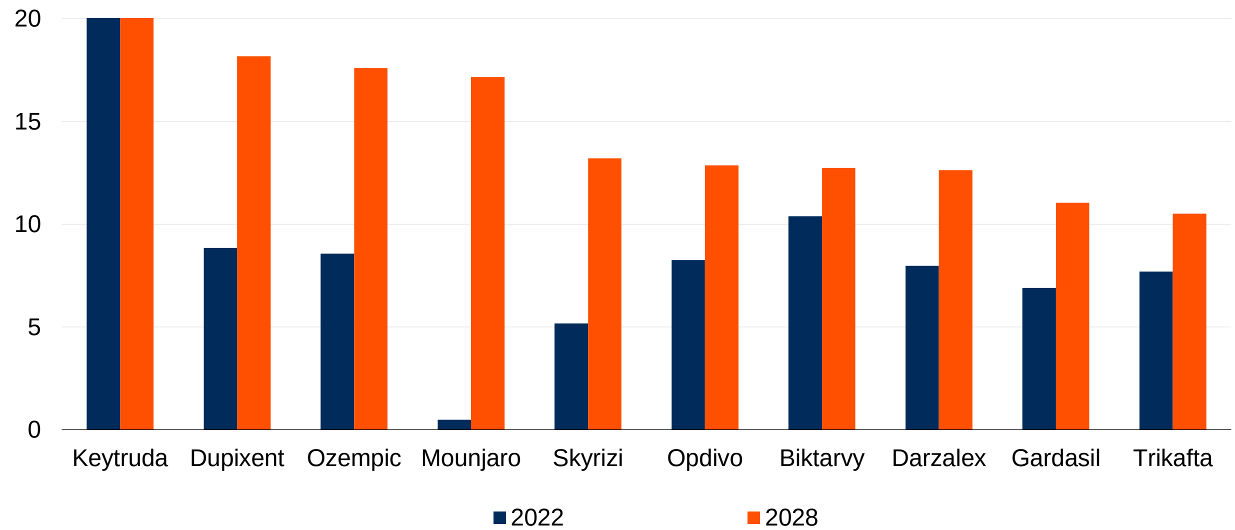
Biotech refers to the application of biological and biochemical sciences in the large-scale production of products to change human health, food supplies, or the environment.

Key Biotechnologies

Monoclonal antibodies (mAb) have been and continue to be a key industry driver, as mAbs are used in many leading drugs for the treatment of cancer and inflammatory disease. Leading mAbs for inflammatory diseases include Johnson & Johnson's Remicade, AbbVie's Humira, and Roche's Avastin. Evaluate estimates that four of the top 10 best-selling biotechnology products in 2028 will be based on mAb technology.

Other biotechnologies that we expect to be marketed in the future include cell therapies, gene therapies, recombinant products, and bioengineered vaccines. There are even newer technologies being considered for commercial development, such as CRISPR/Cas9 (a type of gene therapy). We could see significant changes in the landscape of the biotechnology market as new technologies gain prominence.

TOP 10 SELLING DRUGS WORLDWIDE IN 2028
(in $, billions)



Source: Evaluate.

Spending on R&D

Investment in research & development (R&D) is crucial to building a long-term sustainable organization. Biotech R&D as a percentage of product sales has traditionally been high, but it has declined as industry revenues have expanded substantially. While declines in R&D spending can negatively affect investor sentiment because of R&D's role in innovation, R&D spending for the whole industry has been increasing. Successful drug companies are those, in CFRA's view, that can manage and develop robust pipelines and combine them with commercial success. Peak drug sales typically occur five to seven years following the launch of a new drug.

RESEARCH & DEVELOPMENT EXPENDITURES FOR U.S. BIOTECHNOLOGY COMPANIES*
(arranged by 2022 R&D expenditures)

COMPANY	R&D EXPENDITURES ($ MILLION)						R&D / REVENUES (%)					
	2017	2018	2019	2020	2021	2022	2017	2018	2019	2020	2021	2022
Gilead Sciences	3,734	5,018	9,106	10,895	5,540	8,621	14	23	41	44	20	32
AbbVie	5,334	10,753	6,792	7,755	8,046	7,207	19	33	20	17	14	12
Amgen	3,562	3,737	4,116	4,207	6,324	4,434	16	16	18	17	24	17
Biogen	2,374	2,710	2,281	4,066	2,519	2,231	19	20	16	30	23	22
Regeneron Pharmaceuticals	2,075	1,469	2,450	2,735	2,908	3,593	35	22	31	32	18	30
Incyte	1,329	1,198	1,154	2,224	1,488	1,638	87	64	53	83	50	48
Vertex Pharmaceuticals	1,580	1,445	1,755	1,830	3,051	2,540	63	47	42	29	40	28
Exelixis	112	182	337	548	694	892	25	21	35	55	48	55
United Therapeutics	265	358	1,183	358	540	323	15	22	82	24	32	17
Emergent BioSolutions	97	143	226	235	234	193	17	18	20	15	13	17
Xencor	72	98	119	170	193	200	201	240	76	138	70	121
REGENXBIO	57	84	124	166	181	242	551	38	352	108	39	215
Coherus BioSciences#	167	110	94	143	363	199	107,06	N/A	26	30	111	94
Arrowhead Pharmaceuticals	51	58	87	142	236	315	167	122	53	178	163	113
Enanta Pharmaceuticals	63	112	140	141	186	157	48	47	75	138	200	191
Cytokinetics	90	89	86	97	160	241	675	283	321	174	227	255
Myriad Genetics	71	80	83	73	82	85	9	10	10	13	12	13
Ligand Pharmaceuticals	27	28	56	59	69	36	19	11	46	32	25	18
Vanda Pharmaceuticals	39	44	49	56	75	86	23	23	21	22	28	34
Halozyme Therapeutics	151	150	141	34	36	67	48	99	72	13	8	10
Eagle Pharmaceuticals	33	44	37	31	51	34	14	21	19	16	30	11
Anika Therapeutics	19	18	17	26	28	28	17	17	15	20	19	18
Average	928	1,217	1,327	1,570	1,439	1,516	558	58	66	56	55	62
Median	97	112	140	166	234	242	25	23	38	30	29	29

*Based on companies in the S&P Composite 1500 Biotechnology Index.

#No revenue in 2018.

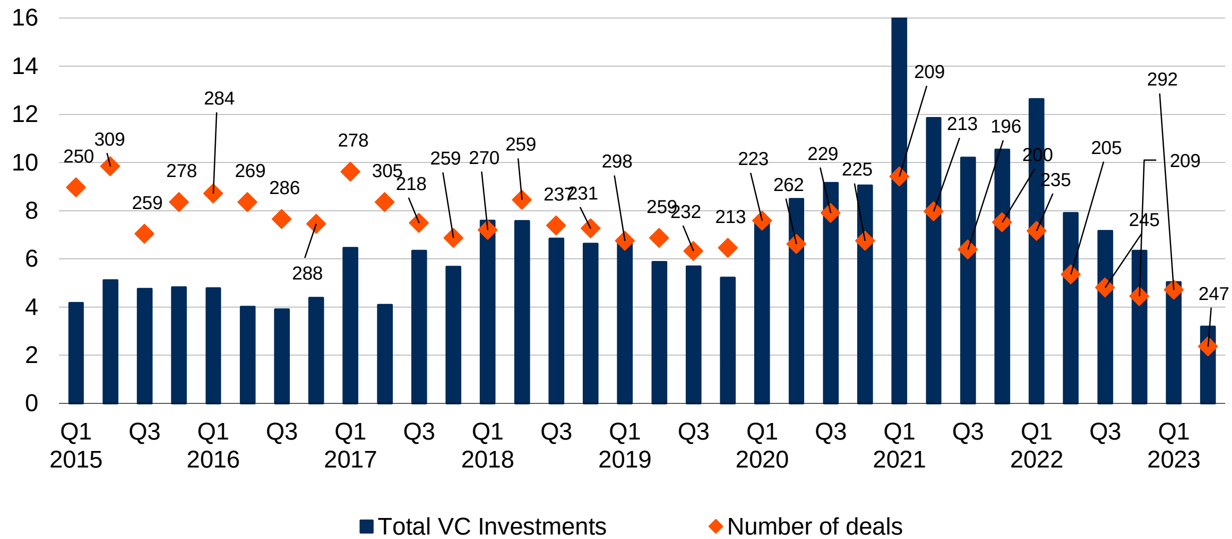
Source: S&P Global Market Intelligence.

Access to Capital Is Crucial

Given the high costs of biologic R&D, access to capital is critical for biotech companies, particularly for those that have not had significant commercial success. New biotech entities are usually funded through seed money from wealthy private investors or small groups of investors, called "angels," and by venture capitalists. In market downturns, funding can become especially scarce, which can derail R&D plans. CFRA recommends reviewing the access to funding, cash flow, and cash and cash equivalent balances for biotechnology companies to assess the capacity for a company to continue funding its clinical pipeline. This is especially pertinent for young biotech firms that may not have had much commercial success yet.

GLOBAL QUARTERLY BIOPHARMA VENTURE INVESTMENTS*

($, in billions)



*Data as of May 22, 2023; includes MedTech investments.
Source: Evaluate.

The Importance of Partnerships

Once a small firm has a promising investigational drug candidate, the firm often chooses to team up with a major pharmaceutical or biotech company. The larger company may supply upfront fees, R&D funding, milestone payments, royalties, and co-promotion rights. In addition, the partner often supplies regulatory know-how, production facilities, and sales organizations for new products. It usually makes sense for small companies to license their initial products or collaborate with big players since it is difficult to navigate regulatory and commercial payor landscapes. In addition, establishing support within a physician community often requires significant effort and cost. Eventually, small companies gain enough experience, scale, and financial support to hopefully commercialize their own products.

Many approved biotech products have been developed through collaborative agreements. Such agreements have become a hallmark of the Biotechnology and Pharmaceuticals industries. These agreements have often led to acquisitions between partnering firms after the larger firms gain first-hand insights into a smaller company's management, breadth of research capabilities, and prospects for pipeline advancement.

These agreements aren't only beneficial to small companies. Large companies benefit because they can often acquire the rights to innovative assets with a high chance of commercial success. This saves time a lot of time and R&D costs. In addition, large companies usually already have well-established sales and marketing infrastructure that they can leverage to sell new drugs similar to the ones they already sell.

Patents Make It Happen

Patents are among the most important benchmarks of progress in developing new biotechnology products. When a company obtains a patent for a new process or product, competitors are prohibited from commercial use of that discovery. In the Biotechnology industry, patents are critical to raising capital for continued R&D spending. Patents granted by the U.S. Patent and Trademark Office (USPTO) can be challenged via either the Inter Partes Review (IPR) or through court proceedings. IPRs tend to be faster, cheaper, and more successful.

Nevertheless, there have been several ongoing patents feud between the biopharmaceutical companies in the industry. One of the ongoing feuds involves the “skinny label” patent battle between Teva Pharmaceuticals and Glaxo Smith Kline (GSK). In 2007, Teva launched its Coreg generic in two of the branded med’s three indications and the Food and Drug Administration (FDA) later instructed the company to add the med’s third indication for congestive heart failure in 2011, although GSK owned a patent for that particular use through 2015. In light of this, GSK filed a lawsuit in 2014 claiming that Teva prompted doctors to prescribe its copycat for congestive heart failure, while Teva countered that it was merely acting as per the FDA’s instructions. In 2017, a jury sided with GSK and ordered Teva to pay $235 million, which Teva later induced a district court to overturn the verdict. However, an appeals court reversed the ruling and reinstated the original finding of infringement including $235 million in damages. In February 2022, Teva requested for the U.S. Court of Appeals for the Federal Circuit to rehear its case, but its request was denied. Nonetheless, in July 2022, Teva once again urged the U.S. Supreme Court to consider overturning its $235 million loss in the patent feud. The company argues that this litigation could substantially impact the common practice among generic drug makers and could potentially cause “competition-killing uncertainty” that would hurt the U.S. health care system. However, on May 15, 2023, the U.S. Supreme Court denied Teva a hearing for its appeal of a 2020 appellate court ruling over the patent dispute.

On the other hand, Gilead and Bristol-Myers Squibb have been rivals in developing drugs for CAR T-cell therapy in the industry. In April 2022, Gilead made its mark when Yescarta became the first drug to receive FDA approval for CAR T-cell therapy for initial treatment of relapsed or refractory Large B-cell Lymphoma (LBCL). Bristol-Myers Squibb merged as a contender when the FDA gave the nod on Breyanzi for CAR T-cell therapy with broader approval shortly after in June 2022. Gilead’s Yescarta is intended for LBCL patients who are refractory to one prior therapy or who relapse within 12 months of first-line chemoimmunotherapy. On the other hand, Bristol-Myers Squibb’s Breyanzi covers the same patient population but includes a specific line about patients who are not eligible for stem cell transplants, an untapped population by Yescarta.

On August 26, 2022, another patent feud emerged between Moderna and Pfizer, where Moderna sued Pfizer for infringement of three of its patents associated with messenger RNA, the fundamental genetic material of their vaccines. Moderna asserts that its patents may cover technology that could also be imperative to future vaccines, where it could leverage on potential licensing of its innovations to pharmaceutical companies attempting other medical breakthroughs. We think that the companies involved in developing Covid-19 vaccines may encounter more lawsuits in the near future, as the mRNA technology becomes more renowned in the Biotechnology industry.

Clinical Trials: Putting Candidates to the Test

The U.S. drug approval system is one of the world’s most stringent. Biotechnology medications undergo the same lengthy testing process as any other pharmaceutical product to prove safety and efficacy.

The clinical testing period in humans usually consists of three phases. During Phase I, the drug is administered to a small number of healthy people to test its safety in small doses. If this initial test appears successful, the dosage is slowly increased to determine its safety at higher levels. During Phase II, the drug is given to patients suffering from the disease or a condition that the drug is intended to treat. This round of tests is designed to evaluate the drug’s effectiveness and safety, and generally includes a larger patient population and a lengthier test period than Phase I. Determining a drug's efficacy earlier in the clinical process can boost R&D productivity and allow companies to fail faster and devote resources to the most promising candidates.

Drugs that pass these hurdles then undergo Phase III, in which the most complex and rigorous tests are performed on large groups of ill patients to verify the drug's safety, effectiveness, and optimum dosage regimens. Physicians closely monitor patients to determine efficacy and identify adverse reactions. Usually, Phase III trials employ randomized, double blind tests with placebo control to remove any chance for bias. This means that one group of patients is given the drug, and another is given an inert substance (*i.e.*, a placebo); however, if there is already an approved drug for the indicated use, it will be used instead of the placebo. Neither the patients nor their doctors are aware of which patients are receiving which drug.

After the development work is complete, company scientists analyze the data. If the data are positive, the company compiles it into a biologics license application (BLA) or a new drug application (NDA), which is submitted to the FDA for review. The application has results of preclinical and clinical research, and includes details of the product's formula, production, labeling, and intended use. According to Evaluate, approximately 68% of drugs make it from Phase I to Phase II, 33% from Phase II to Phase III, 55% make it from Phase III to Filed, and 93% make it from Filed to Approved status. Overall, 11% of drugs make it from Phase I to approval. The FDA approval is a rigorous process; out of 5,000 compounds discovered in the preclinical stage, only about five will make it through the entire approval process. Because drug manufacturers often endure losses related to failed drug candidates, they try hard to maximize and protect the profits of the drugs that do find commercial success.

Regulatory Filing and Review

The FDA's Center for Drug Evaluation and Research (CDER) reviews therapeutic biological products and chemical-based drugs. The Center for Biologics Evaluation and Research (CBER) reviews blood products, vaccines, and tissue-based products.

BLAs and NDAs are typically voluminous documents, sometimes exceeding 100,000 pages. Once an NDA or BLA is approved, the FDA determines the drug's official labeling, including a detailed description of the drug and its composition, indicated uses (also called indications), contraindications, and side effects. This information is included in a drug's package insert.

Following approvals, the FDA continues to monitor drugs because side effects or other unexpected developments may arise or become known. The FDA may require additional post-market studies (Phase IV) to evaluate long-term effects. Such studies are becoming more common. Often, after marketing has begun, the manufacturer sends supplemental applications to request approval to use a drug for added indications. For the initial application, manufacturers tend to seek narrow indications that target a well-defined set of patients. Added approvals can expand the market size and commercial potential of a biologic.

Shortage of Clinical Trial Candidates Slows Industry Pipeline

As of May 23, 2023, the number of registered clinical studies totaled 453,293, according to the National Institutes of Health (NIH). Because of the high number of studies, we have reason to believe that drug makers are finding it increasingly difficult to recruit enough patients to take part in clinical studies, resulting in frequent clinical trial delays. These delays are also caused by increasing demands to show the efficacy of new drugs over existing treatments. Competitive drug therapies often require larger and more expensive studies to show statistically meaningful results.

Expedited Processes for Drugs That Treat Serious Diseases

The FDA has several pathways in place to enable quicker access to treatments for serious diseases, especially for treatments targeting diseases with an unmet need or treatments that have significant advantages over existing ones. The main pathways for expedited approval include priority review, breakthrough therapy, accelerated approval, and fast track. Use of these designations has had a significant effect on rapidly increasing access to drugs treating conditions such as AIDS and cancer.

A priority review designation means that the FDA aims to take action on the application within six months. The breakthrough therapy designation is meant to expedite the development and review of drugs that may demonstrate a substantial improvement over available therapy. Accelerated approval is geared towards drugs for serious conditions that fill an unmet medical need. Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions that fill an unmet medical need. Drugs that receive the fast-track designation are eligible for the accelerated approval and priority review pathways if the relevant criteria are met.

Examples of approvals granted under the accelerated approval program include Pomalyst and Kyprolis, by Celgene and Amgen, respectively. These were approved ahead of their action dates based on completed Phase II studies. However, accelerated approval does not always result in the eventual grant of full approval.

In rare cases, drugs can be made available before marketing approval is granted through the FDA's investigational new drug (IND) policy for treatments, which allows manufacturers to sell drugs for serious or immediately life-threatening conditions while final clinical work is conducted, and FDA review takes place.

Also, during the pandemic, most Covid-19 therapeutics used the Emergency Use Authorization (EUA) pathway to reach patients. Under the EUA pathway, the FDA may authorize unapproved medical products or unapproved uses of approved medical products for emergency purposes. Products approved under EUA must go through typical approval routes if they are to be sold during non-emergency conditions.

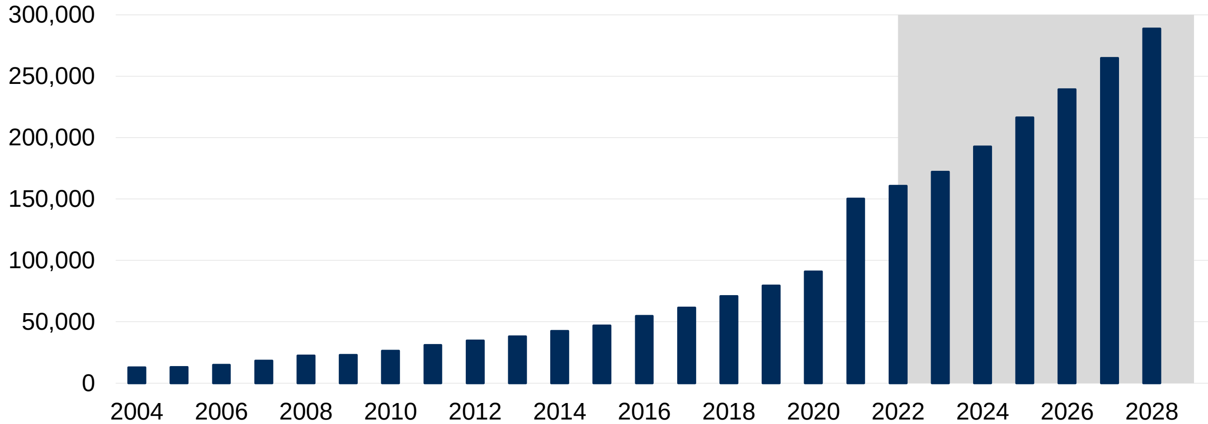
Orphan Drugs

Enacted in 1983, the Orphan Drug Act (ODA) was designed to encourage companies to develop drugs to treat rare diseases afflicting fewer than 200,000 Americans by providing research grants, tax breaks, and seven years of exclusive marketing rights to manufacturers of drugs aimed at patient markets that would otherwise be too small to justify commercial development. As a result, orphan drugs have become more profitable, and development of such drugs has become more prevalent. Data provider Evaluate forecasts an increased presence of pharmaceutical companies in rare diseases.

Orphan drugs have been a key growth driver for the Biotechnology industry despite the small patient populations that are targeted. In fact, according to an estimate by Evaluate, worldwide prescription orphan drug sales experienced a CAGR of 16.3% during the 2012-2022 period and are projected to increase at a CAGR of 10.9% from 2022 to 2028.

In the U.S., an estimated 25 to 30 million Americans are living with at least one type of the 7,000 rare conditions identified by the NIH. Because orphan drugs have market exclusivity and typically target life-threatening or debilitating diseases or conditions, drug developers are often able to demand high prices from third-party payers. We think that the average cost could continue rising, especially if companies increasingly manufacture curative therapies. In 2019, the FDA approved the first therapy to cost more than $1 million. Zolgensma, a therapy that alters the underlying genetic cause of spinal muscular atrophy (SMA), launched with a list price of slightly more than $2 million.

ORPHAN DRUGS: WORLDWIDE PRESCRIPTION SALES
($, in millions)



Note: Shaded region denotes estimated figures.
Source: Evaluate.

Pricing Considerations

FDA-approved treatments for hard-to-treat, potentially fatal diseases have significant pricing power unless there is substantial competition for such indications. Breakthrough therapies for life-threatening conditions are usually priced exceptionally high as the value of these treatments is bolstered by the high value that American society places on human life. Biotechnology companies often focus their R&D efforts on rare and undertreated diseases. As such, new biopharmaceuticals are typically lucrative, and manufacturers have had wide discretion in pricing them. Many factors go into the pricing decision, such as the relative efficacy of a given drug versus its rivals, the size of the target market(s), the price of competing therapeutics, and costs incurred in development.

The successful commercialization of a drug is based, in part, on the availability of third-party payer reimbursement, including private health insurers and government payers. Private third-party payers, such as health insurers and prescription benefit managers, have increasingly exerted their influence on drug prices by often demanding discounts and rebates on listed drug prices.

CRISPR Gene Editing Potentially Reshaping Cancer Research

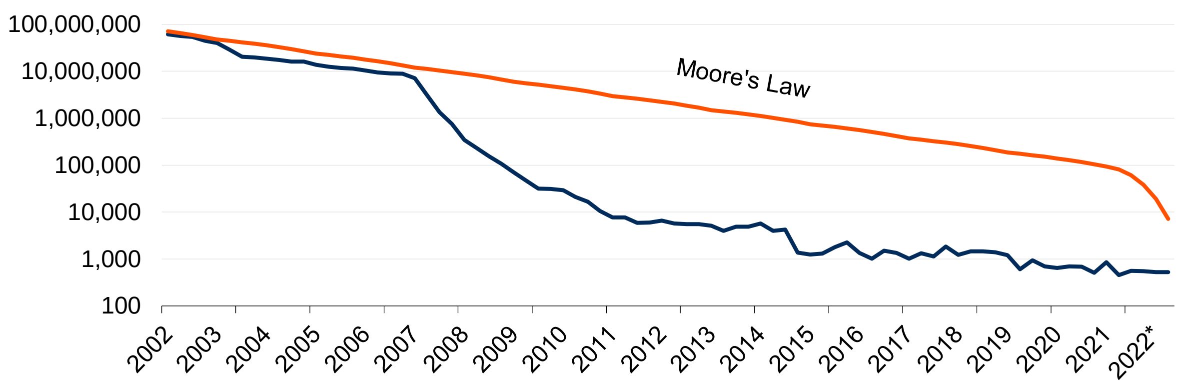
CRISPR or Clustered Regularly Interspaced Short Palindromic Repeats is a gene-editing technique that scientists believe can lead to many medical breakthroughs. In theory, CRISPR, used in conjunction with a CRISPR enzyme, usually Cas9 or Cpf1, allows scientists to cut, edit, and replace DNA sequences to change gene function easily and quickly. The modification could correct genetic defects to treat and potentially cure a wide range of diseases, including cancer. Many innovators working on CRISPR editing tools are small biotech firms, such as Editas Medicine, Intellia Therapeutics, and Crispr Therapeutics. Several larger biotech companies have shown interest by entering into partnerships and collaborative agreements to develop CRISPR-based therapies.

In late 2018, a few firms received regulatory approval to begin human clinical trials in the U.S. and Europe. Although U.S. scientists helped develop CRISPR-Cas9 back in 2012, human clinical trials have generally been prohibited in the U.S. and Europe due to safety and ethical concerns. Some safety issues concern the potential of unintended and irreversible changes to a genome. There are also ethical concerns surrounding gene-editing for non-therapeutic purposes, such as choosing hair or eye colors, etc. In the second half of 2019, several companies began testing CRISPR gene editing on patients, such as CRISPR Therapeutics in collaboration with Vertex Pharmaceuticals and Allergan in collaboration with Editas Medicine.

China has taken a leading role in CRISPR development involving human clinical trials. Since 2016, researchers in China have started human clinical trials with CRISPR modified genes to treat various diseases and cancers, including lung, liver, throat, stomach, head, and neck cancer, among others. Despite many human trials in China, including one that caused a global outcry when a researcher gene-edited a pair of twin baby girls when they were just embryos, not much is known about them. Several patients have died after being treated with a CRISPR therapeutic, but researchers believe the deaths were related to their diseases and not the treatment.

Much of the advancement in gene-therapy and gene-editing technology can be attributed to the significant decline in the cost of genomic sequencing, allowing for the discovery and analysis of genetic variations. In late 2017, the FDA approved the first gene-therapy drug. We expect the cost of genetic sequencing will continue to decline, leading more researchers and companies to explore this field, and potentially accelerate the discovery of new treatments. The cost of genetic sequencing has been on a declining trend since the 2000s. The cost back then for one genome was around $62 million (circa 2002), which compares to a cost of less than $1,000 in 2022.

COST PER GENOME



*Latest available data through May.
Source: National Human Genome Research Institute.

CFRA expects funding and financing for the development of innovative technologies such as CRISPR Therapeutics to accelerate. In early 2018, the NIH, the largest biomedical agency in the world, launched an initiative seeking to remove the barriers that have slowed the adoption of CRISPR technology in treating patients. The NIH launched the Somatic Cell Genome Editing program, which will provide research grants, totaling $190 million over six years, to researchers to improve the delivery mechanism for targeting gene editing tools in patients, develop new and improved genome editors, and develop assays for testing the safety and efficacy of gene editing tools.

The goal of this program is to accelerate the development of CRISPR technologies for the development of therapies to treat genetic diseases. Somatic cells are non-reproductive cells of the body and do not pass DNA down to the next generation. By focusing on somatic cells, any changes to the DNA through gene-editing therapeutics will not be inherited. NIH-funded research has led to many innovative therapies over the past several decades. We forecast this initiative could also lead to the development of new therapies.

The NIH has shown continuous support for research that could potentially help the public. In February 2022, the agency awarded a research grant to the University of Rochester for in-depth investigation of phenotypic plasticity. The study examines organisms' evolutionary survival strategy focusing on their ability to change traits in response to their environment. This research also aims to evaluate traits development from the integration between environmental and genetic signals, which could potentially contribute to fundamental findings to reduce prevalence of human diseases. The award, which is distributed over five years, will enable further research on the implication of plasticity on human health and disease.

HOW TO ANALYZE A COMPANY IN THIS INDUSTRY

The analysis of a biotech firm involves a thorough study of both business strategy and financial health. Many biotech firms do not have commercial track records, which makes these companies difficult to analyze. Thus, investors sometimes must rely more heavily on qualitative rather than quantitative methods of valuation.

RESEARCHING THE BUSINESS

The first step is to examine a given company's business strategy, core competencies, and market position. Many biotech companies are still in a development phase, so this analysis may rely heavily on qualitative judgments about management skill, technology, and new product potential.

Products and Pipeline

A biotech firm's product portfolio and clinical pipeline are essential to its success. A company's intrinsic value should be primarily a function of the prospective earnings to be gained from approved products and investigational compounds in development, as well as the probability of successfully developing pipeline candidates.

CFRA thinks that companies with technologies that are scientifically sound and patentable, especially those with the potential to lead to additional developments and applications, generally offer better risk-reward profiles than companies that are developing drugs in competitive therapeutic areas.

Companies with multiple drug candidates in late stages of clinical development tend to be more valuable. At the same time, be wary of companies trying to develop many marginally beneficial products (referred to as "me-too" products) in disease areas that are already well served. Such companies may have limited commercial potential.

Patent Protection

In assessing a biotech company's product portfolio, it is imperative to determine the strength and duration of a company's patents on its proprietary drugs and compounds. The loss of market exclusivity on key products can lead to sales erosion from biosimilars. This concern is particularly grave for markets outside of the U.S., where biotech firms typically have fewer ways to protect their intellectual property once they lose exclusivity. The issue of patent protection is poised to become a larger issue in the coming years, as continued progress toward a smoother regulatory pathway for generic biotech drugs takes shape and concerns of high drug prices fuel political rhetoric.

In the U.S., biotech firms often create a patent thicket – a layer of numerous patents that protect the exclusivity of a drug – to make it more difficult for competitors to enter the market, even after a drug's initial patents have expired. Competitors are deterred from competing with drugs with substantial patent thickets because the legal costs would be considerable.

Current patents can lead to royalties if a company decides to license its technology to other firms.

Assessing R&D

Most leading biotech companies spend between 15% and 25% of operating revenues on research & development (R&D), with most development-stage biotech companies often spending well over 100%. However, success rates – in terms of developing lucrative new drugs and therapeutics – can differ markedly.

The bigger, better-funded firms tend to have the advantage of being able to hire top scientists and conduct the large, costly clinical trials that are often needed to develop new drugs. Furthermore, in a health care market dominated by managed care (such as the U.S.), a key factor in future success will be a company's ability to develop cost-effective new drugs that constitute therapeutic breakthroughs. New products that supply comparable results to existing therapies are unlikely to achieve great commercial success.

Look for companies that are developing drugs for illnesses that are not adequately served by current treatments. Drugs for chronic illnesses that have large patient populations can provide a higher return on R&D expenditures than one-time treatments, such as vaccines.

Management Strength

The quality and experience of a company's management and scientific teams are critical to long-term success. The industry changes rapidly, so it is crucial for a firm to be led by insightful and quick-thinking individuals who can adapt to volatile circumstances.

Ideally, a biotech company should employ executives who have previously helped develop and commercialize pharmaceutical products. Look for a demonstrated ability to reach milestones. Management should be credible in terms of historically meeting stated goals and key development milestones. Be wary of a company that consistently misses its own targets. CFRA appreciates management teams that have operating experience. It is important that the people running the company thoroughly understand and appreciate how expensive and elaborate the drug development process is.

Making the Most of Alliances

Biotech firms often enter into collaborations and partnerships with other firms. Because of the excessive costs of drug development, a significant discovery made by a small biotechnology company may go nowhere unless the firm can find a well-financed partner to fund clinical trials and help commercialize the product. It is important for biotech firms to choose corporate partners that are committed to seeing the product through to commercialization. Large pharma and biotech companies often have areas of focus, where they have significant research experience and an established sales infrastructure.

Deal terms represent the value that the bigger partner places on a budding biotech company's technology. From the junior partner's perspective, a good deal typically includes a sizable upfront fee from the bigger firm, and may include equity, R&D funding for product development, milestone payments for achieving R&D benchmarks, co-promotion rights, and royalties on sales. Co-promotion rights are usually preferable to royalties. Although, if a junior partner has limited resources, upfront payments may be more desirable than payments tied to future R&D benchmarks.

Many biotech companies maintain both formal and informal relationships with scientists at leading medical schools, research institutions, or government organizations, such as the federal government's NIH. Such relationships can be a valuable resource. Companies with connections to the NIH often gain rights to medications or drug targets discovered by the NIH (usually in conjunction with a leading university).

Financial Resources

Is the company well-financed? A biotech firm must have adequate funding for its development programs, or it may be forced to curtail its R&D efforts. CFRA likes to see enough cash on the balance sheet to cover operating expenses for at least two years. Such a position can safeguard a firm from becoming desperate for funding and thus being forced to accept sub-optimal value on its assets.

An ample cash balance provides a firm with stronger negotiation power when it comes to collaborative arrangements and the ability to continue product development with limited added funding. The farther along a product is in the development process, the greater the potential future profits the firm should be able to keep in any negotiated deal. Having enough cash on hand is also important because access to financing tends to change over time. The Biotechnology industry goes through periods when public equity markets are not particularly receptive to funding risky ventures, and it is important for a company to have enough resources to see it through such times.

Regulatory Compliance

How effectively does the company work with the U.S. Food and Drug Administration (FDA)? Because all drugs sold in the U.S. must first be cleared by this agency, it is critical that a firm is able to work closely with the FDA and satisfy the regulatory authority's drug approval requirements.

Firms with experience navigating the FDA's process and resources to do so are better equipped to obtain regulatory approval. Smaller or newer firms are often less proficient at navigating the process and will often meet major snags in obtaining approval for their products. Managers hired from successful biotech or pharmaceutical firms with proven drug development experience, and/or an alliance with a strong corporate partner, can prove to be invaluable. Increasingly, companies are involving the FDA in trial design and protocol throughout the clinical process to prevent delays and negative surprises in the later stages.

ANALYZING FINANCIAL STATEMENTS

The usefulness of analyzing a biotechnology company's financial statements is often limited, as many biotech companies have little to no earnings history. Because many, if not most, biotech companies are in a developmental stage and have little to no product revenues, traditional financial analysis is of limited value. For these companies, analysts tend to focus on the future earnings potential of products in development and on whether the company has the resources to fully develop those products.

Financial analysis of a large, profitable biotech company tends to be like that of a traditional pharmaceutical firm. Key metrics include revenues, costs and expenses, R&D as a percentage of sales, earnings, margins, growth in earnings per share (EPS), and sales and return on equity (ROE). When possible, individual company statistics should be compared with those of rival companies and the industry average.

Income Statement Analysis

Analysis of the income statement, while still important for biotech firms, provides less insight into future operational trends than for most other industries because biotech firms often have significant investments in products that have yet to be commercialized.

Sales. Sales growth expectations vary among biotech firms depending on what stage their drugs are at. Many biotech companies experience extremely rapid growth following the commercialization of a new drug. On the other hand, firms can also experience rapid declines in sales when they face new competition. Often, this competition can result from the loss of exclusivity for a company's existing product. There are also many publicly traded biotech firms that have little to no sales. Some biotech firms have significant revenue volatility because their revenues are tied to the achievement of certain milestones, *e.g.,* achieving certain results in a phase II trial.

CFRA tries to consider how growth has been achieved, *e.g.,* has growth been generated by unit volume gains, price increases, acquisitions, one-time or non-recurring gains from asset sales, or some combination of these? Is the company gaining market share, or just riding market growth or price hikes?

Watch Out! *When companies accelerate revenue into the current period, the reported revenue growth for that period is likely unsustainable. Management can accelerate revenue by allocating a higher proportion of transaction price to elements delivered upfront in contracts with multiple deliverables or performance obligations, faster recognition of deferred revenue, large shipments at period-end, a change in revenue recognition policy, and a change in the interpretation of the revenue recognition policy.*

> ***Watch Out!*** *It is common for biotech companies to monetize certain intangible assets by selling the rights to a product to another entity. CFRA views the sale of product rights as the sale of an asset, which should be included in other income, similar to the sale of real property. In instances where these sales are recognized as revenue, gross margins are likely boosted due to the lack of related cost of goods sold.*

R&D. Significant investment in R&D is critical to the success of any biotechnology company. R&D spending is high for the Biotechnology industry compared to other industries. For developmental-stage companies that have not yet produced commercial products, R&D typically exceeds any revenues that these companies receive from collaboration agreements. When comparing companies, most investors look at ratios such as R&D as a percentage of sales, R&D expenditures per employee, or R&D as a percentage of market capitalization.

> ***Watch Out!*** *R&D costs should be expensed as incurred until the related product has reached commercial feasibility, which, in this industry, normally occurs when the FDA approves a product. A material increase in capitalized R&D costs not explained by the timing of FDA approval may indicate overcapitalization of R&D, which could pressure future earnings growth.*

SG&A expenses. Royalty costs and costs related to product co-promotion may be included in selling, general, and administrative (SG&A) expenses or another line item. Investors should compare royalty obligations and the financial structure of collaborative arrangements between firms to assess the potential profitability of a drug.

Option expense. Companies are required to expense options in the income statement. Investors should be aware of options grants since an elevated level of outstanding options could dilute EPS if these options are eventually exercised. A considerable number of options outstanding could also divert company cash to repurchasing shares to neutralize the dilutive effect of options. This cash could otherwise be used for product promotion, drug development, or dividends. Many biotechnology companies report earnings excluding stock option expenses, described as "adjusted" or "not in conformity with generally accepted accounting principles" (non-GAAP) earnings.

Profit margins. Margins vary significantly for biotech firms and many companies in the industry are unprofitable. Biotech firms incur substantial costs for extended periods of time while researching and developing drugs, which is why these companies are often able to later sell their products for high prices and achieve high margins once they successfully commercialize their drugs. For most biotech firms, SG&A and R&D expenses tend to be as high as the proportion of revenue when compared to most other companies.

EPS. Because product pipelines are so critical in the Biotechnology industry, analysts often consider EPS trends that are several years into the future. Changes in the development and commercialization timeline for pipeline products can significantly alter future EPS trends, which is why biotech valuations can change so rapidly. Many young biotech firms often post losses or volatile earnings because they have yet to commercialize any products or are in the initial stages of commercialization, which limits the utility of historical and near-term EPS analysis. Large, well-established biotechnology firms tend to have more stable earnings.

Balance Sheet Analysis

The balance sheet is a snapshot of a company's financial condition at a specific moment in time, so it should be examined to determine a company's financial health. For biotechnology companies, most balance sheet analysis focuses on liquidity because biotech firms require liquidity to continue funding their R&D activities. A promising drug candidate is worth near nothing if a company cannot eventually sell it; therefore, it is crucial to assess a company's ability to fund the development and commercialization of its drugs. Liquidity is especially important in market downturns when funding typically becomes difficult to obtain.

Cash. Investors look at a company's level of cash and marketable securities to assess short-term liquidity. The proper level of cash and cash equivalents varies from company to company. For development-stage biotech companies with no earnings, CFRA likes to see at least two years' worth of cash on hand to fund operations at the current burn rate, *i.e.*, the rate at which cash is being consumed by R&D and other expenditures. Investors should also consider the amount of convertible debt outstanding, if any, since several biotech firms issue convertible notes.

Debt-to-capitalization ratio. This ratio is calculated by dividing debt by total capital (the sum of debt and stockholders' equity). Companies with lower levels of debt to capital are generally less burdened by interest payments and more capable of raising debt. Biotech firms that are not mature often have little debt because their typically weak cash flows make it difficult to service interest payments. Investors should investigate sudden changes in a company's attitude toward taking on debt.

Equity Valuation

Biotech companies are notoriously difficult to value because their expected earnings are tied more heavily to future expectations than most other companies. For the few profitable and well-established companies, a price-to-earnings (P/E) ratio can be used to compare a company's valuation versus its peers.

Most publicly traded biotech companies are at the development stage and without near-term commercial prospects. These companies are often valued with some sort of a net present value (NPV) analysis, such as a discounted cash flow (DCF) analysis. An NPV analysis typically gauges the revenue potential for a company's key pipeline candidates, key commercialized products, the costs associated with developing and commercializing those drugs, the probability of successful commercialization, and then discounts the expected profits to the present year.

GLOSSARY

Biologics—Also known as biologic drugs, biologics are medicinal preparations made from living organisms or their byproducts. Vaccines, antigens, serums, and plasmas are examples of biologics.

Biologics license application (BLA)—The formal filing that drug makers submit to the U.S. Food and Drug Administration (FDA) for approval to market new biologics-based drugs. The application must contain clinical evidence of the compound's safety and efficacy.

Biosimilar—A generic copy of a biological molecule, developed using modern biotechnology techniques. A biosimilar has similar activity and is structurally nearly identical to the biologic that it copies. Unlike generic chemical-based drugs, however, a biosimilar is not truly identical and therefore will require a different regulatory process than pharmaceutical generics.

Blockbuster drug—An extremely popular drug that generates annual sales of at least $1 billion for the company that sells it.

CAR T-cell therapy—Chimeric antigen receptor (CAR) T-cells are T-cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy.

Cell therapy—A therapy in which viable cells are injected, grafted, or implanted into a patient in order to effectuate a medicinal effect.

Clinical trials—Tests, typically consisting of three stages, in which experimental drugs are administered to humans to determine their safety and efficacy before being submitted for regulatory marketing approval.

Deoxyribonucleic acid (DNA)—The basic molecule that contains genetic information for most living systems. The DNA molecule consists of four nucleotide bases (adenine, cytosine, guanine, and thymine) and a sugar-phosphate frame arranged in two connected strands forming a double helix.

Enzyme—A substance that acts as a catalyst in living organisms, regulating the rate at which chemical reactions proceed without itself being altered in the process.

Gene sequencing—A scientific technique whereby DNA strands are decoded to quantify the exact order of DNA's four nucleotides (A, C, G, and T). This method allows scientists to analyze the sequence of strands and identify specific genes embedded in DNA.

Gene therapy—The introduction of specific genes into a patient's body to replace defective ones or to suppress the action of a harmful one.

Investigational new drug—Regulatory classification of an experimental new compound that has successfully completed animal studies and has been approved by the FDA to proceed to human trials.

Legacy drug—A drug that has been prescribed for at least 25 years and has gained a history for safety and efficacy.

Monoclonal antibodies (mAbs)—Large protein molecules produced by white blood cells, which seek out and destroy harmful foreign substances.

New drug application (NDA)—The formal filing that drug makers submit to the FDA for approval to market new chemical-based drugs. The application must contain clinical evidence of the compound's safety and efficacy.

New molecular entities (NMEs)—Drugs that contain an active moiety that has never been approved by the FDA or marketed in the U.S.

Orphan drug—A drug designed to treat a rare disease afflicting a relatively small patient population (currently fewer than 200,000 cases in the U.S.). The U.S. government provides special incentives to encourage development of such drugs.

Patent thicket—A layer of numerous patents that protect the exclusivity of a drug.

Pharmacy benefit manager (PBM)—A third-party administrator of prescription drug programs for commercial health plans, self-insured employer plans, Medicare Part D plans, the Federal Employees Health Benefits Program, and state government employee plans in the U.S.

Phenotypic plasticity—The ability of an organism to change in response to stimuli or inputs from the environment.

Protein—Any class of nitrogenous organic compounds that have large molecules composed of one or more long chains of amino acids and are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, etc., and as enzymes and antibodies.

Recombinant products—A subset of biologics that are produced by genetic engineering techniques.

Specialty drugs—Often biologics, these drugs are derived from living cells and are used to treat complex or rare chronic conditions such as cancer, rheumatoid arthritis, hemophilia, H.I.V.

Third-party payer reimbursement—A payment for services by an entity other than the patient or the patient's family.

INDUSTRY REFERENCES

PERIODICALS

Drug Trend Report
https://www.evernorth.com/drug-trend-report
An annual publication with detailed analysis of prescription drug costs and utilization.

Financial Times
ft.com
A British daily newspaper that focuses on business and economic current affairs.

The Use of Medicines in the U.S. 2022
https://www.iqvia.com/insights/the-iqvia-institute/reports/the-use-of-medicines-in-the-us-2022
An annual trend report from IQVIA that covers usage and spending trends of medicines in the U.S.

GOVERNMENT AGENCIES

European Medicines Agency
ema.europa.eu/ema
A regulatory body that is responsible for approvals and oversight of medications in the European Union.

National Human Genome Research Institute
genome.gov
An institute that carries out the International Human Genome Project and applies genome technologies to the study of specific diseases.

National Institutes of Health
nih.gov
A federal agency of the U.S. government responsible for biomedical and public health research.

U.S. Department of Health & Human Services
hhs.gov
A federal agency charged with enhancing and protecting the health and well-being of all Americans.

U.S. Food and Drug Administration
fda.gov
A federal agency charged with supervising the U.S. food, pharmaceuticals, and biotechnology industries.

TRADE ASSOCIATIONS

Biotechnology Innovation Organization
bio.org
Represents biotech companies, academic institutions, and state biotech centers in legislative and regulatory affairs; publishes industry statistics and information.

Kaiser Family Foundation
kff.org
A nonprofit foundation that publishes reports on government programs, medical spending trends, and various policy initiatives.

Pharmaceutical Research and Manufacturers of America
phrma.org
Represents prescription drug firms in legislative and regulatory affairs; publishes industry statistics and information.

ONLINE RESOURCES

Amgen
https://www.amgen.com/
A multinational biopharmaceutical company headquartered in Thousand Oaks, California.

ClinicalTrials.gov
clinicaltrials.gov
A centralized database listing information on public and private clinical drug trials in the U.S.

Drug Channels Institute
drugchannels.net
Analyzes pharmaceutical economics and the drug distribution system in the U.S.

Evaluate
evaluategroup.com
Provides consensus forecasts and analysis of the pharmaceuticals and biotechnology industries.

Milken Institute
milkeninstitute.org
An independent economic think tank that publishes research and hosts conferences that apply market-based principles and financial innovations.

S&P Global Market Intelligence
https://www.spglobal.com/marketintelligence/en/
A division of S&P Global that provides essential intelligence for individuals, companies, and governments to make decisions with confidence.

Tufts Center for the Study of Drug Development
csdd.tufts.edu
A nonprofit academic research group that provides strategic information on the quality and efficiency of pharmaceutical development and utilization.

World Health Organization
who.int
A specialized agency of the United Nations responsible for international public health.

COMPARATIVE COMPANY ANALYSIS

				Operating Revenues																
				Million $							CAGR (%)			Index Basis (2012=100)						
Ticker		Company	Yr. End	2022	2021	2020	2019	2018	2017	2016	10-Yr.	5-Yr.	1-Yr.	2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																			
ABBV	[]	ABBVIE INC.	DEC	58,054.0	56,197.0	45,804.0	33,266.0	32,753.0	28,216.0	25,638.0	12.2	15.5	3.3	226	219	179	130	128	110
AMGN	[]	AMGEN INC.	DEC	26,323.0	25,979.0	25,424.0	23,362.0	23,747.0	22,849.0	22,991.0	4.3	2.9	1.3	114	113	111	102	103	99
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	156.2	147.8	130.5	114.6	105.6	113.4	103.4	8.2	6.6	5.7	151	143	126	111	102	110
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	243.2	138.3	88.0	168.8	16.1	31.4	0.2	109.8	50.6	75.9	153623	87341	55575	106610	10195	19837
BIIB	[]	BIOGEN INC.	DEC	10,173.4	10,981.7	13,444.6	14,377.9	13,452.9	12,273.9	11,448.8	6.3	-3.7	-7.4	89	96	117	126	118	107
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	211.0	326.6	475.8	356.1	0.0	1.6	190.1	60.2	167.0	-35.4	111	172	250	187	0	1
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	94.6	70.4	55.8	26.9	31.5	13.4	106.4	28.7	47.9	34.3	89	66	52	25	30	13
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	316.6	171.5	187.8	195.9	213.3	236.7	189.5	62.0	6.0	84.6	167	91	99	103	113	125
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	1,120.9	1,792.7	1,555.4	1,106.0	782.4	560.9	488.8	14.8	14.9	-37.5	229	367	318	226	160	115
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	86.2	97.1	122.5	205.2	206.6	102.8	88.3	7.5	-3.5	-11.2	98	110	139	232	234	116
EXEL	†	EXELIXIS, INC.	DEC	1,611.1	1,435.0	987.5	967.8	853.8	452.5	191.5	42.3	28.9	12.3	841	750	516	505	446	236
GILD	[]	GILEAD SCIENCES, INC.	DEC	27,281.0	27,305.0	24,689.0	22,449.0	22,127.0	26,107.0	30,390.0	10.9	0.9	-0.1	90	90	81	74	73	86
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	660.1	443.3	267.6	196.0	151.9	316.6	146.7	31.6	15.8	48.9	450	302	182	134	104	216
INCY	[]	INCYTE CORPORATION	DEC	3,394.6	2,986.3	2,666.7	2,158.8	1,881.9	1,536.2	1,105.7	27.6	17.2	13.7	307	270	241	195	170	139
LGND	§	LIGAND PHARMACEUTICALS INCORPORATED	DEC	196.2	241.5	163.6	120.3	251.5	141.1	109.0	20.1	6.8	-18.8	180	222	150	110	231	129
MYGN	§	MYRIAD GENETICS, INC.	DEC	678.4	690.6	557.0	851.1	743.7	728.7	740.5	3.2	-1.4	-1.8	92	93	75	115	100	98
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	12,172.9	16,071.7	8,497.1	6,557.6	5,145.6	5,872.2	4,860.4	24.3	15.7	-24.3	250	331	175	135	106	121
RGNX	§	REGENXBIO INC.	DEC	112.7	470.3	154.6	35.2	218.5	10.4	4.6	NA	61.1	-76.0	2456	10249	3368	768	4761	226
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	1,936.3	1,685.5	1,483.3	1,448.8	1,627.8	1,725.3	1,598.8	7.8	2.3	14.9	121	105	93	91	102	108
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	254.4	268.7	248.2	227.2	193.1	165.1	146.0	22.8	9.0	-5.3	174	184	170	156	132	113
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATEI	DEC	8,930.7	7,574.4	6,205.7	4,162.8	3,047.6	2,488.7	1,702.2	19.3	29.1	17.9	525	445	365	245	179	146
XNCR	§	XENCOR, INC.	DEC	164.6	275.1	122.7	156.7	40.6	46.2	109.0	33.0	29.0	-40.2	151	252	113	144	37	42

Note: Data as originally reported. CAGR-Compound annual growth rate.
[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
Souce: S&P Capital IQ.

Net Income

Ticker		Company	Yr. End	Million $ 2022	2021	2020	2019	2018	2017	2016	CAGR (%) 10-Yr.	5-Yr.	1-Yr.	Index Basis (2012=100) 2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																			
ABBV	[]	ABBVIE INC.	DEC	11,836.0	11,542.0	4,616.0	7,882.0	5,687.0	5,309.0	5,953.0	8.4	17.4	2.5	199	194	78	132	96	89
AMGN	[]	AMGEN INC.	DEC	6,552.0	5,893.0	7,264.0	7,842.0	8,394.0	1,979.0	7,722.0	4.2	27.1	11.2	85	76	94	102	109	26
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	-14.9	4.1	-24.0	27.2	18.7	31.8	32.5	NA	NM	NM	-46	13	-74	84	58	98
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	-176.1	-140.8	-84.6	68.0	-54.5	-34.4	-81.7	23.6	38.6	25.0	215	172	103	-83	67	42
BIIB	[]	BIOGEN INC.	DEC	3,046.9	1,556.1	4,000.6	5,888.5	4,430.7	2,539.1	3,702.8	8.2	3.7	95.8	82	42	108	159	120	69
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	-291.8	-287.1	132.2	89.8	-209.3	-238.2	-127.3	24.3	4.1	1.6	229	225	-104	-71	164	187
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	-389.0	-215.3	-127.3	-121.7	-106.3	-127.8	16.5	25.4	24.9	80.6	NM	NM	-774	-740	-646	-777
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	35.6	-8.6	12.0	14.3	31.9	51.9	81.5	NA	-7.3	NM	44	-11	15	18	39	64
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	-223.8	230.9	305.1	54.5	62.7	82.6	51.8	NA	NM	NM	-432	446	589	105	121	159
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	-121.8	-79.0	-36.2	46.4	72.0	17.7	21.7	NA	NM	54.1	-562	-365	-167	214	332	82
EXEL	†	EXELIXIS, INC.	DEC	182.3	231.1	111.8	321.0	690.1	154.2	-70.2	NA	3.4	-21.1	-260	-329	-159	-457	-983	-220
GILD	[]	GILEAD SCIENCES, INC.	DEC	4,592.0	6,225.0	123.0	5,386.0	5,455.0	4,628.0	13,501.0	5.9	-0.2	-26.2	34	46	1	40	40	34
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	202.1	402.7	129.1	-72.2	-80.3	63.0	-103.0	NA	26.3	-49.8	-196	-391	-125	70	78	-61
INCY	[]	INCYTE CORPORATION	DEC	340.7	948.6	-295.7	446.9	109.5	-313.1	104.2	NA	NM	-64.1	327	910	-284	429	105	-300
LGND	§	LIGAND PHARMACEUTICALS INCORPORATED	DEC	-33.4	57.1	-3.0	629.3	143.3	12.6	-1.6	51.4	NM	NM	2039	NM	182	NM	NM	-767
MYGN	§	MYRIAD GENETICS, INC.	DEC	-112.0	-27.2	-223.7	4.6	133.3	17.4	117.2	NA	NM	311.8	-96	-23	-191	4	114	15
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	4,338.4	8,075.3	3,513.2	2,115.8	2,444.4	1,198.5	895.5	19.2	29.3	-46.3	484	902	392	236	273	134
RGNX	§	REGENXBIO INC.	DEC	-280.3	127.8	-111.3	-94.7	99.9	-73.2	-63.0	NA	30.8	NM	445	-203	177	150	-159	116
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	727.3	475.8	514.8	-104.5	589.2	417.9	713.7	9.1	11.7	52.9	102	67	72	-15	83	59
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	6.3	33.2	23.3	115.6	25.2	-15.6	-18.0	NA	NM	-81.1	-35	-184	-130	-642	-140	86
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATED	DEC	3,322.0	2,342.1	2,711.7	1,176.8	2,096.9	263.5	-112.1	NA	66.0	41.8	NM	NM	NM	NM	NM	-235
XNCR	§	XENCOR, INC.	DEC	-55.2	82.6	-69.3	26.9	-70.4	-38.5	45.1	20.4	7.5	NM	-122	183	-154	60	-156	-85

Note: Data as originally reported. CAGR-Compound annual growth rate.
[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
Souce: S&P Capital IQ.

Ticker		Company	Yr. End	Return on Revenues (%) 2022	2021	2020	2019	2018	2017	Return on Assets (%) 2022	2021	2020	2019	2018	2017	Return on Equity (%) 2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																					
ABBV	[]	ABBVIE INC.	DEC	20.4	20.5	10.1	23.7	17.4	18.8	8.5	7.9	3.1	8.8	9.6	7.5	72.4	81.0	187.7	NM	NM	109.1
AMGN	[]	AMGEN INC.	DEC	24.9	22.7	28.6	33.6	35.3	8.7	10.1	9.6	11.5	13.1	12.6	2.5	126.5	73.2	76.1	70.7	44.5	7.2
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	NM	2.8	NM	23.7	17.7	28.1	NM	1.2	NM	8.2	6.7	11.3	NM	1.5	NM	9.9	7.1	13.1
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	NM	NM	NM	40.3	NM	NM	NM	NM	NM	19.4	NM	NM	NM	NM	NM	40.1	NM	NM
BIIB	[]	BIOGEN INC.	DEC	29.9	14.2	29.8	41.0	32.9	20.7	12.4	6.5	16.3	21.6	17.5	10.7	24.3	16.0	33.8	44.7	34.9	21.6
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	NM	NM	27.8	25.2	0.0	NM	NM	NM	15.7	22.0	NM	NM	NM	NM	68.5	269.7	NM	NM
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	11.3	NM	6.4	7.3	15.0	21.9	8.8	NM	4.7	5.6	13.4	19.2	17.4	NM	6.6	8.4	18.8	31.4
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	NM	12.9	19.6	4.9	8.0	14.7	NM	7.8	10.6	2.3	2.8	7.7	NM	15.1	24.1	5.2	6.5	11.0
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	NM	NM	NM	22.6	34.8	17.2	NM	NM	NM	9.5	17.4	5.4	NM	NM	NM	10.8	20.7	6.2
EXEL	†	EXELIXIS, INC.	DEC	11.3	16.1	11.3	33.2	80.8	34.1	5.9	8.8	5.2	17.0	48.5	23.5	7.8	11.3	6.3	21.6	87.8	82.4
GILD	[]	GILEAD SCIENCES, INC.	DEC	16.8	22.8	0.5	24.0	24.7	17.7	7.3	9.2	0.2	8.7	8.6	6.6	21.6	31.6	0.4	24.3	26.0	23.3
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	30.6	90.8	48.2	NM	NM	19.9	11.0	36.5	22.3	NM	NM	12.1	110.2	231.4	106.3	NM	NM	71.6
INCY	[]	INCYTE CORPORATION	DEC	10.0	31.8	NM	20.7	5.8	NM	5.8	19.2	NM	13.0	4.1	NM	8.4	29.7	NM	19.8	6.2	NM
LGND	§	LIGAND PHARMACEUTICALS INCORPORATED	DEC	NM	23.7	NM	523.2	57.0	8.9	NM	4.4	NM	42.1	11.4	1.9	NM	10.0	0.9	94.8	29.3	3.2
MYGN	§	MYRIAD GENETICS, INC.	DEC	NM	NM	NM	0.5	17.9	2.4	NM	NM	NM	0.3	11.3	1.4	NM	NM	0.0	0.4	15.4	2.3
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	35.6	50.2	41.3	32.3	47.5	20.4	14.9	31.7	20.5	14.3	20.8	13.7	20.9	54.2	31.8	21.3	32.8	22.6
RGNX	§	REGENXBIO INC.	DEC	NM	27.2	NM	NM	45.7	NM	NM	11.5	NM	NM	18.4	NM	NM	22.4	NM	NM	28.9	NM
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	37.6	28.2	34.7	NM	36.2	24.2	12.0	9.2	11.2	NM	17.3	14.5	16.6	12.9	16.7	NM	24.1	21.1
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	2.5	12.3	9.4	50.9	13.1	NM	1.0	5.6	4.4	23.9	7.6	NM	1.2	6.9	5.4	33.7	12.4	NM
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATED	DEC	37.2	30.9	43.7	28.3	68.8	10.6	18.3	17.4	23.1	14.1	33.6	7.4	27.7	24.9	36.7	22.4	64.4	5.4
XNCR	§	XENCOR, INC.	DEC	NM	30.0	NM	17.2	NM	NM	NM	9.9	NM	4.0	NM	NM	NM	12.7	NM	4.8	NM	NM

Note: Data as originally reported. CAGR-Compound annual growth rate.
[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
Souce: S&P Capital IQ.

				Current Ratio						Debt/Capital Ratio (%)						Debt as a % of Net Working Capital					
Ticker		Company	Yr. End	2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																					
ABBV	[]	ABBVIE INC.	DEC	1.0	0.8	0.8	3.2	1.0	1.3	77.5	80.6	85.6	114.9	145.7	87.0	NM	NM	NM	185.7	NM	684.3
AMGN	[]	AMGEN INC.	DEC	1.4	1.6	1.8	1.4	2.8	5.5	91.1	83.2	77.8	73.6	70.2	57.5	574.8	461.4	346.6	480.8	122.3	84.5
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	6.1	5.7	4.8	14.4	18.0	15.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	2.9	2.6	7.9	2.7	6.4	3.6	0.0	0.0	0.0	0.0	2.2	2.8	0.0	0.0	0.0	0.0	3.2	4.7
BIIB	[]	BIOGEN INC.	DEC	3.0	1.8	1.8	1.7	2.3	2.3	31.9	36.4	41.0	25.1	31.3	32.0	96.4	176.3	236.1	126.7	136.6	131.7
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	2.7	3.6	5.3	3.0	2.5	5.1	141.2	80.7	59.0	62.9	159.8	76.9	194.2	93.4	65.0	78.2	201.5	86.8
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	9.4	7.5	15.2	9.0	9.4	8.5	121.5	36.9	54.5	109.2	60.6	22.4	85.8	30.8	30.6	62.2	21.5	13.1
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	1.7	2.3	4.4	4.6	4.1	4.0	21.6	14.5	11.9	15.8	19.2	19.3	80.4	26.1	19.6	23.9	30.7	30.3
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	1.0	3.4	3.1	3.2	3.1	4.8	24.5	33.4	37.0	42.4	43.7	1.5	NM	90.3	104.8	170.3	186.6	3.5
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	10.5	8.8	18.1	17.8	23.7	11.3	0.4	0.4	0.3	0.4	0.4	0.3	0.5	0.5	0.4	0.4	0.4	0.4
EXEL	†	EXELIXIS, INC.	DEC	5.0	5.4	7.1	7.1	8.5	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GILD	[]	GILEAD SCIENCES, INC.	DEC	1.3	1.3	1.4	3.1	3.4	2.7	52.0	54.4	61.1	49.4	53.3	63.4	716.1	796.3	622.9	107.6	97.4	161.2
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	5.7	7.9	1.3	6.3	2.9	3.9	89.8	80.0	0.0	80.7	12.3	37.5	245.4	97.3	0.0	83.7	12.5	33.0
INCY	[]	INCYTE CORPORATION	DEC	3.5	3.7	3.7	4.8	4.3	4.0	0.0	0.0	0.0	0.0	0.9	1.0	0.0	0.0	0.0	0.0	1.2	1.5
LGND	§	LIGAND PHARMACEUTICALS INCORPORATED	DEC	2.7	11.2	5.0	66.1	10.6	1.0	0.0	28.1	38.4	45.4	52.1	0.0	0.0	75.8	110.4	57.7	77.4	0.0
MYGN	§	MYRIAD GENETICS, INC.	DEC	2.0	2.4	2.7	3.0	3.2	1.4	0.0	0.0	20.3	17.7	1.0	11.4	0.0	0.0	92.3	101.2	4.1	117.7
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	5.1	3.6	3.6	3.7	4.5	3.8	8.0	9.5	15.2	0.0	0.0	0.0	15.5	19.6	27.9	0.0	0.0	0.0
RGNX	§	REGENXBIO INC.	DEC	3.2	4.0	6.5	10.2	15.2	11.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	9.8	7.6	6.7	4.0	6.4	3.3	14.3	16.8	19.1	17.7	8.2	10.6	26.3	39.6	43.4	42.8	16.8	24.9
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	5.7	6.4	6.2	6.0	5.6	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATED	DEC	4.8	4.5	4.3	3.6	3.4	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
XNCR	§	XENCOR, INC.	DEC	10.6	6.0	5.3	8.4	5.9	3.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Note: Data as originally reported. CAGR-Compound annual growth rate.

[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.

Souce: S&P Capital IQ.

Ticker		Company	Yr. End	Price/Earnings Ratio (High-Low)						Dividend Payout Ratio (%)						Dividend Yield (High-Low, %)					
				2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																					
ABBV	[]	ABBVIE INC.	DEC	26 - 20	21 - 16	40 - 24	17 - 12	34 - 21	30 - 18	84.9	80.2	167.2	80.8	98.1	77.4	4.1 - 3.6	4.9 - 3.2	5.1 - 4.3	7.3 - 4.7	6.8 - 4.6	5.4 - 2.3
AMGN	[]	AMGEN INC.	DEC	24 - 18	25 - 19	21 - 15	19 - 13	16 - 13	71 - 54	64.0	68.1	51.7	44.7	41.8	170.0	3.8 - 2.7	3.8 - 2.7	3.5 - 2.5	3.5 - 2.5	3.5 - 2.5	3.2 - 2.5
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	NM - NM	167 - 113	NM - NM	38 - 15	53 - 22	27 - 19	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	NM - NM	NM - NM	NM - NM	48 - 15	NM - NM	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
BIIB	[]	BIOGEN INC.	DEC	15 - 9	40 - 21	14 - 10	11 - 7	18 - 12	29 - 21	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	NM - NM	NM - NM	12 - 6	18 - 7	NM - NM	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	20 - 9	NM - NM	68 - 39	62 - 37	39 - 17	28 - 14	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	NM - NM	29 - 8	23 - 9	63 - 38	59 - 36	24 - 14	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	NM - NM	NM - NM	NM - NM	45 - 25	34 - 12	49 - 24	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
EXEL	†	EXELIXIS, INC.	DEC	41 - 26	35 - 22	76 - 40	23 - 14	14 - 6	59 - 28	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
GILD	[]	GILEAD SCIENCES, INC.	DEC	24 - 16	15 - 11	858 - 583	17 - 15	21 - 14	24 - 18	80.8	57.9	2804.1	59.8	54.5	59.0	3.9 - 3.3	5.1 - 3.3	4.8 - 3.9	4.7 - 3.2	4.1 - 3.2	3.5 - 2.3
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	40 - 22	18 - 11	46 - 15	NM - NM	NM - NM	45 - 21	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
INCY	[]	INCYTE CORPORATION	DEC	55 - 43	23 - 15	NM - NM	46 - 30	196 - 113	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
LGND	§	LIGAND PHARMACEUTICALS INCORPORATEI	DEC	NM - NM	63 - 29	NM - NM	4 - 3	41 - 19	246 - 168	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
MYGN	§	MYRIAD GENETICS, INC.	DEC	NM - NM	NM - NM	NM - NM	752 - 334	26 - 14	146 - 60	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	19 - 14	9 - 6	20 - 10	23 - 14	18 - 13	47 - 30	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
RGNX	§	REGENXBIO INC.	DEC	NM - NM	17 - 10	NM - NM	NM - NM	27 - 8	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	18 - 10	20 - 14	13 - 7	NM - NM	11 - 7	18 - 12	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	156 - 62	36 - 22	39 - 17	14 - 6	63 - 28	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATE	DEC	25 - 17	27 - 19	29 - 19	49 - 35	23 - 18	157 - 70	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
XNCR	§	XENCOR, INC.	DEC	NM - NM	38 - 22	NM - NM	97 - 59	NM - NM	NM - NM	0.0	0.0	0.0	0.0	0.0	0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0

Note: Data as originally reported. CAGR-Compound annual growth rate.
[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
Souce: S&P Capital IQ.

Ticker		Company	Yr. Enc	Earnings per Share ($)						Tangible Book Value per Share ($)						Share Price (High-Low, $)					
				2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017	2022	2021	2020	2019	2018	2017
BIOTECHNOLOGY																					
ABBV	[]	ABBVIE INC.	DEC	6.6	6.5	2.7	5.3	3.7	3.3	-46.5	-52.5	-58.3	-28.7	-30.7	-24.0	175.9 - 128.3	136.8 - 101.8	109.2 - 62.6	92.3 - 62.7	125.9 - 77.5	99.1 - 59.3
AMGN	[]	AMGEN INC.	DEC	12.1	10.3	12.3	12.9	12.6	2.7	-52.3	-41.9	-37.8	-41.3	-15.3	2.6	296.7 - 214.4	276.7 - 198.6	265.0 - 177.1	245.0 - 166.3	210.2 - 163.3	191.1 - 147.1
ANIK	§	ANIKA THERAPEUTICS, INC.	DEC	-1.0	0.3	-1.7	1.9	1.3	2.1	13.9	13.6	12.1	19.1	17.4	16.7	36.8 - 20.0	48.4 - 32.3	55.1 - 22.0	75.7 - 29.0	69.8 - 28.5	60.3 - 41.6
ARWR	†	ARROWHEAD PHARMACEUTICALS, INC.	SEP	-1.7	-1.4	-0.8	0.7	-0.7	-0.5	3.6	3.8	4.4	2.4	0.9	0.8	70.1 - 26.8	93.7 - 57.9	86.8 - 19.5	73.7 - 11.7	22.4 - 3.6	4.5 - 1.4
BIIB	[]	BIOGEN INC.	DEC	20.9	10.4	24.8	31.4	21.6	11.9	40.2	19.8	12.2	23.3	21.4	19.4	311.9 - 187.2	468.6 - 221.7	375.0 - 223.3	344.0 - 215.8	388.7 - 249.2	348.8 - 244.3
CHRS	§	COHERUS BIOSCIENCES, INC.	DEC	-3.8	-3.8	1.6	1.2	-3.2	-4.5	-1.8	1.2	3.8	1.4	-0.6	0.5	16.5 - 5.6	22.2 - 12.2	23.0 - 10.9	23.9 - 8.3	20.7 - 8.4	29.6 - 8.1
CYTK	§	CYTOKINETICS, INCORPORATED	DEC	-4.3	-2.8	-2.0	-2.1	-2.0	-2.6	-1.1	2.9	1.6	-0.2	0.5	2.0	55.8 - 29.3	47.9 - 17.7	30.1 - 8.0	14.9 - 5.8	10.3 - 5.9	17.2 - 7.0
EGRX	§	EAGLE PHARMACEUTICALS, INC.	DEC	2.7	-0.7	0.9	1.0	2.1	3.3	5.4	9.9	10.2	9.1	7.4	7.8	53.8 - 24.4	58.3 - 36.5	60.7 - 33.8	64.9 - 38.4	85.7 - 36.0	97.2 - 45.1
EBS	§	EMERGENT BIOSOLUTIONS INC.	DEC	-4.5	4.3	5.7	1.0	1.2	1.7	8.7	15.4	9.7	1.5	-1.2	15.1	52.3 - 10.6	127.2 - 29.9	137.6 - 46.4	67.5 - 39.1	73.9 - 42.7	47.9 - 27.9
ENTA	§	ENANTA PHARMACEUTICALS, INC.	SEP	-5.9	-3.9	-1.8	2.2	3.5	0.9	15.5	19.7	22.7	23.5	20.3	15.8	79.5 - 37.6	102.0 - 40.4	62.1 - 38.4	106.8 - 57.2	127.8 - 52.4	59.9 - 25.9
EXEL	†	EXELIXIS, INC.	DEC	0.6	0.7	0.4	1.0	2.2	0.5	7.5	6.7	5.8	5.3	4.1	0.7	23.4 - 14.9	25.8 - 15.5	27.8 - 13.7	25.3 - 15.0	32.2 - 13.4	32.5 - 14.2
GILD	[]	GILEAD SCIENCES, INC.	DEC	3.6	4.9	0.1	4.2	4.2	3.5	-12.8	-16.5	-18.4	3.7	1.2	-0.6	89.7 - 57.2	74.1 - 57.9	86.0 - 56.6	70.5 - 60.9	89.5 - 60.3	86.3 - 63.8
HALO	†	HALOZYME THERAPEUTICS, INC.	DEC	1.4	2.7	0.9	-0.5	-0.6	0.5	-5.8	1.4	1.1	0.7	1.7	1.5	59.5 - 31.4	56.4 - 31.8	44.5 - 12.7	19.7 - 13.8	21.5 - 13.2	21.1 - 9.7
INCY	[]	INCYTE CORPORATION	DEC	1.5	4.3	-1.4	2.1	0.5	-1.5	18.3	15.7	10.4	10.4	7.3	5.9	84.9 - 65.1	101.5 - 61.9	110.4 - 62.5	96.8 - 62.0	102.6 - 57.0	153.2 - 92.9
LGND	§	LIGAND PHARMACEUTICALS INCORPORATED	DEC	-2.0	3.3	-0.2	31.9	6.0	0.5	8.2	19.6	-5.4	26.2	10.7	4.0	156.3 - 57.8	219.8 - 98.6	127.8 - 57.2	145.0 - 84.5	278.6 - 128.2	149.3 - 95.1
MYGN	§	MYRIAD GENETICS, INC.	DEC	-1.4	-0.4	-3.0	0.1	1.9	0.3	2.6	4.0	-0.4	-0.2	2.7	-0.6	28.5 - 13.9	37.0 - 19.5	30.1 - 9.2	48.4 - 20.1	50.4 - 26.8	37.3 - 15.2
REGN	[]	REGENERON PHARMACEUTICALS, INC.	DEC	38.2	72.0	30.5	18.5	21.3	10.3	203.3	176.0	106.0	101.6	80.7	57.1	779.0 - 538.0	686.6 - 441.0	664.6 - 328.1	442.0 - 271.4	416.5 - 281.9	543.6 - 340.1
RGNX	§	REGENXBIO INC.	DEC	-6.5	2.9	-3.0	-2.6	2.7	-2.5	11.9	17.8	10.1	12.2	14.1	5.8	35.7 - 18.7	50.3 - 27.0	55.0 - 20.0	63.2 - 30.4	85.1 - 23.3	36.1 - 16.3
UTHR	†	UNITED THERAPEUTICS CORPORATION	DEC	15.0	10.1	11.5	-2.4	13.4	9.3	103.2	86.8	72.7	59.7	60.1	47.6	283.1 - 158.4	218.4 - 150.7	152.8 - 75.6	128.9 - 74.3	152.6 - 100.1	169.9 - 112.0
VNDA	§	VANDA PHARMACEUTICALS INC.	DEC	0.1	0.6	0.4	2.1	0.5	-0.4	9.0	8.7	7.9	7.2	4.8	2.3	16.9 - 6.7	21.9 - 13.1	17.0 - 7.1	31.3 - 11.8	33.4 - 13.8	19.0 - 11.9
VRTX	[]	VERTEX PHARMACEUTICALS INCORPORATEL	DEC	12.8	9.0	10.3	4.5	8.1	1.0	47.6	34.2	28.0	18.1	17.2	7.7	324.8 - 214.7	243.0 - 176.4	306.1 - 197.5	225.7 - 161.0	194.9 - 144.1	167.9 - 73.3
XNCR	§	XENCOR, INC.	DEC	-0.9	1.4	-1.2	0.5	-1.3	-0.8	11.8	12.1	9.6	10.2	9.1	6.5	42.3 - 19.4	58.3 - 30.1	47.9 - 19.4	46.3 - 27.8	48.4 - 20.2	28.6 - 18.6

Note: Data as originally reported. CAGR-Compound annual growth rate.
[]Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
Souce: S&P Capital IQ.

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