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POLICY BRIEF

Pharmaceutical Innovation and the Inflation Reduction Act: First Half of 2024

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A Note on Authorship
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ATI Advisory

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Overview

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Developments in the first half of 2024 show companies responding to a significant wave of patent expirations, which will continue through the 2nd half of this decade. Macroeconomic factors have also affected the funding environment and by extension, valuations of smaller biotech companies, which are an important part of the drug discovery ecosystem.

Companies are responding at the portfolio level and in their development plans for individual products. Across the industry, R&D budgets have grown, while comprehensive pipeline reviews and increased discipline in asset-allocation are driving capital and resources towards "best-in-class", "first-in-disease" treatments in large therapeutic areas with unmet medical need. "Me-too" drugs are less likely to make the cut. Throughout earnings calls, we heard comments that companies have to accept greater risks to develop new drugs.

These trends coincide with changes introduced by the Inflation Reduction Act (IRA). Among other things, the law's Medicare negotiation provision alters the time horizon to generate return on investment. This is a fundamental input to investment decisions being made now, and we should expect the IRA to increase its influence on biopharmaceutical investment and development strategies. We note several current trends that are in-line with its changes to R&D incentives, including faster development of follow-on indications, an emphasis on clinical differentiation, and strategies to reformulate existing products in ways that reduce the impact of negotiation.

Still, the extent of the law's impacts, and management expectations for them, remain unclear. Negotiations between companies and Centers for Medicare and Medicaid Services (CMS) were ongoing in the first half of the year. Although negotiated prices hadn't yet been published, several executives —including from Johnson & Johnson (J&J), Novartis, and Bristol-Myers Squibb (BMS) —characterized the financial impact of negotiations as manageable. The absence of changes to financial outlooks suggests that prices were in-line with management expectations; investors seemed to share this view given the muted stock reaction following CMS' disclosure. But companies continue to navigate uncertainties, as future rounds of negotiated drugs may have a more significant financial impact, and Part D plan sponsors become more sensitive to high drug prices once the benefit's redesign takes effect in 2025.

We examine recent trends in investment and R&D, and discuss the extent to which these align or diverge from the expected impact of the IRA.

Key Findings

The industry is investing heavily in R&D to counteract impending losses of exclusivity for established revenue drivers.

As we've discussed in previous reports, the industry faces a significant patent cliff. This prompted several corporate restructuring and reprioritization efforts even before IRA was signed into law. A few companies, including Roche and Bristol-Myers Squibb, continue intensive pipeline reviews whereas others are winding down their R&D restructuring initiatives.

Despite reorganization programs at some companies, overall R&D investment continues to increase at a healthy clip. The companies we follow increased their R&D spending by an average of 12.9% and aggregate R&D spend by the group was up 27% compared with 1H23. Only three companies decreased R&D spending year-over-year.

Dealmaking continues, but at smaller transaction values.

M&A remains an important source of external drug development; however, the deals this quarter were smaller than in late 2023 and early 2024. At that time, many transactions centered on de-risked late-stage products that could contribute sales in the near term. In 2Q24, we saw a shift toward acquisitions with earlier-stage lead assets. The biggest deal this half was Gilead's $4.3 bn acquisition of CymaBay whereas 4Q23 saw several above $5 bn, including two over $10 bn (BMS/Karuna and AbbVie/Immunogen, both of which closed in 1Q24). Of the 14 M&A transactions with deal value of over $1 bn in the first half of 2024, oncology and immunology remained the top therapeutic areas, with five and three deals, respectively.

Recent trends in development are in line with incentives altered by the IRA.

We note that companies appear to be accelerating development and pursuing multiple indications in parallel. This compression of the drug's life cycle is aimed at achieving peak sales sooner and maximizing the lifetime value of the drug across the full range of its uses. This contrasts with the more traditional process of launching with a smaller indication and gradually adding additional indications (and potentially longer market exclusivity). Though these decisions are unlikely to be only due to the IRA, the law's incentives may amplify them. Shifting costs forward to more rapidly generate revenue requires companies to take on more development risk, forcing a more direct reckoning with products' true clinical prospects.

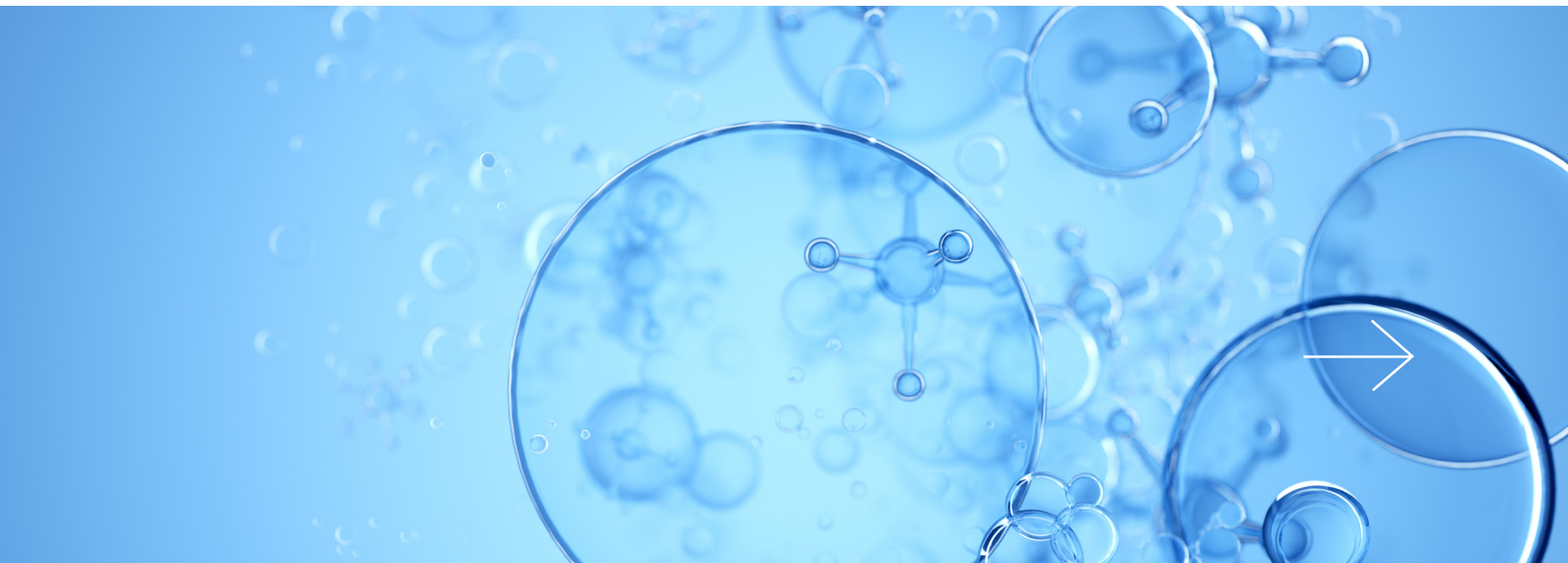
The higher hurdle for R&D investment also means "me-too" drugs are less likely to make the cut. This also tracks with changes to incentives resulting from the IRA. Two of the law's key provisions, negotiation

and Part D redesign, increase the value of demonstrating incremental benefits over standard of care and competitors in clinical trials. This is harder to achieve with drugs with similar mechanisms of action. Clinically differentiated products have more leverage – both in terms of Medicare negotiation and the ability to obtain favorable formulary placement and rebate terms with Part D plans, which are likely to become more exacting in their management of patient access.

Exemptions from negotiation for certain types of drugs may also elevate the priority of some programs. For example, we see a heightened focus on developing fixed-dose drug combinations (including subcutaneous formulations of cancer drugs), which CMS evaluates separately from their individual components. Consequences of other exemptions from negotiation, such as for drugs with orphan indications, have yet to become evident. Other federal policies to encourage orphan drug development appear to have created expectations that their market is sufficiently lucrative to trigger selection for negotiation. Some executives argue that companies will therefore limit development of orphan indications to qualify for the exemption. We are monitoring whether the pendulum is swinging to a new equilibrium between more common conditions and rare diseases, given that the latter have taken a growing share of FDA approvals in recent years.

Company executives characterized the financial impact of the first round of price negotiations as 'manageable'.

Management teams' responses to investors' questions during the 2nd quarter earnings relayed confidence in their ability to meet previously set growth targets. None of the companies made changes to their earnings or growth outlooks for the period after announcement of negotiated prices. The implication was that the prices were in-line with their expectations and were already incorporated in financial planning—a view shared by investors given the muted stock reaction following the announcement. Nevertheless, several executives reiterated claims that future impacts could be more severe and therefore negative for innovation. Companies are clearly trying to strike a delicate balance between reassuring investors about their financial strength while lobbying hard to change or even legally overturn aspects of the IRA.



Company and Portfolio-Level Developments

Pipeline rationalization and prioritization initiatives remain a dominant theme within the R&D divisions of the companies we follow. During the first half, Roche and Bristol-Myers Squibb provided additional details on their progress. Other companies are already in the later stages of their restructuring programs.

Each company's challenges and opportunities shape their reorganization plans. Several factors continue to predominate, including:

- Steep patent cliffs later in the decade are driving an urgency to develop and optimize growth drivers for the future
- Top-line pressure from loss of Covid sales or slower-than-expected product launches
- Changes in top management, with newcomers reviewing strategy to make their mark.

Table 1. Features of recent pipeline rationalization programs

Company	Pipeline Restructuring Initiatives
Biogen	⇢ Reduced products in development from 29 to 23 since early 2023 to diversify its pipeline away from heavy concentration in neurology after the controversy around aducanumab (Aduhelm), expanding efforts in immunology and rare disease. ⇢ Reduced overall R&D spending but increased investment in assets in which they have the most conviction.
Bristol-Myers Squibb	⇢ Restructuring initiative in progress and will include a "pipeline rationalization" program as well as a reduction of management layers. ⇢ Plans to reinvest savings in the most promising drug-development programs that are most likely to produce high returns.
Johnson & Johnson	⇢ Largely exited the vaccine and infectious disease space after COVID-19.

Company	Pipeline Restructuring Initiatives
Novartis	⇢ Reduced R&D projects by nearly 33% from 3Q21 to 3Q23, concentrating resources on those with the greatest potential to be blockbusters (which they defined as >$2 bn). ⇢ Most dramatic cull was in oncology, cutting 37 products and reflecting the company's prioritized focus on 4 key therapeutic areas: cardiovascular, renal and metabolic; immunology; neuroscience; and oncology.
Roche	⇢ Raised "the bar" in terms of what has to be met to remain in portfolio ⇢ Terminated 20% of its NMEs since 3Q23 while adding other assets, resulting in net reduction of NMEs (down 4) and line extensions (flat); most terminated products were based on clinical data and in Phase 1. ⇢ Upgraded their pipeline and required higher clinical hurdles before committing to continued investment ⇢ Acquired high-profile new drugs in obesity, immunology and cardiology. More details to be disclosed at Pharma Day on 9/30/24 but implementing fast-track status for high-priority research programs such as its obesity program acquired through Carmot earlier this year.

Despite their variations, these initiatives share the goal of concentrating resources on the most promising assets and cutting losses sooner on products when they show less differentiated clinical and competitive promise. We are also hearing about efforts to increase coordination between the R&D and commercial functions, as economic and financial considerations are likely to come into play earlier in the R&D process. As companies raise the bar, candidates with marginal advantages may be discontinued or deprioritized. (See Discontinued and Divested Products section below for more detail.)

R&D SPENDING

R&D investment continues to grow even as discipline around capital allocation tightens. On average, the companies we follow increased their R&D spend by 12.9% over 1H23 (outpacing 8.5% sales growth). The median increase was 8.9% (in line with last year), though with a wide range (-16% to +79%). Biogen showed the largest decline (-16%) following the mid-2023 approvals of three products and associated reductions in development costs, as well as an extremely disciplined approach to capital allocation. Meanwhile, NovoNordisk increased R&D spending nearly 80% to support numerous late-stage trials, primarily in its obesity and diabetes portfolio.

Of the 18 companies that have reported results, 13 increased R&D spending year-over-year while three decreased. Half of the companies reported increases of 10% or more. Growth in R&D spending tracks with restructuring plans and rationalization of

clinical programs. Not surprisingly, the three companies that reduced R&D spending (Novartis, Biogen and J&J) are farther along or have completed their pipeline prioritization programs, having culled certain programs but increased spending behind others.

While most companies have announced plans to reinvest cost-savings in their priority programs, decelerating spending growth is to be expected once these plans are implemented. This is not yet playing out in the recent financial results, but it's worth noting that Evaluate Pharma projects a deceleration in R&D growth for the industry between now and 2030. The report describes a number of reasons for this forecast, including the streamlining of pipelines due to growing commercial pressure; more reliance on M&A to replace genericizing blockbusters; and potential improvements in operational efficiencies due to technology and AI.

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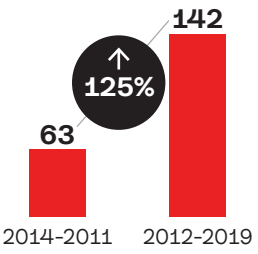
SHIFTS IN THERAPEUTIC FOCUS WITHIN R&D

Several companies have shifted their priorities to focus more intensively on therapeutic areas where they have greatest competency as they strive to improve their probability of success across the entire pipeline. Reducing the level of risk at the portfolio level is critical to this process, even if means assuming more financial risk from accelerating development on individual products. This exercise looks different for different companies; for some, it has been about narrowing their scope (e.g., J&J) while others seek more diversification (e.g., Biogen).

At the industry level, we see renewed attention on large disease areas that had received declining investment in recent years. For example, the breakthrough successes of Eli Lilly's and Novo Nordisk's obesity drugs have fueled investment in related cardiovascular and metabolic diseases, as well. Across companies, cardiovascular programs have seen the highest increase of any therapeutic area, up 29% in the last year (from mid-2023 to mid-2024). We have also seen renewed interest in psychiatric and respiratory drugs, which are among the highest-profile pipeline candidates, including late-stage products for schizophrenia (Bristol Myers' newly approved KarXT and AbbVie's Emraclidine) and COPD (Regeneron/Sanofi's Dupixent and other candidates by Amgen, AstraZeneca and GSK). Evaluate Pharma attributes this trend of "big drugs for big diseases" to pharma's shift away from drugs for rare diseases and cancer in favor of products that can more quickly fill post-patent-expiry gaps, of which there are more to come."

Nevertheless, oncology, central nervous system and immunology remain the three largest therapeutic areas in companies' pipelines and have been the focus of recent deal flow. Notably, the number of oncology programs has remained stable, and oncology as a proportion of total pipeline programs has ticked up slightly. However, part of this is driven by expansion into new platforms such as antibody-drug candidates and radioligands through recent acquisitions.

Novel orphan drugs CDER approved



Orphan drugs and indications appear to remain a priority for many companies. According to Citeline's annual R&D review, the number of pipeline drugs and clinical trials for rare diseases increased 7.6% and 4%, respectively, compared with last year. Since 2020, orphan drugs have made up more than 50% of drugs approved by FDA every year. From 2012-2019, CDER approved more than twice as many novel orphan drugs than in the previous 8-year period from 2004-2011 — 142 vs. 63, a 125% increase.

Nevertheless, perceptions about the likelihood of orphan drugs being selected for negotiation could contribute to a rebalancing from their current dominance in drug development. One area to watch is whether orphan drug development programs narrow in focus to indications within one designation. Another is whether development plans shift away from orphan indications or later stage/ treatment-resistant diseases as "gateways" to establish proof of concept or reach the market earlier. Because this is a common approach in oncology, it has become the basis for assertions that development of oncology drugs, particularly small molecules, could be disproportionately impacted by IRA.

DEALMAKING: M&A

M&A activity year-to-date remains relatively positive compared to 2022 and 2023, though the landscape has evolved over the last six months. According to *Scrip*, biopharma deal volume in 1H24 increased by 18% compared to the same period in 2024; however, overall deal value declined 28%. The 19 companies on our watchlist announced 14 deals in 1H24 at individual transaction values of $1 bn or more each (five of which were in the 2nd quarter).

Compared with late 2023 and early 2024, recent deals have been smaller, with a median value this quarter of $1.75 bn and a greater focus on earlier stage assets. The biggest deal announced in 1H24 came in February, with Gilead's $4.3 bn acquisition of CymaBay whereas 4Q23 saw several above $5 bn. Despite being flush with cash to invest, Novo-Nordisk's head of M&A recently observed that there are "fewer late-stage drugs and commercial-stage companies available for purchase". And although there is still an appetite for clinically proven and derisked candidates, companies likely need time to integrate recently acquired assets before pursuing additional transactions.

Beyond CymaBay, significant deals in the first quarter included Novartis's $2.84 bn acquisition of MorphSys, AstraZeneca's purchase of Fusion for $2 bn, J&J's acquisition of Ambrx for $1.9 bn, Sanofi 's $1.67 bn deal for Inhibrx, and the GSK/Aiolos Bio deal valued at $1.0 bn. Acquisitions of Eyebiotech (Merck), HiBio (Biogen) and Mariana Oncology (Novartis) led the deal flow in the 2nd quarter, with upfront outlays above $1 bn and total potential value in the $1.8-$3 bn range including future milestone payments.

Of the 14 M&A transactions with values of $1 bn or more in the first half of 2024, oncology and immunology remained the top therapeutic areas, with six and three deals, respectively. There were also two each in cardiometabolic and respiratory medicines, consistent with the increased focus in these areas.

Within oncology, we continue to see more deals with antibody-drug conjugates (ADCs) and radiopharmaceuticals rather than pure immuno-oncology plays. Notably, in May, AstraZeneca's CEO emphasized the strategic importance he places on "drug modalities that could be less vulnerable to generic and biosimilar competition",

Of the 14 M&A transactions with values of $1 bn or more in the first half of 2024, oncology and immunology remained the top therapeutic areas.

pointing to recent investments the company has made in cell and gene therapies, ADCs and radioconjugates. He noted that these new technologies "will deliver products that will be very difficult to copy rapidly by some generic companies". Pfizer's CEO expressed a similar view in the first quarter earnings call, when he said the company hopes to drive a tenfold increase in the proportion of oncology revenue from biologics *vs* small molecules. He sees this as important due to the prospect of a more durable revenue base, both because of the IRA but also the difficulty of copying complex biologics. For this year's $1 bn+ transactions, the lead assets are evenly split between small molecules and biologics (six each), while two have been radiopharmaceuticals.

Table 2. Select M&A transactions over $1 bn in total deal value

	Total potential transaction value ($ bn)	Key asset	Therapeutic area	Indication(s)	Molecule Size
AstraZeneca	**Total deal value: $5 bn**				
Amolyt Pharma	$1.05	AZP-3601	Endocrine	Hypoparathy-roidism; rare endocrine diseases	SM
Fusion	$2.4	FPI-2265	Oncology	mCRPC (castration-resistant prostate cancer)	Radio-conjugates
Biogen	**Total deal value: $1.8 bn**				
Human Immunology Biosciences (Hi-Bio)	$1.8 bn	felzartamab	Immunology		Bio
Boehringer Ingelheim	**Total deal value: $1.3 bn**				
Nerio Therapeutics	$ 1.3 bn	PTPN1 and PTPN2 inhibitors	Oncology	Cancers	SM
Eli Lilly	**Total deal value: $4.2 bn**				
Morphic	$3.2	MORF-057	Immunology, rheumatology	IBD (Crohn's disease, ulcerative colitis)	SM
Gilead	**Total deal value: $4.3 bn**				
CymaBay Therapeutics	$4.3	Livdelzi	Rare disease, liver disease	Primary biliary cholangitis	SM
GSK	**Total deal value: $1.45 bn**				
Aiolos Bio	$1.4	AIO-001	Respiratory	Asthma	Bio

	Total potential transaction value ($ bn)	Key asset	Therapeutic area	Indication(s)	Molecule Size
Johnson & Johnson	**Total deal value: $4.0 bn**				
Ambrx Biopharma	$1.9	ARX517	Oncology	Prostate, breast, and renal cell carcinoma	Bio
Yellow Jersey Therapeutics	$1.25	NM26	Immunology	Atopic dermatitis	Bio
Merck	**Total deal value: $3.9 bn**				
Eyebiotech (EyeBio)	$3.0	Restoret (EYE103)	Ophthalmology	Diabetic macular edema	Bio
Novartis	**Total deal value: $5.9 bn**				
Mariana Oncology	$1.75	MC-339	Oncology	Small cell lung cancer	SM (radio-pharmaceutical)
MorphoSys	$2.9	pelabresib	Oncology	Myelofibrosis	SM
Novo Nordisk	**Total deal value: $17.7 bn**				
Cardior	$1.1	CDR132L	Cardiovascular	Heart failure	SM
Sanofi	**Total deal value: $2.2 bn**				
Inhibrx	$2.2	INBRX-101	Respiratory	AATD	Bio

DEALMAKING: PRODUCT LICENSING AND COLLABORATIONS

In 1H24, companies announced 24 licensing and product-centered deals, including option agreements and research collaborations, but excluding manufacturing or technology partnerships. Similar to M&A activity, the transactions seem to be moving to earlier-stage assets and with relatively small upfront payments. Although the deals have a potential total value of nearly $30 bn. (including all milestone payments), the upfront payments were only 10% of this amount. Such terms also reflect big pharma's relatively strong negotiating position compared with a few years ago.

Of the 12 product deals with upfront payments of $100 mn or more, four were in oncology, which remains the largest therapeutic area. The transactions spanned a range of deal types, including option agreements and research collaborations in addition to product licensing deals. While ADCs and radiopharmaceuticals remain attractive lead assets as companies diversify within oncology, it's noteworthy that Takeda signed two strategic collaborations and option agreements focused on oral small molecule candidates. Immunology occupied the 2nd largest number of transactions above the $100 mn cutoff, though neuroscience agreements had the highest number overall (but at lower deal values reflecting the higher risk of these programs, several of which are still in preclinical development).

Table 3. Select product licensing deals and collaborations with over $100 mn upfront value

	Terms ($ mn) upfront	Key asset	Therapeutic profile	Molecule size
AbbVie				
FutureGen	$150	FG-M701	Immunology	Bio
Landos Biopharma	$137.5	NX-13	Immunology	SM
Gilead				
Arcus	$320	domvanalimab	Oncology	Bio
Novartis				
Arvinas	$150	ARV-766	oncology	SM
Calypso	$250	CALY-002	Immunology	Bio
Shanghai Argo Biopharmaceuticals	$185	RNAi	Cardiovascular	SM
Voyager	$100	TRACER capsids for GT	Rare diseases; gene therapy	Bio
Sanofi				
Novavax	$500	COVID vaccine	Infectious disease	Vaccine
Takeda				
AC Immune	$100	ACI-24.060	Neurology	Vaccine
Protagonist	$300	rusfertide	Rare disease; blood disorder	Bio
Kumquat Biosciences	$130	Immuno-oncology drug	oncology	SM
Ascentage Pharma	$300	Olverembatinib	oncology	SM

The lead assets in these larger transactions were evenly split between small molecules and biologics (5 each), while two are vaccines. Takeda and Novartis led the pack in announcing four deals each, though Sanofi's licensing agreement for Novavax' covid vaccine was the largest in-terms of upfront payments ($500 mn). Novartis and Shanghai Argo's agreement for RNAi therapeutics has the largest potential value of nearly $4.4 bn, though the upfront payment was just $185 mn for this phase 1 program.

Product-Level Developments and Updates

At the product-level we saw two noteworthy trends:

- lifecycle compression, including accelerated development and parallel processing of multiple indications and
- emphasis on fixed-dose combinations (FDCs) of existing blockbusters and pipeline candidates given their separate evaluation during the negotiation process.

Although parallel development can introduce more risk and cost into the drug development process (particularly in phase 3), companies appear to be accepting this tradeoff in efforts to achieve peak sales sooner and maximize overall returns. (This is also a potential factor contributing to manufacturers' efforts to mitigate risk at the company and portfolio level mentioned earlier.)

Some companies also appear to be employing strategies that could protect portions of a drug franchise from negotiation. For purposes of negotiation, CMS treats FDCs as distinct drugs from others containing a subset of the same ingredients. There has been increased discussion about FDCs, including in the obesity space as well as the subcutaneous formulations of cancer antibodies being developed by Merck, BMS and J&J.

These new formulations are generally comprised of a combination of hyalurinidase plus immuno-oncology agents, such as Keytruda, Opdivo and Darzalex. These formulations were already in development as a play to convert a large share of the market ahead of upcoming loss of exclusivity; however, IRA increases the importance of these line extensions. In its 2nd quarter earnings call, J&J management expressed confidence that Darzalex Faspro will be treated separately from the original IV formulation in negotiation. Merck's

CEO is now referring to Keytruda's loss of exclusivity as likely to be more of a "hill" than a "cliff" due to the subcutaneous opportunity. Evaluate's recent list of the top ten most valuable pipeline candidates listed the subcutaneous version of Keytruda (MK-3475 SC) in 5th place, with $8 bn in 2030 sales. Moreover, Keytruda is expected to still be in the top 10 in 2030, even after its 2028 patent expiration and a 40% decline in annual sales to $14.6 bn.

DISCONTINUED OR DIVESTED PRODUCTS

The majority of product and indication discontinuations that occurred this year were for clinical reasons, which is normal course of business for this industry. Other programs were terminated or deprioritized for insufficient differentiation from existing products or products in development,

as manufacturers refined their focus on specific therapeutic areas and applied higher hurdles for capital allocation. Both the numbers and management commentary reflected heightened discipline and more willingness to discontinue a trial or program if the data did not support continued investment. Indeed, BMS, Roche and Takeda have culled the most programs as they implement LOE-driven pipeline rationalization programs and reinvested the proceeds into higher quality assets.

Below are several examples of programs where strategic and competitive factors were considered in their terminations, which reinforced the message that "me-too" drugs may no longer make the cut. (*Note: Companies are not required to disclose products or programs they discontinue unless the decision is financially material, so this count is not comprehensive.*)

Table 4. Selected Products/ Research Programs Terminated for Strategic/ Competitive Reasons

Company	Product or Indications	Comments
Novartis	Omnusarib (PIII; lung cancer)	Decision made "in light of increasing options available to patients with KRAS G12C-driven cancers".
AbbVie	ABBV-916 (PII: Alzheimer's Disease monotherapy)	Terminated because "emerging efficacy and safety profile in this study is similar to what has been demonstrated by approved agents".
Amgen	AMG786 (PI; obesity)	Not better than its other candidates in development.
GSK	HPV vaccine (PII)	Decided it wouldn't be "best in class"
BMS	Alnuctamab (PII; multiple myeloma)	Company cited existing competition and company's priority on "investing in opportunities where it can deliver the highest return for patients and stakeholders."

In the first half of 2024, the companies we follow discontinued 70 products (see Table 5). This reflects an increase compared with 84 product discontinuations during FY 2023. We also note a slight increase in the percentage of discontinuations that were in oncology, which was 44% through mid-year compared with 38% in 2023. (It's worth noting that oncology is also where we saw the most dealmaking activity so the number of development programs is roughly flat year over year). Of the 31 discontinued cancer products, only six were small molecules.

We continue to see little evidence that the time differential before negotiation has driven decisions to terminate small molecule R&D programs, though executives frequently claim to factor it into decision making. Year-to-date, 20 small molecules and 41 biologics were discontinued, with the former comprising 29% of the total compared with 45% in 2023. (It's also worth bearing in mind that biologics have made up nearly half of the FDA's novel approvals for the last two years.) Discontinuation decisions, to the extent that they were disclosed in earnings releases, appeared primarily driven by scientific and competitive considerations.

Small molecules will continue to have an advantage over biologics in many situations because they are easier to manufacture, reformulate and combine with other agents, and are preferred by patients over injectables. Moreover, small molecules are better suited biologically to treat certain chronic conditions, including several that are common in the Medicare population.

Based on data from Evaluate for the companies in our sample, the number of programs in clinical development (Phase 1 to Phase 3) declined about 2% between mid-2023 and September 2024. Thirteen of 18 companies reporting earnings have decreased their total number of programs, including line extensions, with the greatest reduction in phase 2.

We continue to monitor changes from this baseline to detect any emerging trends in therapeutic areas or molecule size.

Table 5. Product discontinuations by therapeutic area and molecule size

Company	Therapeutic areas	Small molecule: biologic*	No. products or projects
AbbVie	Oncology	0:1	1
Amgen	Oncology, metabolic	1:1	2
AstraZeneca	Hematology	1:0	1
Biogen	Neurology	1:4	5
BMS	Oncology, immunology	1:4	5
Gilead	Oncology	0:1	1
GSK	Rare disease, infectious disease	2:3	7
J&J	Oncology	0:1	1
Eli Lilly	Oncology, metabolic, immunology	1:1	4
Merck	Oncology	0:1	1

Company	Therapeutic areas	Small molecule: biologic*	No. products or projects
Novartis	Oncology	1:1	2
Novo Nordisk	Metabolic	2:0	2
Pfizer	Oncology, neurology, infectious disease, rare disease, respiratory	1:4	6
Roche	Oncology, neurology, infectious disease	7:9	17
Sanofi	Oncology, metabolic, immunology, musculoskeletal	0:3	4
Takeda	Oncology, immunology, rare disease, neurology, infectious disease	2:7	11
TOTAL		**20:41**	**70**

*Excluding vaccines and programs with undisclosed technologies
Note: Counts reflect unique products, and do not reflect discontinuations at the indication level. Counts based on disclosures by companies based on materiality thresholds and are not comprehensive.

Discussion

Current trends in pipeline prioritization and the acceleration of clinical development programs are largely driven by the industry's response to LOEs for many of its biggest blockbuster products. This process naturally pushes companies to direct resources to their most promising drugs and pipeline candidates.

Given the urgency of pipeline replenishment, it remains the primary driver of investment decisions through the first half of 2024. As Genentech's new CEO said in an August interview, although they "constantly track what are the potential downstream effects of this legislation,... at this point, [they] have not made any changes to the science [they]'re pursuing." Executives at Merck and Amgen have expressed similar views, though there is variability among manufacturers.

Nevertheless, efforts to optimize investments and development plans fall in line with incentives created by the IRA, and may be amplified by it. For example, Medicare negotiation and increased plan sponsor liability in Part D heighten the value of differentiation and improvement over standard of care, adding to the likelihood that drug candidates offering marginal improvements don't make the cut. It also amplifies the appeal of parallel development across indications and favors larger indications over smaller ones.

Similarly, manufacturers have already taken note that line extensions involving additional active ingredients – many already underway – allow them avoid qualifying for negotiation for this portion of their franchise. Paradoxically, we expect that this gives small molecules an advantage over biologics, because they are easier to manufacture, reformulate and combine with other agents, are preferred by patients over injectables, and often better suited biologically to treat certain chronic conditions that are common in the Medicare population.

Yet as the intersection between ongoing R&D efforts and the IRA becomes more obvious, new uncertainties are also emerging. The first round of Medicare negotiation held few negative surprises for industry, but executives and analysts question whether this year's process and results are representative of future iterations, which are expected to include a growing share of drugs that have been largely immune from rebate negotiations in Part D. The redesign of Part D, which goes into effect in 2025, is likely to prompt significantly more restrictive management of formularies as plans attempt to manage spending on high priced drugs, and also raises questions about the formulary placement of drugs that have been negotiated by Medicare.

Unsurprisingly, companies voice a desire for more transparency about how prices were negotiated and what factored into CMS' acceptance or refusal of offers, including the roles of clinical attributes

Medicare negotiation and increased plan sponsor liability in Part D heighten the value of differentiation and improvement over standard of care, adding to the likelihood that drug candidates offering marginal improvements don't make the cut.

and therapeutic alternatives. There are also questions about how R&D spending, including post-marketing investment, and other cost data were incorporated into the decisions, which are particularly salient in light of the large investments still flowing into new indications for drugs that could be subject to negotiation in coming years.

As the year moves to a close, we expect that companies will move to wrap up their restructuring programs and commence in earnest with the development efforts needed to bring recent acquisitions and licensing deals to the commercial stage.

Trends to watch with regard to influence of the IRA include launch sequence and continued efforts to develop multiple indications in parallel; development of orphan indications within one or multiple designations; and how aggressively companies prune underperforming or undifferentiated pipeline candidates. In addition, we will be monitoring whether companies continue to invest in post-marketing studies of drugs that appear likely to be selected for negotiation in the future or that might benefit from additional differentiation against their competitors.

Appendix

Companies included in our analysis

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

ATI Advisory

About ATI Advisory

ATI Advisory is a healthcare research and advisory services firm dedicated to system reform that improves health outcomes and makes care better for everyone. ATI guides public and private leaders in solving the most complex problems in healthcare through objective research, deep expertise, and bringing ideas to action. For more information, visit atiadvisory.com.

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