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POLICY BRIEF

Pharmaceutical Innovation and the Inflation Reduction Act: 2023 in Review

MAY 2024

A Note on Authorship

This report was researched and published by the authors during their tenure at ATI Advisory from 2023 to 2025. With continued support from Arnold Ventures, the authors carry forward this work under Verdant Research.

ATI Advisory

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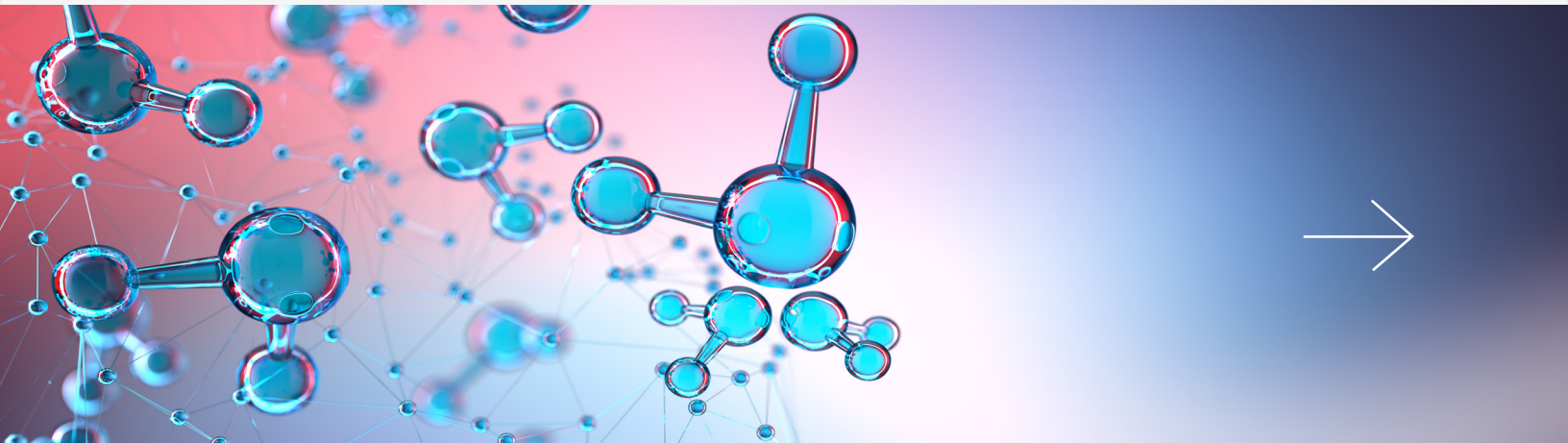

Overview

At the time of our last report, we took an early look at R&D-related decision-making among 19 biopharma companies most likely to have a drug selected for Medicare negotiation. Despite assertions by industry stakeholders that this new policy would stifle innovation, we found few actions by these companies through the first half of 2023 that could be attributed to it. We're back for another check-in now that companies have reported earnings for 2023 and the negotiation process for the first 10 selected drugs is underway.

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This work is supported by Arnold Ventures.

Key Findings

Many companies in our analysis face an unprecedented patent cliff over the next several years. In preparation for these sales declines, they have been focusing significant attention on their R&D pipelines and investments.

In 2023, the companies on our watchlist generated 62% of their worldwide pharmaceutical sales from products with US patents expiring within five years. In fact, approximately 90% of Bristol-Myers Squibb's (BMS) and Merck's sales come from products expected to lose exclusivity during this time period. In addition to enriching their pipelines through M&A and external development, management teams are accelerating key pipeline projects. Several executives acknowledged that maximizing sales over a product's life cycle will require taking more risk during late-stage development. This includes starting costly outcomes trials earlier and developing drugs for multiple indications in parallel.

Companies are increasing R&D spending but allocating it differently than in the past.

In the aggregate, the 17 companies that reported fiscal year earnings spent $157 bn on R&D, a nearly 22% increase over 2022's $129 bn. The median increase was 8%, with a range of -7% to +151%. Despite the increased spending, companies are focusing their resources on priority programs and more targeted therapeutic areas.

Deal activity has picked up, but most transactions have been relatively small and in targeted therapeutic areas.

Several of the year's larger deals centered on late-stage pipeline assets and even approved products, driven by the urgent need of companies to address current or anticipated sales declines of key products. Acquirors included Pfizer, BMS, Merck and AbbVie. M&A and licensing deals are consuming substantial shares of R&D capital, with Merck and Pfizer leading the pack. However, "bolt-on" or smaller and more targeted deals, rather than mega-mergers, have been the norm this year. Companies have also been exercising discipline and waiting for more robust clinical data before pulling the trigger.

We are not seeing signs that the "pill penalty" is a significant barrier to investment in small molecules.

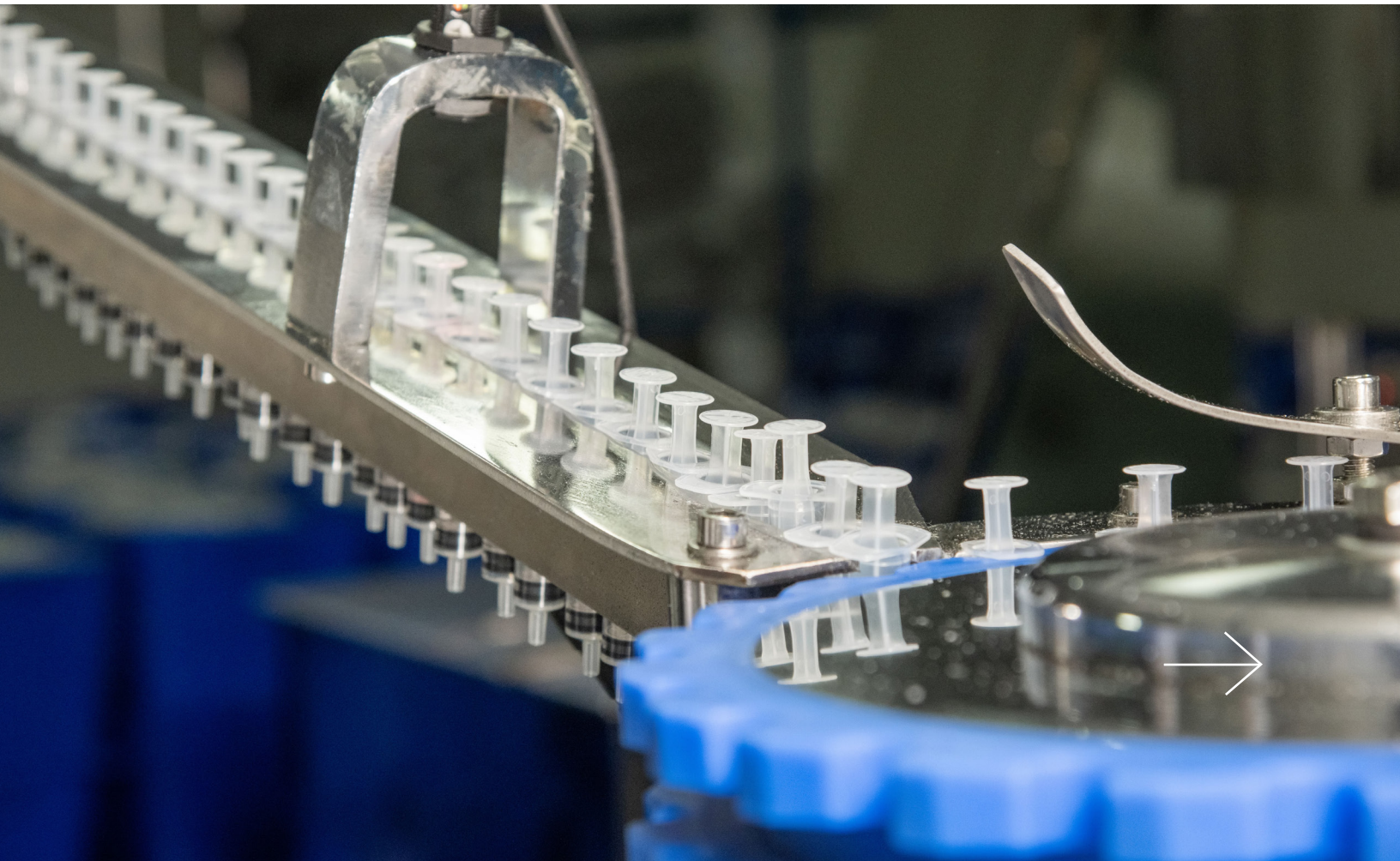
In fact, several recent deals in the neuroscience and cardiovascular space have small molecules as lead assets. One exception seems to be Pfizer, which pointed to this aspect of the Inflation Reduction Act (IRA) as a key factor in its emphasis on biologic drugs in its oncology business following its acquisition of Seagen. At an analyst event in late February, the commercial president of Pfizer oncology stated that the time differential before negotiation "...has driven us to be deliberate intentionally not just on our tumor types but on the modalities...-

-the ADCs (antibody drug conjugates) as well as the bispecifics." Since this has been the primary complaint about the legislation, we will be watching to see how this plays out. Thus far, it seems that small molecules remain appealing for the same reason they always have: ease of administration, cost and manufacturing advantages, improved access and compliance, and better suitability for desired therapeutic benefits, such as crossing the blood-brain barrier or combining with other drugs.

Despite objections to the IRA, companies' actions suggest that the "innovation" wheels are turning.

With pipeline assets undergoing stricter review before progressing, programs with the most compelling profiles are getting more internal resources (including both cash and managerial attention). We also are watching for pipeline developments that may allow manufacturers to circumvent negotiation for a portion of a drug franchise's sales, even if the original product is selected by CMS. For example, fixed-dose combinations figured prominently in a few analyst calls, particularly with respect to immuno-oncology and obesity medicines. Meanwhile, commentary on the IRA by company executives has softened. When CMS issued its first round of offers on February 1, 2024, most companies refrained from commenting directly about the negotiation process or the opening bids.

During 2023, several companies including Biogen, Novartis, and Johnson & Johnson executed significant R&D reorganizations.



Analysis

OVERALL MARKET PERFORMANCE

The biopharma sector closed out 2023 on an optimistic note in terms of stock performance, M&A activity and overall sentiment during company-hosted investor events and conference calls early this year. To the extent that stock prices are an indicator, it's noteworthy that the XBI[1] appreciated 60% from its low in late October to the end of February. The DRG large-cap pharma index was also strong, with 19% appreciation over the same time period. The higher valuations and increased investor interest in the stocks are helping to ease the funding logjam for earlier stage biotech companies, which will be positive for innovation longer term. As companies go public or are acquired, venture capital (VC) firms should begin executing on long-awaited exit strategies, freeing them up to deploy more capital into promising early-stage companies after a slow couple of years.

COMPANY AND PORTFOLIO-LEVEL DEVELOPMENTS

R&D STRATEGY AND REORGANIZATIONS

During 2023, several companies including Biogen, Novartis, and Johnson & Johnson executed significant R&D reorganizations—some of which started before the IRA. Their decisions around organizational structure and asset prioritization – tough, but part of the normal business cycle – are now largely completed. Since our last report, Biogen reported taking "a layer out of the organization structure" to increase agility and accountability and continuing to diversify its multiple sclerosis-dominated portfolio. Novartis reduced its total number of R&D projects by approximately one-third from Q3 2021 to Q3 2023, concentrating resources on those with the greatest potential to be blockbusters (which they defined as >$2 bn). Their most dramatic cull was in oncology, cutting 37 products and reflecting the company's prioritized focus on four key therapeutic areas: cardiovascular, renal and metabolic, immunology, neuroscience, and oncology.

These reflect an industry-wide trend to prioritize assets and then concentrate resources on them to accelerate and optimize their development and commercial potential. That strategy also included cutting losses more quickly. At a recent press event, AstraZeneca's CEO said the company has "had to really ruthlessly prioritize our R&D projects". This exercise has included discipline in terminating pipeline candidates that aren't considered best-in-class or don't fill an unmet need, which results in fewer pipeline projects—but should ultimately be beneficial for innovation.

1 SPDR S&P Biotech ETF

Restructuring announcements from second half of 2023*	
Sanofi	In late 2023, Sanofi announced plans to "…increase its R&D investments to fully realize its pipeline potential" and accelerate innovation. Although Sanofi is undertaking steps to improve its cost structure and efficiency, most of these ~2 bn Euros in cost savings will be reinvested in R&D, where it is concentrating investment in more immunology and neurology projects. Sanofi reduced its margin targets and near-term earnings outlook as a trade-off for this higher level of R&D spending.
Novo Nordisk	Novo Nordisk made good on its statements to the press that the company would "focus more heavily on growing its US presence" by opening a new campus in Boston in February. "When we start clinical development, we start in the US. When we start commercial activity, we always start in the US."
Pfizer	Following the completion of its Seagen acquisition and in parallel with its previously announced $3.5 bn cost-cutting initiative, Pfizer unveiled plans to create a separate division focused on oncology.
GSK	After its head of research departed in September, GSK communicated plans to reorganize its research organization into three unique teams focused on separate therapeutic areas. The stated aim of the approach is to "accelerate delivery of new medicines and vaccines for patients" and to integrate their investments in new technologies even further into drug discovery and research.

*Restructuring announcements from the first half of 2023 are described here.

R&D BUDGETS

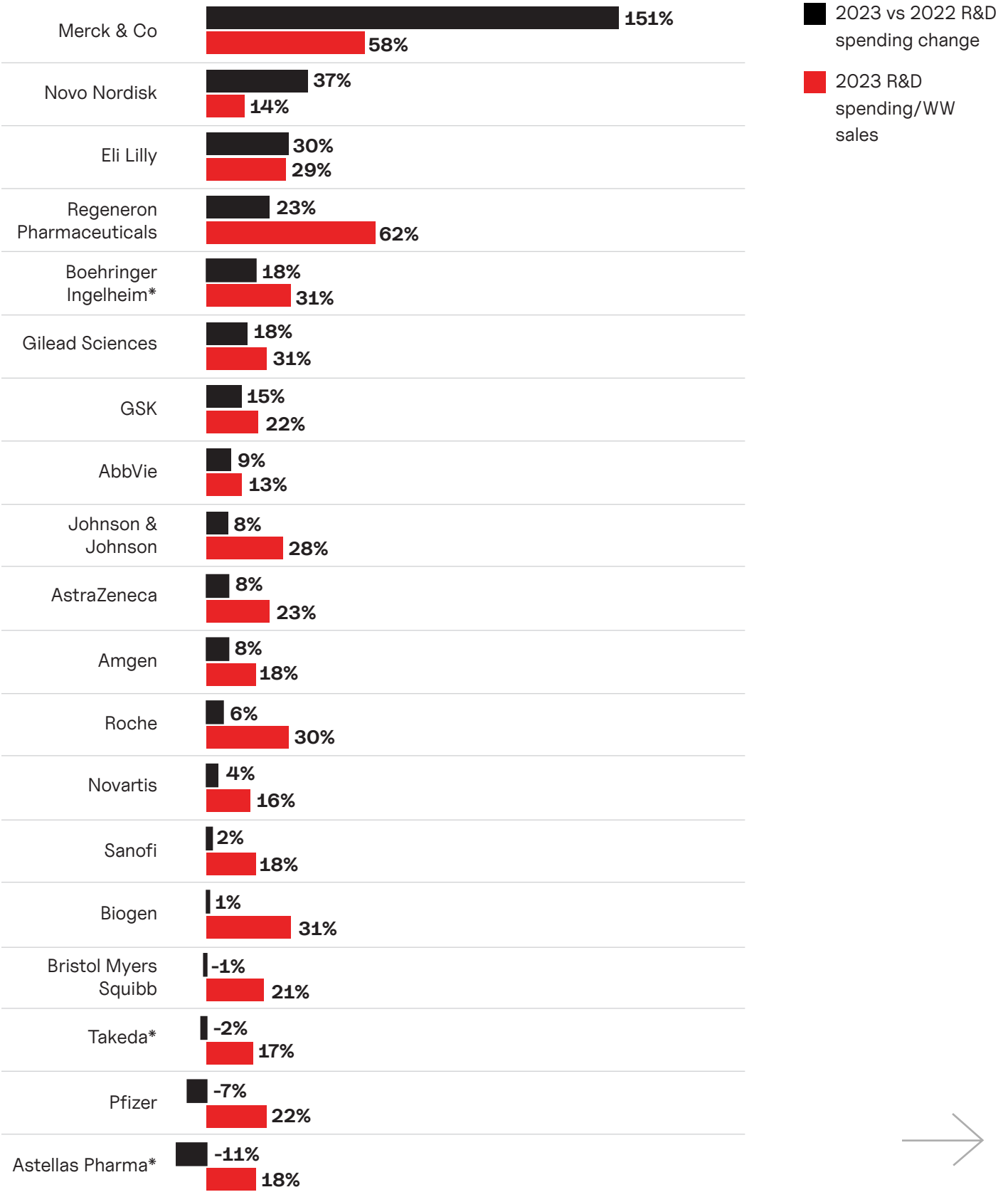
In aggregate and at the company level, R&D investment grew at a healthy clip in 2023. Overall R&D spend outpaced sales by five percentage points and nearly all companies in our sample increased R&D spending in 2023. Merck, Novo Nordisk, and Eli Lilly recorded the highest jumps. (Table 2) Merck's ~150% increase was largely attributable to its significant investment in acquisitions and licensing deals, while Novo Nordisk and Lilly are reinvesting their robust sales from diabetes and obesity drugs to broaden these franchises. Even the two companies with lower R&D spending in 2023 (Pfizer and BMS) saw an increase in their ratio of R&D expense to worldwide sales. In fact, each of the companies increased R&D as a percentage of sales compared with 2022, with the median percentage now 22% compared with 19% the previous year.

For the full year of 2023, R&D spending for our companies increased a median of 8% (excluding Astellas, Takeda and Boehringer Ingelheim (BI), who have not yet reported or have a different fiscal year-end). The YOY change in R&D expense ranged from -7% to +151%. We expect continued growth in R&D spending in 2024, even if it puts pressure on earnings, as in the case of Sanofi. (Table 1)

Table 1. Sales and spending

	Total pharma sales ($ bn)		R&D spending ($ bn)	
	2022	2023	2022	2023
Merck & Co	49.5	50.8	11.8	29.7
Johnson & Johnson	50.7	53.5	13.7	14.8
Roche	46.4	49.1	13.9	14.7
Pfizer	90.4	48.2	11.4	10.7
AstraZeneca	43.0	43.8	9.5	10.3
Eli Lilly	26.7	31.9	7.2	9.3
Bristol Myers Squibb	45.4	44.4	9.2	9.1
Novartis	51.3	52.5	8.3	8.6
Sanofi	40.3	40.8	7.2	7.3
GSK	35.8	36.8	6.3	7.2
AbbVie	56.3	52.7	6.4	7.0
Boehringer Ingelheim*	17.6	20.6	5.4	6.3
Gilead Sciences	26.6	26.5	5.0	5.7
Novo Nordisk	25.4	33.7	3.5	4.7
Amgen	24.5	26.6	4.3	4.7
Takeda*	29.6	27.5	4.8	4.7
Regeneron Pharmaceuticals	6.9	7.1	3.6	4.4
Biogen	8.0	7.2	2.2	2.3
Astellas Pharma*	11.2	10.3	2.1	1.8

*2023 based on analyst estimates as FY not yet reported; excluded from averages; sourced from Evaluate Pharma


Merck & Co
151%
58%
Novo Nordisk
37%
14%
Eli Lilly
30%
29%
Regeneron Pharmaceuticals
23%
62%
Boehringer Ingelheim*
18%
31%
Gilead Sciences
18%
31%
GSK
15%
22%
AbbVie
9%
13%
Johnson & Johnson
8%
28%
AstraZeneca
8%
23%
Amgen
8%
18%
Roche
6%
30%
Novartis
4%
16%
Sanofi
2%
18%
Biogen
1%
31%
Bristol Myers Squibb
-1%
21%
Takeda*
-2%
17%
Pfizer
-7%
22%
Astellas Pharma*
-11%
18%
2023 vs 2022 R&D spending change
2023 R&D spending/WW sales

Management's commentary reflected the desire to optimize revenue opportunities for their pipelines' high-potential and latest stage assets. For instance, Amgen noted that they focused spending on later pipeline programs (i.e., Phase 3 and marketed products), while slightly reducing spending in research and early pipeline. This trend bears watching as companies may aim to accelerate development of new indications in late-stage products.

In addition, several companies have been shifting the clinical focus of their R&D organizations. For example, Biogen and Sanofi announced they were rebalancing their pipelines away from neuroscience and oncology, respectively. Both are therapeutic areas in which they had costly stumbles in recent years – including Biogen's aducanumab and Sanofi's tusamitamab, a high-profile late-stage ADC it finally dropped in December. Despite these shifts, oncology remains the dominant therapeutic area, accounting for 37% of our companies' R&D projects in 2023.

Several executives also noted that these strategic changes mean taking greater risk. Historically, drugs have often launched in smaller indications first, allowing them to generate some revenue before spending more on clinical trials for larger (and often riskier) patient populations, particularly in cancer drug development. More recently, R&D teams are accelerating clinical programs and developing indications in parallel rather than sequentially. At the September Morgan Stanley investor conference, Merck's R&D head Dean Li pointed to this strategy as an example of how companies would take on more risk in response to the IRA.

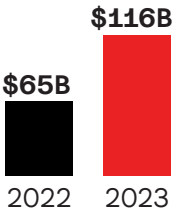
In 2023, external innovation was already the source of most clinical development expenditures. Using Evaluate Pharma estimates of 2023 trial costs as a proxy, we estimate that nearly 60% of clinical trial costs were spent on products discovered externally, i.e., through acquisitions or licensing agreements. There was a broad range, however, as 89% of Eli Lilly's clinical trial costs were on internally discovered candidates while eight companies spent less than a quarter on organic drugs.

Pfizer spent $10.7 bn on internal R&D projects this year, but $43.8 bn on completed business development transactions (Seagen acquisition). Similarly, Merck spent $10.4 bn on internal R&D, but an additional $18.5 bn on external development, fueling its industry-high R&D budget this year. On the other end of the spectrum, Lilly has developed most of its pipeline products in-house and is now spending substantially on their late-stage development and commercialization.

DEALMAKING: M&A

On the deal front, late 2023 saw a flurry of acquisitions and licensing agreements, including several multi-billion dollar transactions. According to Fierce Pharma, the value of the top 10 M&A deals in 2023 exceeded the 2022 level by 78%, with those transactions reaching nearly $116 bn. compared with $65 bn. in 2022.

M&A in 2023 reflected an urgent need to secure future revenues as major products approach their loss of exclusivity (LOE). The number of M&A deals and their aggregate value had been decreasing since 2019, but 2023 reversed the downward trend with the uptick in activity in the 4th quarter and several relatively large transactions. For the full year 2023, companies in our sample announced a total of $166 bn in M&A deals. Excluding Pfizer's $43 bn Seagen acquisition, the average transaction among deals over $1 bn was around $3.5 bn, which is generally



The value of the top 10 M&A deals in 2023 exceeded the 2022 level by **78%**

considered small by industry standards. Endpoints News recently commented acquirors "... either rolled the dice on the back of their blockbuster bonanzas, were forced to address gaping holes in the pipeline in the face of looming patent expirations, or simply had no choice in the face of repeated setbacks." Many recent transactions were centered on lead assets that are in late-stage clinical development or ready for commercialization, poised to fill projected revenue gaps from major products losing market exclusivity. (Table 2)

Table 2. Percentage of 2023 worldwide pharma sales from products with expected US LOE <5 years

Company	2023 pharma sales	Key Asset(s)
BMS	91%	Eliquis, Opdivo, Revlimid*, Pomalyst, Orencia, Sprycel, Yervoy, Orencia
Merck	90%	Keytruda, Gardasil, Januvia
Astellas	82%	Xtandi
Regeneron	81%	Eylea
GlaxoSmithKline	77%	Trelegy Ellipta, Benlysta, Triumeq, Dovato, Nucala
Pfizer	73%	Prevnar, Ibrance, Vyndaqel, Xeljanz
Biogen	67%	Tysabri
Johnson & Johnson	64%	Stelara, Xarelto, Uptravi, Opsumit
Boehringer Ingelheim	63%	Jardiance, Ofev, Tradjenta
Amgen	61%	Prolia, Otezla, Xgeva
AbbVie	56%	Humira*, Imbruvica
Eli Lilly	53%	Trulicity
Takeda	53%	Vyvanse
Novartis	52%	Entresto, Promacta
Sanofi	52%	Aubagio
AstraZeneca	51%	Soliris, Farxiga, Lynparza
Roche	49%	Perjeta
Novo Nordisk	29%	Saxenda
Gilead	6%	Tecartus

LOE = loss of exclusivity; *Recent US LOE; Source: Evaluate Pharma

It's no coincidence that companies anticipating significant LOEs were also among the ones shelling out the most on acquisitions. For example, BMS, Pfizer and Merck are all near the top of the list in terms of LOE exposure (Table 2) and acquired companies with drugs that are approved or filed (Tables 3 and 4).

BMS's situation stands out as particularly challenging, because seven of its nine top selling drugs face possible LOE by 2026 and 8 of 9 by 2028. In fact, nearly 90% of the company's 2023 sales came from drugs losing exclusivity by 2028.

While losing market exclusivity is the most visible source of sales declines, Pfizer and Biogen are also navigating other challenges, such as the loss of COVID vaccine and treatment revenues and the failed launch of Aduhelm. Eli Lilly and Novo Nordisk, on the other hand, are leveraging their windfall from their diabetes and obesity programs to reinvest in complementary approaches and the next generation of metabolic drugs.

Of the 19 M&A transactions with upfront value of over $1 bn in 2023, oncology remained the dominant therapeutic area—particularly in specialized segments such as ADCs and radiopharmaceuticals. Seven acquired companies have a focus on oncology, followed by three in obesity and two each in neurology, immunology and rare diseases. Whereas these have occupied dominant or increasing shares of M&A and drug development, the emergence of endocrinology and radiotherapy was noteworthy this year. There also seems to be a bit of a bandwagon effect, as one transaction would lead other companies to follow in the same therapeutic area, as was the case with ADCs, obesity, schizophrenia and the TL1A inhibitors.

Of the 19 M&A transactions with upfront value of over $1 bn in 2023, oncology remained the dominant therapeutic area

Table 3. Select company deals over $1 bn

	Terms ($ bn)	Key Asset	Theraputic Profile	Indication	SM/Bio
AbbVie	**Total deal value: $19.5 bn**				
Immunogen	10.1	Elahere, pivekimab sunirine	Oncology	Ovarian, rare blood cancer	Bio
Cerevel	8.7	Emraclidine	Neurology	Schizophrenia	SM
Astellas	**Total deal value: $6.1 bn.**				
Iveric	5.9	Zimura	Ophthalmology	Geographic atrophy	Bio
AstraZeneca	**Total deal value: $4.2 bn.**				
CinCor	1.3	Baxdrostat	Cardiovascular	Hypertension	SM
Gracell	1	GC012F	Oncology	Multiple myeloma	Bio
Biogen	**Total deal value: $7.3 bn.**				
Reata	7.3	Skyclarys	Neurology	Freidreich's ataxia	SM

	Terms ($ bn)	Key Asset	Theraputic Profile	Indication	SM/Bio
BMS	**Total deal value: $22.9 bn.**				
Karuna	14	KarXT	Neurology	Schizophrenia	SM
Mirati therapeutics	4.8	Krazati	Oncology	Lung cancer, others	SM
Rayze Bio	4.1	RYZ101	Oncology	Radiopharmaceuti-cals	SM (radiopharma-ceutical)
Eli Lilly	**Total deal value: $6.2 bn.**				
Versanis	1.9	Bimagrumab	Metabolic	Obesity	Bio
Point BioPharma	1.4	PNT2002	Oncology (radi-oligand)	Prostate cancer	Radioligand
Dice Therapeutics	2.4	DC806	Immunomodula-tors	Psoriasis	SM
GSK	**Total deal value: $2.0 bn.**				
Bellus Health	2.0	Camplixiant	Respiratory	Chronic cough	SM
Merck	**Total deal value: $12.8 bn.**				
Prometheus	10.8	PRA023	Immunology	Bowel disease	Bio
Novartis	**Total deal value: $4.6 bn.**				
Chinook Therapeutics	3.5	Astrasentan; zigakibart	Genitourinary	Kidney disorders	SM
Novo Nordisk	**Total deal value: $1.1 bn.**				
Inversago	1.1	INV202	Metabolic	Obesity; diabetic kidney disease	SM
Pfizer	**Total deal value: $43 bn.**				
Seagen	43	ADC platform	Oncology	Multiple tumor types	Bio
Roche	**Total deal value: $2.7 bn.**				
Carmot	2.7	CT-388; CT-868	Metabolic	Obesity	SM
Sanofi	**Total deal value: $2.9 bn.**				
Provention	2.9	Tzield	Metabolic	T1DM	Bio

Source: Evaluate Pharma, company earnings

Some acquiring companies now seem to be shifting their focus to integration and development of key assets. 2023's largest acquiror, Pfizer, has said it's now in "execution mode". Merck, Lilly and Novartis have indicated a willingness to do more deals in the future, but management commentary suggests that "bolt-on" acquisitions rather than mega-mergers seem to be where activity will continue.

DEALMAKING: PRODUCT LICENSING AND COLLABORATIONS

In addition to company acquisitions, there were a number of noteworthy product licensing and collaboration deals announced in 2023, with 25 total potential deals valued at $1 bn or more. The most substantial collaboration is Merck's deal with Daiichi Sankyo for the development of ADCs, including one that is already filed and one in Phase 3. Merck paid $4 bn. upfront, but the potential value including milestone payments could reach as high as $22 bn. In fact, ADC collaborations make up the top three spots in terms of potential deal value, with the Merck/ Sichuan Kelun and BMS/ Sichuan Biokin agreements in 2nd and 3rd. The 4th largest product deal was Roche's acquisition of Roivant's Telavant, an ulcerative colitis drug that Pfizer externalized in December 2022 (though it retains a share of the economics), for $7.25 bn.

The most substantial collaboration is Merck's deal with Daiichi Sanyo for the development of ADCs.

Table 4. Select product deals over $1 bn*

	Terms ($ bn)	Key Asset	Theraputic Profile	Molecule Size
AbbVie	**Total potential deal value: $1.1 bn, $142 m cash upfront**			
AstraZeneca	**Total potential deal value: $4.2 bn, $272 m cash upfront**			
Shanghai Eccogene Biotechnology	2	ECC5004	Metabolic	SM
Boehringer ingelheim	**Total potential deal value: $1.8 bn, $19 m cash upfront**			
BMS	**Total potential deal value: $8.7 bn, $950 m cash upfront**			
Sichuan Biokin Pharmaceutical	8.4	BL-B01D1	Oncology, ADC	Bio
Eli Lilly	**Total potential deal value: $4.7 bn, $210 m cash upfront**			
Gilead	**Total potential deal value: $2.8 bn, $285 m cash upfront**			
GSK	**Total potential deal value: $3.3 bn, $360 m cash upfront**			
Jiangsu Hansoh Pharmaceutical	1.6	HS-20089	Oncology, ADC	Bio
Johnson & Johnson	1	JNJ-3989	Infectious disease, Hepatitis B	Bio

	Terms ($ bn)	Key Asset	Theraputic Profile	Molecule Size
Johnson & Johnson	**Total potential deal value: $3.4 bn, $425 m cash upfront**			
LegoChem Biosciences	1.7	LCB84	Oncology	Bio
Contineum Therapeutics	1.1	PIPE-307	CNS	SM
Merck	**Total potential deal value: $37.1 bn, $4.3 bn cash upfront**			
Daiichi Sankyo	22	MK-1022	Oncology, ADC	Bio
AQILION	1	Alnitak		
Sichuan Kelun-Biotech Biopharmaceutical	9.5	Kelun-Biotech-Merck ADC Oncology Program	Oncology, ADC	Bio
Novartis	**Total potential deal value: $2.7 bn, $368 m cash upfront**			
Bicycle Therapeutics	1.8	Bicycle-Novartis Oncology Research Project		
Novo Nordisk	**Total potential deal value: $2.7 bn, $60 m cash upfront**			
Valo Health	2.8	Novo Nordisk-Valo Health Cardiometabolic		
KBP Biosciences	1.3	ocedurenone	cardiovascular; hypertension	SM
Pfizer	**Total potential deal value: $1.1 bn, $53 m cash upfront**			
Harbour BioMed	1.1	HBM9033		
Roche	**Total potential deal value: $18.5 bn, $7.7 m cash upfront**			
Roivant Sciences	7.3	Telavant	Immunology, IBD	Bio
Alnylam Pharmaceuticals	3.1	Zilebesiran	cardiovascular, hypertension	SM
Sanofi	**Total potential deal value: $4.1 bn, $820 m cash upfront**			
Teva	1.5	TEV-48574	Immunology, IBD	Bio
Recludix Pharma	1.3	STAT6 Research Program		
Takeda	**Total potential deal value: $2.5 bn, $439 m cash upfront**			
Hutchmed	1.1	Fruzaqla	Oncology	SM

*Excludes research project deals over $1 bn

Source: Evaluate Pharma, company earnings

Merck, Roche and BMS spent the most overall on product deals during 2023. While Merck and BMS were also among the top three in M&A, Roche has been more targeted in structuring transactions around individual products. With the exception of Telavant, most of its licensing deals have been for earlier stage products and involved relatively small upfront payments with much larger potential payments if certain regulatory or commercial milestones are achieved. This trend was common among this year's product deals—as it was in M&A. Of the 58 product deals in our sample, only 12 involved upfront cash of $100 mn or more. Framed differently, only ~17% of total potential deal value was paid upfront, with remaining payouts contingent on future success. Such terms reflect big pharma's relatively strong negotiating position compared with a few years ago.

PRODUCT LEVEL DEVELOPMENTS AND UPDATES

We also continue to monitor product-level changes to company pipelines. For the most part, these were discontinuations of product candidates that failed for clinical reasons or that fell outside of newly prioritized therapeutic categories. When companies do terminate drug candidates with less competitive clinical profiles, resources are freed for more innovative programs with better prospects of benefiting patients. With 38 small molecules and 40 biologics being dropped, our sample does not suggest the "pill-penalty" is a significant factor for most companies' decisions.

DISCONTINUED OR DIVESTED PRODUCTS

Product discontinuations for clinical reasons are par for the course in this industry. However, corporate restructuring initiatives and pipeline reprioritizations also contributed to discontinuations this year.

Based on data from Evaluate Pharma for the companies in our sample, the number of programs in clinical development (Phase I to Filed) declined 2% to 1,787 in 2023 from 1,829 in 2022. This decline departs from the norm in recent years, which has been a steady increase in programs.

Consistent with its stated goal of reducing the number of R&D programs and narrowing its therapeutic focus, Novartis had the most cuts in 2023, resulting in 38 fewer products in development. Its largest reductions were in oncology and hematology, though assets were pruned across the range of therapeutic areas. One of the most noteworthy moves was its cancellation of its collaboration with BeiGene, which included nine development programs for the PD-1 inhibitor tislelizumab as well as ociperlimab, a TIGIT inhibitor in Phase 3 development for non-small cell lung cancer. A handful of other programs were discontinued based on business decisions or stringent benefit/ risk assessments. Biogen diversified its pipeline away from neurology. Cuts reduced their number of products in development from 29 to 23 products. Meanwhile, Johnson & Johnson effectively exited the vaccine and infectious disease space, dropping or divesting 8 products throughout 2023.

Companies are not required to disclose products they discontinue unless the decision is financially material, leaving us able to track only the subset of their product terminations they elected to announce. In 2023, this included 84 products discontinuations (Table 5), of which 32 (38%) were in oncology. This proportion appears consistent with the 39% of total pipeline assets currently represented by this therapeutic area. Products in Phase 3 accounted for 24% of discontinuations; 42% were small molecules.

17%

of total potential deal value was paid upfront, with remaining payouts contingent on future success.

A number of decisions were for strategic or non-clinical reasons, including some late-stage assets. This included AstraZeneca's cotadutide for diabetes/ nonalcoholic steatohepatitis (NASH), brazikumab for irritable bowel disease and Johnson & Johnson's aprocitentan. We will monitor changes from this baseline to detect any emerging trends in therapeutic areas or molecule size.

In several instances throughout the year, clinical trials or programs were dropped for reasons other than efficacy or safety concerns, including BMS' decision to stop developing its auto-injector for subcutaneous Opdivo, despite moving forward with the provider-administered subcutaneous injection.

Table 5. Product discontinuations by therapeutic area and molecule size

Company	Therapeutic areas	Small molecule: biologic*	No. products or projects
AbbVie	Oncology, immunology, respiratory	1:7	8
Amgen	Oncology, immunology	0:2	2
AstraZeneca	Oncology, immunology, metabolic, cardiovascular, hematology	3:5	8
Biogen	Neurology	4:1	5
BMS	Oncology, immunology, metabolic	1:3	4
Eli Lilly	Oncology, immunology, metabolic	2:1	3
GSK	Oncology, infectious disease, gastrointestinal	2:1	4
Johnson & Johnson	Infectious disease, cardiovascular	3:3	9
Novartis	Oncology, immunology, neurology, infectious disease, rare metabolic, cardiovascular, ophthalmology	10:5	16
Pfizer	Oncology, immunology, infectious disease, rare	3:4	7
Roche	Oncology, neurology, ophthalmology, hematology	5:5	10
Sanofi	Oncology, immunology, infectious disease, gastrointestinal	1:2	3
Takeda	Oncology, infectious disease, gastrointestinal	3:1	5

Company	Therapeutic areas	Small molecule: biologic*	No. products or projects
		38:40	84

*Excluding vaccines and programs with undisclosed technologies

Note: Counts reflect unique products, and do not reflect discontinuations at the indication level.

CHANGES TO LAUNCH SEQUENCE OR PRIORITIZATION

Throughout the year, several executives have suggested that IRA would influence the launch sequence or prioritization of a product's indications. While this remains plausible, we have seen limited evidence that it is happening as of now.

One could argue that we are now seeing less "sequencing" of indications as companies pull development forward and run multiple large-scale trials in parallel. Sanofi, AbbVie and Lilly have pointed to the necessity to run multiple late-stage trials in parallel in order to secure the labels they believe will be required to achieve blockbuster returns over a shorter time horizon.

Despite the desire to accelerate clinical development, we do not sense a willingness to cut corners and risk delivering a less differentiated product. When an analyst asked Novartis about the possibility of unblinding a cardiovascular outcomes trial for pelacarsen early "given the nine year timeline of IRA", the response was that they had no plan to make such a change since by having longer follow-up they would be more likely to deliver differentiated results in ORION 4 and HORIZON.

OTHER TRENDS WORTH WATCHING

INVESTMENTS RELATED TO DRUGS SELECTED FOR NEGOTIATION

Many of the drugs selected for negotiation were already expecting LOEs in the near future. Losing exclusivity generally kicks off a cycle of innovation, which was already under way for several of the selected companies that are developing new products for the same indications. For example, in anticipation of patent expirations for Eliquis and Xarelto, BMS, Johnson & Johnson and Bayer have been developing Factor XI drugs as their next generation oral anti-coagulants. Although Bayer's asundexian program had disappointing Phase 3 data in one of its large indications, BMS and Johnson & Johnson continue to prioritize milvexian as one of their most important pipeline products, with hopes of shifting market share and mitigating the declines of expiring products.

Several drugs were in clinical development for follow-on indications when they were selected for negotiation. Imbruvica is currently in Phase 3 development for follicular lymphoma and mantle cell lymphoma (in combination with Venclexta). While we are not aware of changes to clinical programs, the product bears

watching—especially in light of its market share losses to competitive agents. (As a reminder, AbbVie cited IRA as a factor in its $2.1 bn impairment charge for Imbruvica; IRA critics cited this as an example of how IRA "reduces the amount of capital available to invest in new treatments and trials.")

With the breakout success of their GLP-1 drugs Ozempic and Mounjaro, Novo Nordisk and Lilly are deepening their dominant foothold in diabetes, which will mitigate any negative impact from negotiation of Novolog/ Fiasp and Jardiance. Finally, in anticipation of biosimilar versions of Stelara next year, Johnson & Johnson is running seven Phase 3 programs in various immunology indications for Tremfya, which is already a $3 bn product.

INNOVATING AROUND THE IRA

Despite business as usual on many measures of R&D decision-making, we do expect that pharmaceutical companies will consider IRA in their development and lifecycle management plans. In particular, we are watching for pipeline developments that could allow manufacturers to circumvent negotiation for a portion of a drug franchise's sales, even if the original product is selected by CMS.

One such area is fixed dose combinations (FDCs), which are formulations that combine multiple active ingredients. For purposes of negotiation, CMS considers FDCs to be distinct products from an original including one (or different) active ingredients.

This takes immediate importance for drugs that appear likely to be selected for negotiation, but remain in development for additional indications. For example, Merck is developing fixed dose combinations of Keytruda to address the large percentage of patients that do not respond to Keytruda alone. Obesity medicines are also viewed as attractive candidates for combinations given the high incidence of cardiovascular comorbidities. This offers opportunities and rationale to combine cholesterol or hypertension agents with GLP-1s.

Besides FDCs, new formulations with ingredients that do not have a standalone therapeutic effect but enhance the performance of existing drugs are considered the same as the original formulation for purposes of negotiation. It's worth watching whether manufacturers attempt to reclassify adjuvant ingredients as active ones in these combinations. Several companies are developing subcutaneous formulations of existing drugs, including Keytruda and Opdivo for cancer and Ocrevus for multiple sclerosis. Merck has described its version of hyaluronidase in combination with Keytruda as an important innovation with distinct clinical benefits.

TECHNOLOGY

Opportunities to reduce expenses and improve efficiency may take on greater importance in the post-IRA environment. As in other industries, AI and other new technologies are gaining prominence as a

AI and other new technologies are gaining prominence as a powerful tool to boost R&D productivity.

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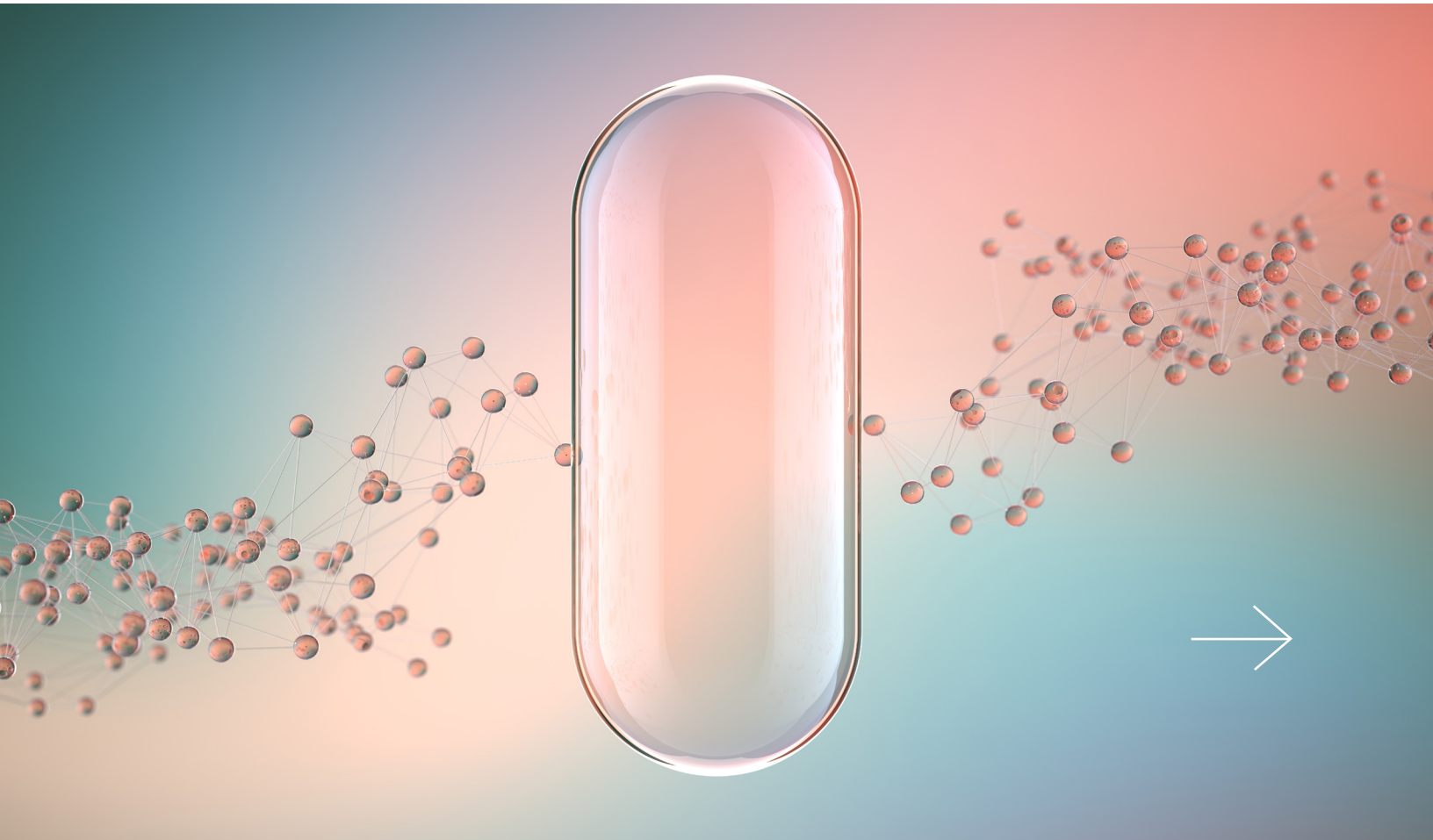
powerful tool to boost R&D productivity. The industry's focus on technological enablers, including AI and data science, has never seemed as visible as it was at the JP Morgan Healthcare conference in January. Though the pharmaceutical industry has a reputation for being a slow adopter, many companies are now integrating tech into a range of workstreams. Some may be realizing a benefit. A recent IQVIA report, concludes that adoption of "technology-driven enablers, including use of predictive biomarkers, novel trial design, and digital and decentralized trial methodologies" contributed to improvements in clinical development productivity in 2023.

Amgen's decision to have its head of R&D transition to the role of chief technology officer underscores its conviction that tech will play a critical role in accelerating innovation within the company. For several years, Reese has said he believes the industry is at a "hinge moment" in which "the union of technology and biotechnology" will bring about profound changes in drug discovery and development. Sanofi, too, has been elevating visibility around its efforts in AI and has discussed its ambition to become the first pharma company powered by AI at scale. Within R&D, it expects that digital and AI capabilities will enhance R&D productivity beginning with target discovery all the way through the regulatory review process.

A number of AI-focused research partnerships have been announced in recent months with Nvidia (Genentech), Alphabet's Isomorphic Labs (Novartis, Lilly) and Microsoft (Novo Nordisk), among others. In September, Novo Nordisk and Valo Health formed a collaboration to leverage Valo's AI and machine-learning platform in discovering treatments for cardiometabolic diseases.



Conclusions

Compared to Medicare negotiation, the coming patent cliff presents a more pressing problem for the biopharma sector and emerged as the most visible driver of change among the companies we follow. 2023 shaped up to be a year of reckoning, with heavy R&D investments and harder lines on where resources are allocated. Companies appear to be cutting their losses sooner on less differentiated and less promising products, and accepting more risk for higher potential rewards. This shift has been accompanied by a pivot away from diversification and towards specialization in areas management perceives as their greatest strengths, increasing the focus on therapeutic areas such as immunology, neuroscience, metabolic, and ADCs for oncology.

After heavy criticism of the IRA in late 2022 and early 2023, investor communications have more recently focused elsewhere. We heard fewer unprompted mentions of the law on investor calls, and discussions of its effects, though not glowing, often acknowledged expectations that that legal and legislative interventions are unlikely to stop its implementation in the near term. AstraZeneca was the rare exception, describing negotiation so far as "relatively encouraging", despite its ongoing suit challenging the law's implementation. Pfizer's CFO recently told investors, "The year that the IRA hits will be obviously a headwind to us, like many others, but we'll work to manage our way through that."

That said, we believe that companies are beginning to factor the law into routine decision-making. While it's still early, clearer evidence of its influence on R&D and investment choices is coming into focus and has to date failed to support several claims leveled by the law's critics. Notably, we found little evidence that companies are turning away from small molecules. Investments in small molecules continued, both in terms of M&A and in pipeline priorities going forward. Lead assets for some of the year's largest deals were small molecules, particularly in the neurology and obesity space. In fact, small molecules may have an advantage relative to biologics when it comes to innovating around the IRA, since they can more readily be reformulated.

Claims that IRA would make the US market less attractive have also failed to play out, as a number of companies have explicitly "leaned in" to the US in the last year, including Novo Nordisk and Bayer. In November, Novo Nordisk's CEO told the Financial Times that the company will "focus more heavily on growing its US presence, which will come at the expense of the EU, unless European regulators initiate some reforms… When we start clinical development, we start in the US. When we start commercial activity, we always start in the US…"

It remains unclear whether the IRA has had an impact on which therapeutic areas companies are pursuing. While we saw no clear IRA-related trend in investment in new product development, on the margin these assets may have slightly less exposure to Medicare. To the extent that VC investors factor any of these signals into future investment decisions, the effects on innovation will not be felt until several years from now as they advance through clinical development. This is an area that we will continue to follow.

"The year that the IRA hits will be obviously a headwind to us, like many others, but we'll work to manage our way through that."

– PFIZER CFO

These claims aside, we see some signs that the IRA has become an additional lens through which companies are making R&D decisions at both the portfolio and product level. For example, recent acknowledgments of taking more risk in launch sequencing to achieve peak sales sooner are in line with the revenue constraints created by Medicare negotiation later in products' life cycles. Companies are also responding in their plans following LOE of their major assets by directing capital and resources towards the therapeutic areas and drug candidates they see as having the highest likelihood of success, which raises the bar on pipeline decisions. For example, companies may set higher hurdles for safety and efficacy before committing to continued investment in a drug candidate. This will take time to play out, and if it does, the products with marginal clinical benefits and less competitive profiles in more crowded therapeutic areas are most likely to be terminated.

Once the negotiated prices become public for the first ten drugs, industry watchers will have a clearer sense of how CMS is considering therapeutic alternatives. This information may further influence pipeline decisions and could place additional weight on novelty and differentiation. ■

Appendix

Using a combination of published lists and our own assessment, we identified 19 companies as likely to have a drug selected for negotiation in the early years of the program. We follow these companies over time to track their R&D approach over time, including restructurings or reprioritizations, R&D budgets, discontinuation or changes to clinical development of specific drugs and candidate molecules, and deal-making and M&A decisions.

Companies included in analysis

1	Abbvie	11	Eli Lilly
2	Amgen	12	Merck
3	Astellas	13	Novartis
4	AstraZeneca	14	NovoNordisk
5	Biogen	15	Pfizer
6	BMS	16	Regeneron
7	Boehringer Ingelheim (private)	17	Roche
8	Gilead	18	Sanofi
9	GSK	19	Takeda
10	Janssen/ Johnson& Johnson		

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