EvaluatePharma®

World Preview 2019, Outlook to 2024

Evaluate

Welcome to the EvaluatePharma®
World Preview 2019, Outlook to 2024

The twelfth edition of EvaluatePharma's World Preview brings together many of our analyses to provide a top level insight, from the world's financial markets, into the expected performance of the industry between now and 2024. Based on EvaluatePharma's coverage of the world's leading pharmaceutical and biotech companies, the World Preview highlights trends in prescription drug sales, patent risk, R&D spend, global brand sales and market performance by therapy area. Also included this year are analyses on Worldwide Pharma Innovation with insights into risk and reward in the pharmaceutical industry, using data from EvaluatePharma Vision®.

Complimentary copies of the full report can be downloaded at:

www.evaluate.com/PharmaWorldPreview2019

Foreword

The EvaluatePharma® World Preview 2019 comes at one of the most exciting points in the industry's development. The convergence of tech and health is becoming reality, while the promise of cell and gene therapy is finally being delivered to patients.

With such technological advances that could offer hope of real cures and the growing demand from emerging economies, reaching the report's forecast of $1.18trn sales in 2024 could become a reality.

As ever there are potential hurdles to achieve these sales. The advances in cutting edge science are, for now, outpacing the traditional pricing and reimbursement systems the industry has been built on. This disconnect is leaving both patients and payers wondering how accessible these life-altering products will be.

> Spark has charged $850,000 for its gene therapy product Luxturna and many are expecting Novartis to ask upwards of $2m for its SMA product Zolgensma.

And as more and more gene therapies enter the market the questions around their additional burden on an already stretched healthcare industry will only intensify.

The commercialisation of these new technologies come as discussions around wider drug pricing are heating up ahead of the 2020 US presidential elections – and regardless of the outcome, the political and social momentum to address rising drug prices is unlikely to go away.

But the picture is not all gloom. Even with pricing pressure there remains significant unmet need within the industry, which will continue to drive innovation and drug sales. One example of this is that the report finds that the most valuable R&D treatment is Vertex Pharmaceuticals' orphan drug triplet treatment for cystic fibrosis, with 2024 sales forecast to hit $4.27bn.

The increasing convergence of tech and healthcare will also provide fresh opportunities for the industry.

We are already seeing the use of real world evidence to measure the actual performance of drugs post approval and drive future investment decisions. Machine learning techniques are being employed not only to speed up drug discovery, but also drug development with the hope that data-driven approaches will help reduce R&D costs and industry failure rates.

Foreword

> New possibilities are emerging everyday as these novel approaches to healthcare, which also include whole genome sequencing and wearable technology, allow the industry to move into a new era of healthcare.

Ripping up the old models of drug development, discovery and commercialisation to take advantage of this new wave of innovation will be hard, but if pharma wants to meet current growth forecasts change is inevitable.

Ryan Waters
Analyst, Evaluate Ltd

Lisa Urquhart
Editor, EP Vantage

Analysis Highlights

Worldwide Prescription Drug Sales 2019-24 in figures

$+6.9\%$ CAGR* 2019-24

Drivers			Brakes	
62	New FDA NME approvals in 2018, up from 55 in 2017		Sales at risk between 2019 and 2024 due to patent expiries	$198bn
$109bn	Additional sales in 2024 from orphan drugs vs. 2018		Anti-rheumatics decline as Humira, Enbrel and Remicade face competition	-1.0% CAGR 2018-24
19.4%	Proportion of 2024 industry sales from oncology therapies ($237bn)		Clinical development spend per approval for cardiovascular drugs, the highest of any therapy area. Is the risk worth the reward?	$1bn
431	Number of FDA NME approvals anticipated from current clinical pipeline		R&D as a proportion of prescription sales in 2024, down from 21.6% in 2018	18.0%

* Compound Annual Growth Rate.

- Prescription drug sales expected to reach $1.18trn in 2024. Immuno-oncology line extensions significantly contribute to growth; emergence of novel technologies such as cell and gene therapy mark an inflection point in pharma's evolution

- Pfizer will be the leading prescription drug company in 2024 with sales of $51.2bn, ahead of Novartis and Roche

Analysis Highlights

- Keytruda set to be the top selling drug worldwide in 2024, as Humira loses top spot due to adalimumab biosimilar entry in the EU and expected USA biosimilar competition from 2023

- Should Bristol Myers-Squibb complete its intended acquisition of Celgene and forecast projections for a combined portfolio hold, the combined entity would be the 3rd largest pharmaceutical company based on 2024 prescription sales

- Vertex's triple combination, VX-659/VX-445 + Tezacaftor + Ivacaftor, is anticipated to be the most valuable project in the pharmaceutical industry pipeline with an NPV of close to $20bn

- Oncology is the area with the largest proportion of clinical development spending with 40% of total pipeline expenditure, with close to 20% market share of pharma sales in 2024

- R&D spend is forecast to grow at a CAGR of 3.0% to 2024, lower than the CAGR of 4.2% between 2010 and 2018, partially driven by companies focusing on smaller indications with lower clinical development cost burden

- Roche leads the way in biotechnology, with a forecasted $38.7bn of biologic sales in 2024, despite a decrease in biotech market share of -5.4% owing to the effect of biosimilars

- Johnson & Johnson are forecast to narrowly overtake Roche to be the biggest spender on pharmaceutical R&D in 2024

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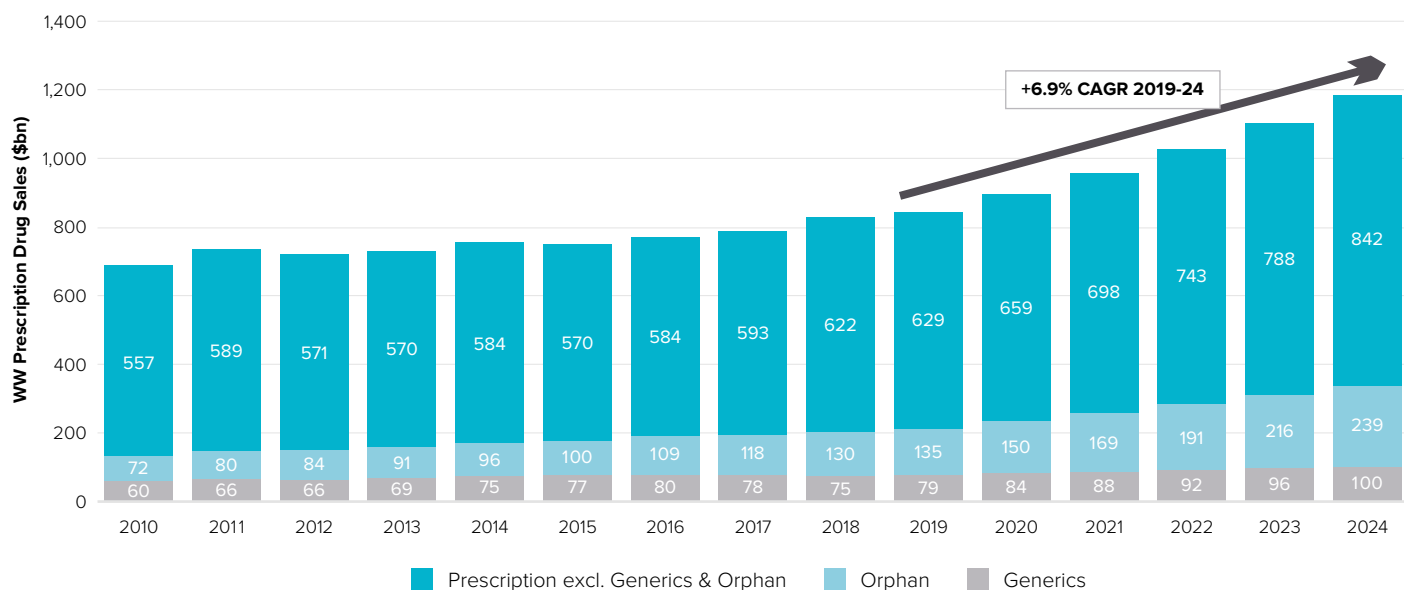**Contents**

Worldwide Prescription Drug Sales (2010-2024)

Prescription drug sales CAGR for 2019 through 2024 three times that in 2010 through 2018; Orphan drug market to almost double.

Prescription drug sales for 2010 through 2018 grew at a CAGR of +2.3%. This can be compared to the forecast annual CAGR of +6.9% for 2019 through 2024 with expected sales to reach $1.18trn. The growth rate for the prescription market in 2019 is forecast to be +2.0%, which depicts a decline in growth rate compared to 2018 (+5.0%). So far the industry has seen a major set-back with one of the biggest failures, aducanumab, which was discontinued in Phase 3 trials for Alzheimer's disease. The Trump administration has been in the news for discussions related to changes to the prescription drug policy which could be implemented in early 2020. These changes could be challenging for pharmaceutical drug manufacturers, as it could affect drug prices in one of the largest markets in the world if implemented. On the positive side, the industry has seen the launch of Ultomiris (Alexion Pharmaceuticals) and Takhzyro (Takeda). Consensus forecasts indicate that $198bn of sales are at risk between 2019 and 2024, with 2023 set to see the expiry of key patents for a number of biologics including Humira and Stelara. Both of these products are still forecast to retain spots within the world's top 10 selling drugs in 2024.

Figure 1: Worldwide Total Prescription Drug Sales (2010-2024)

Source: EvaluatePharma, May 2019

+6.9% CAGR 2019-24

Year	Generics	Orphan	Prescription excl. Generics & Orphan
2010	60	72	557
2011	66	80	589
2012	66	84	571
2013	69	91	570
2014	75	96	584
2015	77	100	570
2016	80	109	584
2017	78	118	593
2018	75	130	622
2019	79	135	629
2020	84	150	659
2021	88	169	698
2022	92	191	743
2023	96	216	788
2024	100	239	842

Figure 2: Worldwide Sales At Risk from Patent Expiration (2010-2024)

Source: EvaluatePharma, May 2019

Year	Total Sales at Risk	Expected Sales Lost	% Market at Risk
2010	29	12	+4.2%
2011	34	20	+4.6%
2012	52	36	+7.2%
2013	33	23	+4.5%
2014	31	20	+4.1%
2015	52	18	+6.9%
2016	39	18	+5.1%
2017	33	30	+4.2%
2018	39	23	+4.7%
2019	39	20	+4.7%
2020	14	19	+1.6%
2021	16	14	+1.6%
2022	40	16	+3.9%
2023	57	23	+5.2%
2024	32	22	+2.7%

Patent Analysis: 'Total Sales at Risk' represents the worldwide product sales in the year prior to patent expiry but allocated to the year of expiry. E.g. Plavix had sales of $7.1bn in 2011, this is shown above as 'At Risk' in 2012.

Table 1: Worldwide Prescription Drug Sales (2010-2014)

Source: EvaluatePharma, May 2019

Year	WW Prescription Sales ($bn)														
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Prescription	689	734	721	730	755	747	772	789	828	844	893	955	1,027	1,100	1,181
Growth per Year		+6.6%	-1.7%	+1.3%	+3.4%	-1.0%	+3.3%	+2.2%	+5.0%	+2.0%	+5.7%	+7.0%	+7.5%	+7.1%	+7.4%
Change vs. June 2018 ($bn)									-2	-28	-34	-43	-43	-34	-23
Generics	60	66	66	69	75	77	80	78	75	79	84	88	92	96	100
Generics as % of Prescription	8.7%	9.0%	9.2%	9.5%	9.9%	10.3%	10.3%	9.9%	9.1%	9.4%	9.4%	9.2%	9.0%	8.7%	8.4%
Prescription excl. Generics	629	668	655	661	680	670	692	710	753	765	809	867	935	1,004	1,081
Growth per Year		+6.3%	-2.0%	+0.9%	+2.9%	-1.4%	+3.3%	+2.6%	+6.0%	+1.6%	+5.8%	+7.1%	+7.8%	+7.4%	+7.7%
Orphan	72	80	84	91	96	100	109	118	130	135	150	169	191	216	239
Prescription excl. Generics & Orphan	557	589	571	570	584	570	584	593	622	629	659	698	743	788	842

Prescription incl. Generics CAGR 2019-24 +6.9%

Note: Sales to 2018 based on company reported sales data. Sales forecasts to 2024 based on a consensus of leading equity analysts' estimates for company product sales and segmental sales.

Table 2: Worldwide Sales At Risk from Patent Expiration (2010-2024)

Source: EvaluatePharma, May 2019

Year	WW Prescription Sales ($bn)														
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Total Sales at Risk	29	34	52	33	31	52	39	33	39	39	14	16	40	57	32
Expected Sales Lost	12	20	36	23	20	18	18	30	23	20	19	14	16	23	22
% Market at risk	4.2%	4.6%	7.2%	4.5%	4.1%	6.9%	5.1%	4.2%	4.7%	4.7%	1.6%	1.6%	3.9%	5.2%	2.7%

Worldwide Prescription Drug Sales in 2024: Top 10 Companies

Pfizer returns to top spot for worldwide sales of prescription drugs in 2024.

As the top three continue to battle it out, EvaluatePharma® finds that Pfizer has once again pushed ahead of Novartis and Roche for the Worldwide Prescription Drug Sales number one spot in 2024. Novartis is also due to jump up to the number two spot after exhibiting 2.3% CAGR between 2018-24 as opposed to Roche's 0.8% CAGR.

Bristol-Myers Squibb has fallen out of the top 10 largely due to loss of Opdivo market-share to Keytruda and being beaten to the mega-merger table by Takeda with its acquisition of Shire in January 2019. As a result, Takeda leaps up seven places in the

ranking between 2018 and 2024 with an impressive 10.8% CAGR. Bristol-Myers Squibb is unlikely to be outside the top 10 for too long however, as on January 3rd, 2019, the company announced a $74bn acquisition of Celgene that is yet to complete.

AstraZeneca has also shown impressive 7.7% CAGR, long promised by CEO Pascal Soriot, due to breakthroughs in the Chinese market and high sales of its oncology products Tagrisso and Lynparza, rather than M&A.

Only Takeda and AstraZeneca are able to increase market share between 2018 and 2024. The Top 10 Pharma companies showed -6.6% market share growth overall, with Roche alone contributing -1.4% to that figure.

Figure 3: Worldwide Prescription Drug Sales in 2024: Top 10 Companies

Source: EvaluatePharma, May 2019
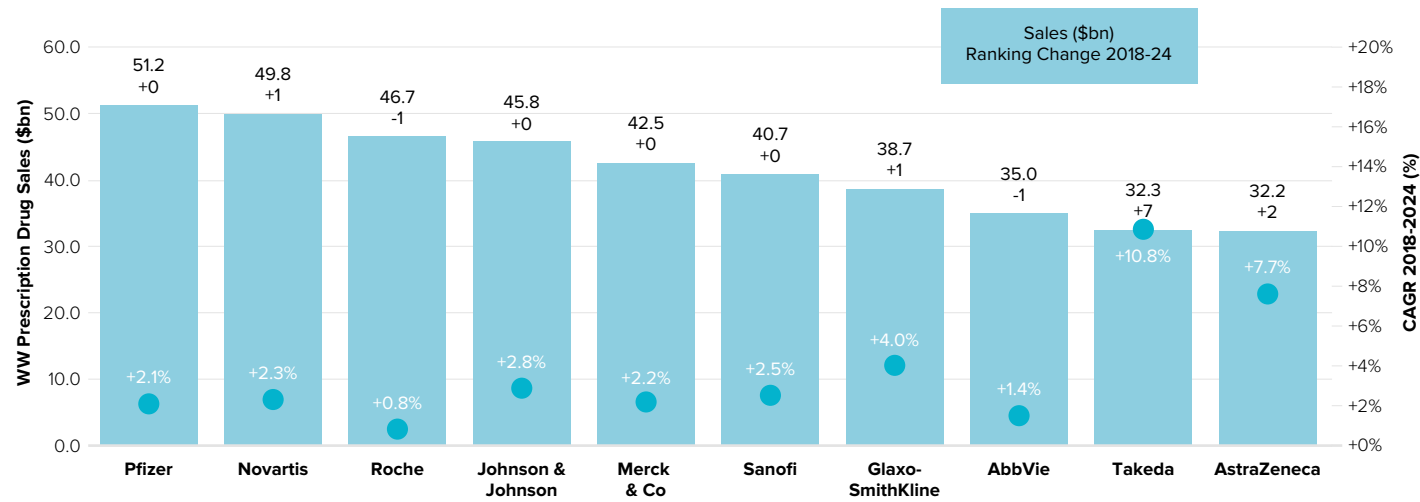
Table 3: Worldwide Prescription Drug Sales (2018-2024):
Top 10 Companies & Total Market

Source: EvaluatePharma, May 2019

| Rank | Company | WW Prescription Sales ($bn) | | | WW Market Share | | | Rank |
		2018	2024	CAGR	2018	2024	Chg. (+/-)	Chg. (+/-)
1.	Pfizer	45.3	51.2	+2.1%	5.5%	4.3%	-1.1pp	+0
2.	Novartis	43.5	49.8	+2.3%	5.3%	4.2%	-1.0pp	+1
3.	Roche	44.6	46.7	+0.8%	5.4%	4.0%	-1.4pp	-1
4.	Johnson & Johnson	38.8	45.8	+2.8%	4.7%	3.9%	-0.8pp	+0
5.	Merck & Co	37.4	42.5	+2.2%	4.5%	3.6%	-0.9pp	+0
6.	Sanofi	35.1	40.7	+2.5%	4.2%	3.4%	-0.8pp	+0
7.	GlaxoSmithKline	30.6	38.7	+4.0%	3.7%	3.3%	-0.4pp	+1
8.	AbbVie	32.1	35.0	+1.4%	3.9%	3.0%	-0.9pp	-1
9.	Takeda	17.4	32.3	+10.8%	2.1%	2.7%	+0.6pp	+7
10.	AstraZeneca	20.7	32.2	+7.7%	2.5%	2.7%	+0.2pp	+2
	Total Top 10	345.4	414.8	+3.1%	41.7%	35.1%	-6.6pp	
	Other	482.3	766.0	+8.0%	58.3%	64.9%		
	Total	827.8	1,180.8	+6.1%	100.0%	100.0%		

Note: Takeda acquired Shire on January 8th 2019 for $64.1bn, thus inheriting all of Shire's forecast revenue. This accounts for the significant increase in Worldwide Prescription Drug Sales between 2018 and 2024. At the time of writing, Takeda 2018 prescription sales are based on a consensus of leading equity analysts' estimates.

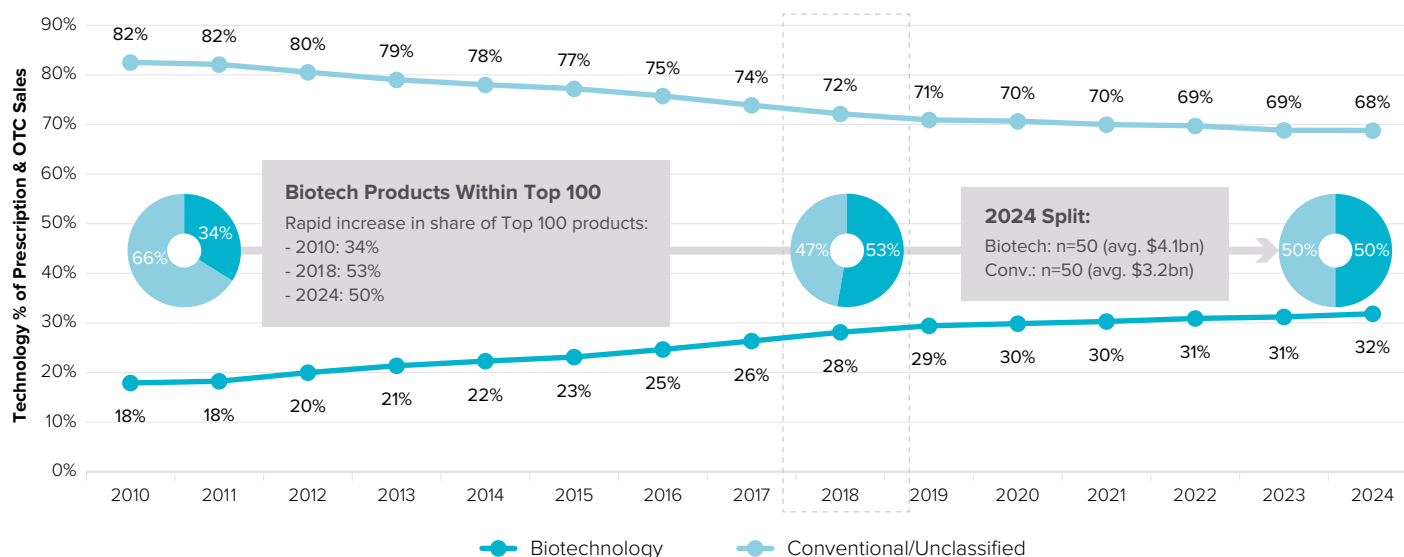# Worldwide Prescription Drug & OTC Sales by Technology (2010-2024)

Biotech product sales overtake conventional product sales in the top 100 product by sales for the first time. Merck & Co is forecast to climb to second position after Roche in biotech sales.

The industry uptake of biotech products is forecast to rise from 28% to 32% between 2018 and 2024. In contrast, the top 100 product sales share of biotech and conventional products is forecast to stabilise around a 50/50 split in 2024. Eli Lilly is set to become the sixth largest seller of biotech products in 2024, mostly driven by an increase in Trulicity forecast. Merck & Co, with a CAGR of 10.9%, is forecast to be the best performer in the next six years gaining five positions in the ranking from 2018. AbbVie has the lowest CAGR (-4.9%) of the top 10 companies, primarily due to Humira's patent expiry.

Figure 4: Worldwide Prescription Drug & OTC Pharmaceutical Sales: Biotech vs. Conventional Technology

Source: EvaluatePharma, May 2019

Biotech Products Within Top 100
Rapid increase in share of Top 100 products:
- 2010: 34%
- 2018: 53%
- 2024: 50%

2024 Split:
Biotech: n=50 (avg. $4.1bn)
Conv.: n=50 (avg. $3.2bn)

Table 4: Worldwide Prescription Drug & OTC Sales by Technology (2010-2024)

Source: EvaluatePharma, May 2019

Technology	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Biotechnology	18%	18%	20%	21%	22%	23%	25%	26%	28%	29%	30%	30%	31%	31%	32%
Conventional/Unclassified	82%	82%	80%	79%	78%	77%	75%	74%	72%	71%	70%	70%	69%	69%	68%
Total Prescription & OTC Sales	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Technology	WW Sales ($bn)														
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Biotechnology	129	140	151	163	176	181	199	217	243	258	277	300	327	356	388
Conventional	439	463	441	433	444	438	443	444	455	455	478	511	547	584	626
Other Unclassified Sales	154	169	166	173	174	163	166	164	165	166	174	182	191	200	209
Total Prescription & OTC Sales	**722**	**771**	**758**	**769**	**794**	**782**	**808**	**825**	**864**	**880**	**929**	**992**	**1065**	**1140**	**1222**

Table 5: Worldwide Prescription Drug Sales from Biotechnology in 2024: Top 10 Companies

Source: EvaluatePharma, May 2019

Rank	Company	WW Sales ($bn)			WW Market Share			Rank Chg.
		2018	2024	% CAGR 18-24	2018	2024	Chg. (+/-)	
1.	**Roche**	37.5	**38.7**	+0.5%	15.4%	10.0%	-5.4pp	+0
2.	**Merck & Co**	15.3	**28.3**	+10.9%	6.3%	7.3%	+1.0pp	+5
3.	**Sanofi**	16.8	**24.4**	+6.4%	6.9%	6.3%	-0.6pp	+2
4.	**Amgen**	19.2	**21.5**	+1.9%	7.9%	5.6%	-2.3pp	-1
5.	**Johnson & Johnson**	16.0	**20.9**	+4.6%	6.6%	5.4%	-1.2pp	+1
6.	**Eli Lilly**	12.8	**19.8**	+7.5%	5.3%	5.1%	-0.2pp	+2
7.	**Novo Nordisk**	17.1	**15.8**	-1.3%	7.0%	4.1%	-2.9pp	-3
8.	**AbbVie**	20.7	**15.3**	-4.9%	8.5%	3.9%	-4.5pp	-6
9.	**Bristol-Myers Squibb**	11.2	**15.1**	+5.1%	4.6%	3.9%	-0.7pp	+0
10.	**Pfizer**	11.0	**14.5**	+4.8%	4.5%	3.8%	-0.8pp	+0

Table 6: Worldwide Prescription Drug Sales from Top 100 Products

Source: EvaluatePharma, May 2019

| Technology	WW Sales ($bn)			As a %		
	2010	2018	2024	2010	2018	2024
Biologics	88	162	178	34%	53%	50%
Small molecules	174	143	179	66%	47%	50%
Total	**262**	**306**	**357**	**100%**	**100%**	**100%**

Pharma Innovation: Risk & Reward

Oncology continues to be the main R&D focus area in the biopharma industry.

EvaluatePharma® finds oncology to be the area with the highest forecasted clinical development expenditure, unsurprisingly leading to the highest forecast number of FDA approvals of any therapy area. At $0.7bn of clinical development spend per approval (based on sunk R&D cost, and product-specific PTRS from EvaluatePharma Vision®), oncology is one of the more expensive areas in which to develop new therapies, but this cost is forecast to result in $78.2bn in net present value (NPV), or 30.6% of the total NPV resultant from the current clinical pipeline. Systemic anti-infectives demonstrate a lower clinical development cost per approval with $0.2bn, but the relatively lower unmet need and recent pricing pressures lead to NPV of the current pipeline of just $8.3bn. With a forecasted clinical development cost per approval of $1.0bn, cardiovascular drugs show the highest R&D cost burden, due to the large-scale nature of their trials; the low number of risk adjusted approvals and relatively low NPV of $5.6bn is perhaps resultant of this financial barrier to entry.

Figure 5: Clinical Development Spend vs Risk Adjusted FDA Approvals by Therapy Area

Source: EvaluatePharma Vision®, May 2019
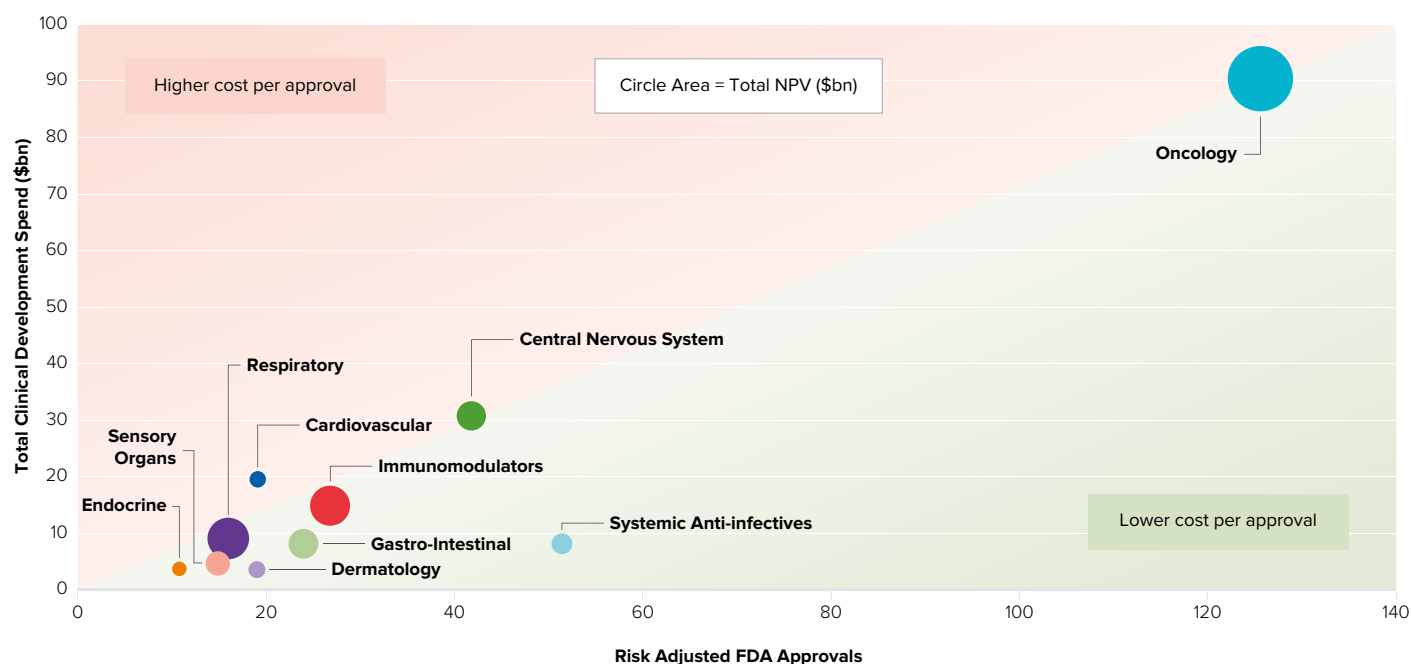
Fill in the gaps on pharma with EvaluatePharma Vision

- Oncology may be one of the most expensive therapy areas, but _____ is forecast to provide the best returns.

- On average, it typically costs _____ to run a phase III trial program for _____.

- Within your portfolio, the product with the highest risk profile is _____ when benchmarked against other drugs in development.

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Table 7: Clinical Development Spend vs Risk Adjusted FDA Approvals by Therapy Area of Current US Pipeline

Source: EvaluatePharma Vision®, May 2019

Rank	Therapeutic Category	Clinical Development Spend ($bn)	Risk Adjusted FDA Approvals	Total NPV ($bn)	Percentage of Total			Clinical Development Spend per Approval ($bn)
					Clinical Development Spend	Risk Adjusted FDA Approvals	NPV	
1.	**Oncology**	91.1	126	78.2	40.0%	29.1%	30.6%	0.7
2.	**Central Nervous System**	31.0	42	16.7	13.6%	9.7%	6.6%	0.7
3.	**Musculoskeletal**	19.9	24	21.2	8.8%	5.6%	8.3%	0.8
4.	**Cardiovascular**	19.7	19	5.6	8.7%	4.4%	2.2%	1.0
5.	**Immunomodulators**	15.0	27	29.3	6.6%	6.2%	11.5%	0.6
6.	**Respiratory**	9.2	16	32.1	4.0%	3.7%	12.6%	0.6
7.	**Gastro-Intestinal**	8.4	24	17.0	3.7%	5.5%	6.7%	0.4
8.	**Systemic Anti-infectives**	8.2	51	8.3	3.6%	11.9%	3.2%	0.2
9.	**Blood**	6.4	21	20.4	2.8%	4.9%	8.0%	0.3
10.	**Sensory Organs**	4.9	15	11.9	2.1%	3.4%	4.7%	0.3
11.	**Dermatology**	3.9	19	5.9	1.7%	4.4%	2.3%	0.2
12.	**Endocrine**	3.9	11	4.5	1.7%	2.5%	1.8%	0.4
13.	**Genito-Urinary**	2.0	8	0.3	0.9%	1.8%	0.1%	0.3
	Various	4.1	29	3.6	1.8%	6.8%	1.4%	0.1
	Total	**227.5**	**431**	**255.2**	**100%**	**100%**	**100%**	

Inclusion criteria: Analysis refers to products which are in US clinical development (Phase 1-3), or filed with the FDA. Only NMEs with no prior global approval are included, with risk adjustments applied to approval of US lead indication only, follow-on indications are excluded.

Methodology: 'Clinical Development Spend' by Therapeutic Category is calculated using EvaluatePharma Vision's proprietary R&D Cost model and represents the sum of the costs of all commercial clinical trials currently listed on ClinicalTrials.gov for products currently in active clinical development (PI-Filed) – clinical development spend is typically 50% of total R&D expenditure. 'Risk Adjusted FDA Approvals' represents the total number of approvals expected from the industry's current pipeline by Therapeutic Category after applying EvaluatePharma Vision's proprietary product-specific PTRS (Probability of Technical & Regulatory Success) to adjust for the level of risk associated with each pipeline candidate. NPV sourced from EvaluatePharma Vision on May 14th, 2019.

Colour coding: The colour applied to 'Risk Adjusted FDA Approvals' and 'WW 2024 Sales' percentages refer to being above (green) or below (red) the 'Clinical Development Spend' percentage. The blue colour scale reflects the range within that column, with the darker shade representing a higher number.

Curious about the data in the table above?

With EvaluatePharma Vision you can drill deeper into each therapy area to quickly discover which companies and products are best positioned for success.

EvaluatePharma Vision fills in the gaps, so you can go beyond top-level trends to understand what they really mean for you and your R&D pipeline.

The only single view of the risk and reward of the R&D landscape.

EvaluatePharma Vision

Top 10 Most Valuable R&D Projects (Ranked by Net Present Value)

Vertex's triple combination, VX-659/VX-445 + Tezacaftor + Ivacaftor, remains the most valuable project in the pharmaceutical industry pipeline.

With Vertex Pharmaceuticals already dominating the cystic fibrosis space, its therapy combining ivacaftor (available as Kalydeco) and tezacaftor (available in combination with ivacaftor as Symdeko) with VX-445 or VX-659, another cystic fibrosis transmembrane regulator (CFTR) corrector, is looking to further reinforce the company's position.

The list is dominated by large-cap pharma companies, however, a couple of other projects from mid-cap companies join Vertex's triplet. Immunomedics is looking to put its stamp on the oncology market with its antibody-drug conjugate sacituzumab govitecan. Meanwhile the FDA has agreed to an accelerated approval pathway for Global Blood Therapeutics' oral therapy, voxelotor, for sickle cell disease.

AbbVie is pushing its own JAK1 inhibitor, upadacitinib, into the rheumatoid arthritis and ulcerative colitis markets and Eli Lilly, its novel dual gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist combination, LY3298176, into the

crowded diabetes drug market. In contrast, Novartis seeks return on investment with Zolgensma's launch into the spinal muscular atrophy space – Novartis gained the gene therapy (previously AVXS-101) when it acquired AveXis in May 2018. Novartis also eagerly awaits the approval of its wet age-related macular degeneration (AMD) project, brolucizumab; the FDA is set to decide later in 2019.

Two of Celgene's acquired assets make it to the list: ozanimod, an immunomodulator in development for multiple sclerosis, ulcerative colitis and Crohn's disease and Liso-cel, its CAR-T cell therapy. They originated from Receptos and Juno Therapeutics respectively, however these projects look likely to change hands again if Bristol-Myers Squibb closes its acquisition of Celgene.

Despite a wide spread of therapeutic areas represented in the top 10, oncology has the highest number of candidates. Daiichi Sankyo prepares for its first regulatory submission of its HER2-targeting antibody drug conjugate, DS-8201 (backed by a collaboration agreement with AstraZeneca) – and this joins Liso-cel and sacituzumab govitecan in the most valuable oncology projects.

Table 8: Top 10 Most Valuable R&D Projects (Ranked by Net Present Value)

Source: EvaluatePharma Vision®, May 2019

Rank	Product	Company	Phase (current)	Mechanism of Action	WW Product Sales ($m) 2024		Today's NPV ($m)
1.	VX-659/VX-445 + Tezacaftor + Ivacaftor	Vertex Pharmaceuticals	Phase III	Cystic fibrosis transmembrane regulator (CFTR) corrector; Cystic fibrosis transmembrane regulator (CFTR) potentiator	4,274		19,984
2.	Upadacitinib	AbbVie	Filed	Janus kinase 1 (JAK1) inhibitor	2,509		10,246
3.	DS-8201	Daiichi Sankyo	Phase III	Epidermal growth factor receptor ErbB-2 (HER2) antibody	1,790	New Entry	9,111
4.	Liso-cel	Celgene	Phase III	B-lymphocyte antigen CD19 CAR-T cell therapy	1,378		8,986
5.	Zolgensma	Novartis	Filed*	Survival of motor neuron 1 (SMN1) gene therapy	1,635	New Entry	8,011
6.	LY3298176	Eli Lilly	Phase III	Gastric inhibitory polypeptide (GIP) agonist; Glucagon-like peptide 1 (GLP-1) receptor agonist	1,012	New Entry	7,460
7.	Sacituzumab Govitecan	Immunomedics	Filed	Tumour-associated calcium signal transducer 2 (TROP2) antibody	1,589	New Entry	6,092
8.	Ozanimod	Celgene	Filed	Sphingosine 1-phosphate (S1P) receptor 1 regulator; Sphingosine 1-phosphate (S1P) receptor 5 regulator	1,516	New Entry	5,957
9.	Brolucizumab	Novartis	Filed	Vascular endothelial growth factor (VEGF) antibody fragment (Fab)	1,322		5,907
10.	Voxelotor	Global Blood Therapeutics	Phase III	Sickle haemoglobin (HbS) polymerisation inhibitor	1,711	New Entry	5,871
	Top 10				18,737		87,625
	Other				175,045		503,317
	Total				193,782		590,943
					NPV of R&D Pipeline MAY 2018:		576,990

Note: Today's NPV ($m) relates to the Net Present Value of the product as of the May 10th, 2019, based on the EvaluatePharma Vision® NPV Analyzer.

VX-659/VX-445 + Tezacaftor + Ivacaftor; Includes sales forecasts for Vertex triples, VX-445 + Tezacaftor + Ivacaftor or VX-659 + Tezacaftor + Ivacaftor.

* Zolgensma was approved by the US FDA on May 24th, 2019.

Worldwide R&D Spend by Pharma & Biotech Companies (2010-2024)

Forecast worldwide R&D CAGR lower in 2018 through 2024 and proportion of R&D spend to pharmaceutical revenue to reduce.

Worldwide pharmaceutical R&D spend totalled $179bn in 2018 representing an increase of +6.5% on the previous year. Going forward, R&D spend is forecast to grow at a CAGR of 3.0% between 2018 and 2024. This is comparable with a CAGR of 4.2% between 2010 and 2018, with an average proportion of R&D spend to pharmaceutical revenue for the same period of 19.8%, compared to 20.2% for 2018-24. Despite an initial peak in 2019, the proportion of R&D spend to pharmaceutical revenue falls quickly in subsequent

years. This reduction in R&D spend could be an indication that companies are investing now to improve their future R&D efficiencies. Use of real world data combined with machine learning techniques in addition to collaborative R&D programs, are a few of the initiatives being employed by companies to help them stay one step ahead in an era demanding more patient targeted drug development. Similarly, this reduction in R&D spend could be an indication that less revenue is being directed towards replenishing pipelines.

Figure 6: Worldwide Total Pharmaceutical R&D Spend in 2010-2024

Source: EvaluatePharma, May 2019
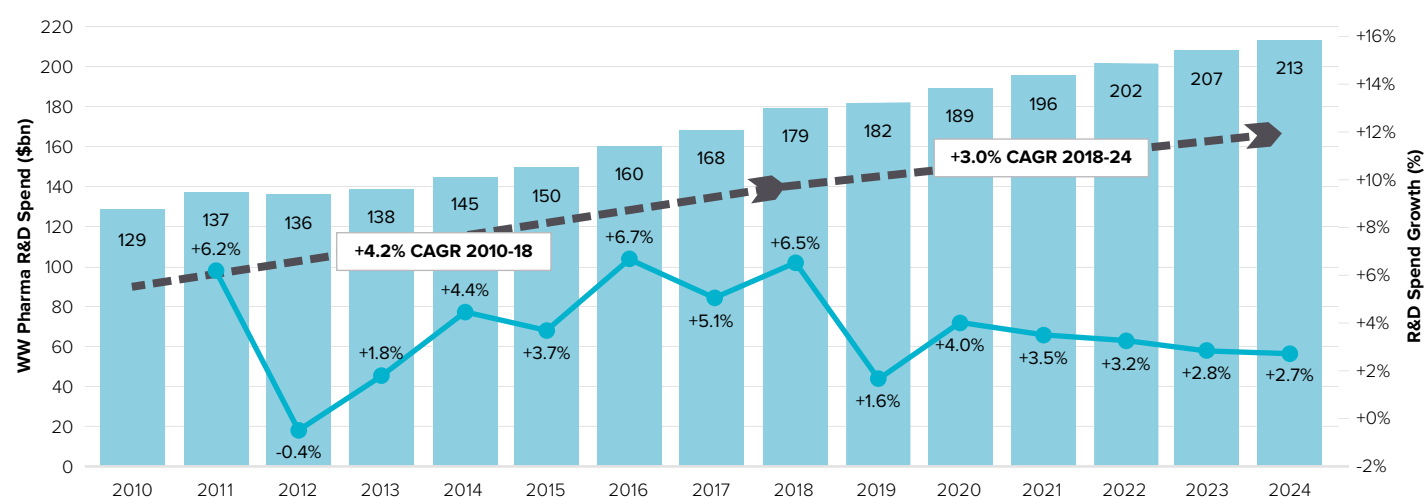
Table 9: Worldwide R&D Spend by Pharma & Biotech Companies (2010-2024)

Source: EvaluatePharma, May 2019

Year	WW Prescription Sales ($bn)														
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Pharma R&D Spend	128.6	136.5	136.0	138.4	144.6	149.9	159.8	168.0	178.9	181.7	189.0	195.5	201.8	207.4	213.0
Growth per Year		+6.2%	-0.4%	+1.8%	+4.4%	+3.7%	+6.7%	+5.1%	+6.5%	+1.6%	+4.0%	+3.5%	+3.2%	+2.8%	+2.7%
WW Prescription Sales	689	734	721	730	755	747	772	789	828	844	893	955	1,027	1,100	1,181
R&D as % of WW Prescription Sales	18.7%	18.6%	18.9%	18.9%	19.1%	20.1%	20.7%	21.3%	21.6%	21.5%	21.2%	20.5%	19.7%	18.9%	18.0%
Generics	60	66	66	69	75	77	80	78	75	79	84	88	92	96	100
Prescription excl. Generics	629	668	655	661	680	670	692	710	753	765	809	867	935	1,004	1,081
R&D as % of Prescription excl. Generics	20.5%	20.4%	20.8%	20.9%	21.3%	22.4%	23.1%	23.7%	23.8%	23.8%	23.4%	22.6%	21.6%	20.7%	19.7%

CAGR 2018-24 on Pharma R&D Spend +3.0%. Cumulative 10 year R&D Spend (2009-18) $1,468bn.

Table 10: NME Approvals per Year (2006-2018)

Source: EvaluatePharma, May 2019

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of NMEs	29	25	31	35	26	35	44	35	51	56	27	55	62
Spend per NME ($bn)	3.8	4.9	4.2	3.6	4.9	3.9	3.1	4.0	2.8	2.7	5.9	3.1	2.9
Spend per NME ($bn) (3 year lag)*				3.2	4.7	3.8	2.9	3.7	2.7	2.4	5.1	2.6	2.4

Note: Forecast pharmaceutical research and development spend based on a consensus of leading equity analysts' estimates for company level R&D spend, extrapolated to pharmaceutical R&D when a company has non-pharmaceutical R&D activity.

*Spend per NME ($bn) (3 year lag) uses the R&D expense for 3 years prior to the NME approval instead of the same year. e.g. the 2018 figure of $2.4bn is the R&D expense in 2015 divided by the number of NMEs in 2018.
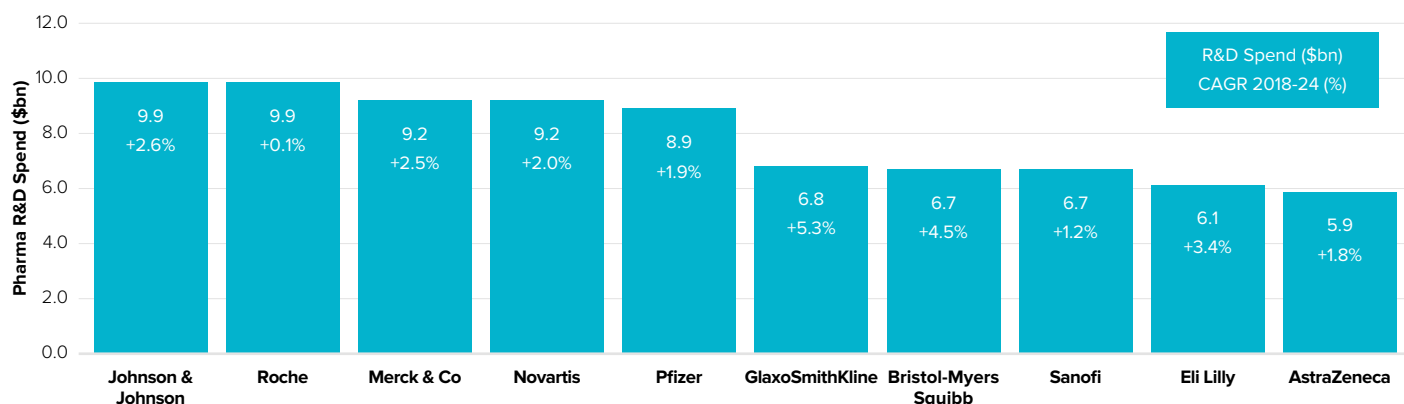
Pharmaceutical R&D Spend in 2024: Top 10 Companies

Johnson & Johnson leads as biggest spender on pharmaceutical R&D in 2024.

EvaluatePharma® finds that J&J just edges Roche to claim the position as the forecasted top spender on R&D in 2024, with a spend of $9.9bn. Novartis drops to fourth place, with Merck forecasted to claim third position by a fine margin. Of the top 10, Eli Lilly is forecast to invest the highest percentage of prescription sales in 2024 with 23.6%. GlaxoSmithKline is forecast to have the highest growth in pharma R&D spend of the top 10. With a decrease in pharma R&D expenditure vs. total Rx sales of 7.3%, AstraZeneca is forecasted to have the greatest return on R&D investment in 2024. Overall, total R&D spend is expected to increase by 3.0% each year, reaching $213.0bn in 2024.

Figure 7: Pharmaceutical R&D in 2024: Top 10 Companies

Source: EvaluatePharma, May 2019

Table 11: Pharmaceutical R&D Spend (2018 & 2024): Top 10 Companies & Total Market

Source: EvaluatePharma, May 2019

Rank	Company	Pharma R&D ($bn)		CAGR 2018-24	R&D As a % of Prescription Sales		
		2018	2024		2018	2024	Chg. (+/-)
1.	Johnson & Johnson	8.4	9.9	+2.6%	21.8%	21.6%	-0.2pp
2.	Roche	9.8	9.9	+0.1%	22.0%	21.1%	-0.9pp
3.	Merck & Co	7.9	9.2	+2.5%	21.2%	21.6%	+0.4pp
4.	Novartis	8.2	9.2	+2.0%	18.8%	18.4%	-0.4pp
5.	Pfizer	8.0	8.9	+1.9%	17.6%	17.4%	-0.2pp
6.	GlaxoSmithKline	5.0	6.8	+5.3%	16.3%	17.6%	+1.3pp
7.	Bristol-Myers Squibb	5.1	6.7	+4.5%	23.8%	22.5%	-1.3pp
8.	Sanofi	6.2	6.7	+1.2%	17.7%	16.4%	-1.3pp
9.	Eli Lilly	5.0	6.1	+3.4%	25.5%	23.6%	-1.9pp
10.	AstraZeneca	5.3	5.9	+1.8%	25.5%	18.2%	-7.3pp
	Total Top 10	68.9	**79.1**	+2.3%	20.4%	19.6%	-0.8pp
	Other	110.0	**133.9**	+3.3%			
	Total	178.9	**213.0**	+3.0%	21.6%	18.0%	-3.6pp

Note: Forecasted pharmaceutical R&D spend based on a consensus of leading equity analysts' estimates for company-level R&D spend.

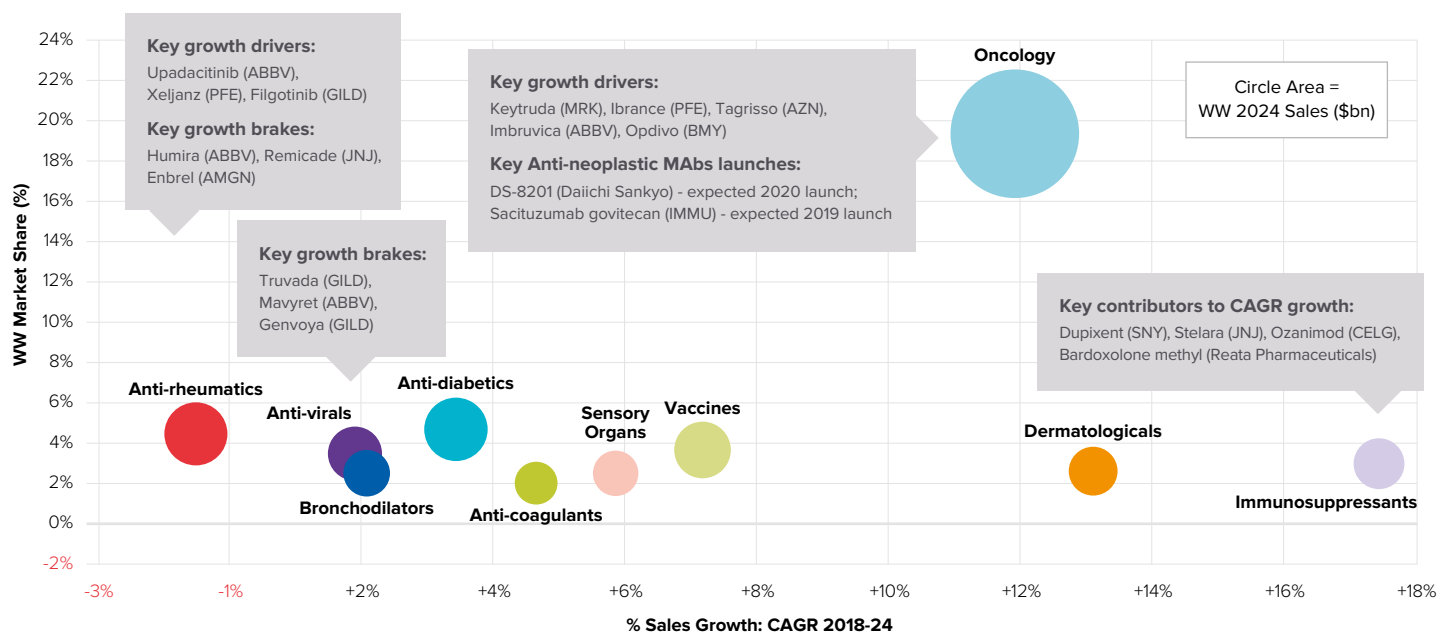# Worldwide Prescription Drug & OTC Sales by Therapy Area in 2024

Merck & Co expected to remain largest oncology player in 2024 with Keytruda.

Oncology prevails as the leading therapy segment in 2024, with a 19.4% market share and sales reaching $237bn, driven in large by the PD-1 inhibitors Keytruda and Opdivo, as well as Pfizer's Ibrance and AstraZeneca's Tagrisso. The immunosuppressants space also continues to see a high level of growth, with the market's largest

CAGR through 2024 of 16.9%, driven by an increase in the incidence of chronic diseases and the use of immunotherapeutic agents in clinical development for other therapy areas. Elsewhere biosimilars are beginning to make their mark on the anti-rheumatic segment, which is expected to see a decline in its CAGR as we enter 2024, with sales dipping to $55bn despite the high drive in sales from JAK inhibitors; upadacitinib and Xeljanz.

Figure 8: Top 10 Therapy Areas in 2024, Market Share & Sales Growth

Source: EvaluatePharma, May 2019

Key growth drivers:
Upadacitinib (ABBV), Xeljanz (PFE), Filgotinib (GILD)
Key growth brakes:
Humira (ABBV), Remicade (JNJ), Enbrel (AMGN)

Key growth drivers:
Keytruda (MRK), Ibrance (PFE), Tagrisso (AZN), Imbruvica (ABBV), Opdivo (BMY)
Key Anti-neoplastic MAbs launches:
DS-8201 (Daiichi Sankyo) - expected 2020 launch; Sacituzumab govitecan (IMMU) - expected 2019 launch

Key growth brakes:
Truvada (GILD), Mavyret (ABBV), Genvoya (GILD)

Key contributors to CAGR growth:
Dupixent (SNY), Stelara (JNJ), Ozanimod (CELG), Bardoxolone methyl (Reata Pharmaceuticals)

Circle Area = WW 2024 Sales ($bn)

Table 12: Worldwide Prescription Drug & OTC Sales by Evaluate Therapy Area (2018 & 2024): Top 15 Categories & Total Market

Source: EvaluatePharma, May 2019

Rank	Therapy Area	WW Sales ($bn)		CAGR % Growth	WW Market Share		Chg. (+/-)	Rank Chg. (+/-)
		2018	2024		2018	2024		
1.	Oncology	123.8	236.6	+11.4%	14.3%	19.4%	+5.0pp	+0
2.	Anti-diabetics	48.5	57.6	+2.9%	5.6%	4.7%	-0.9pp	+1
3.	Anti-rheumatics	58.1	54.6	-1.0%	6.7%	4.5%	-2.3pp	-1
4.	Vaccines	30.5	44.8	+6.6%	3.5%	3.7%	+0.1pp	+1
5.	Anti-virals	38.9	42.2	+1.4%	4.5%	3.5%	-1.0pp	-1
6.	Immunosuppressants	14.2	36.1	+16.9%	1.6%	3.0%	+1.3pp	+6
7.	Dermatologicals	15.8	32.1	+12.6%	1.8%	2.6%	+0.8pp	+4
8.	Bronchodilators	28.0	30.7	+1.6%	3.2%	2.5%	-0.7pp	-2
9.	Sensory Organs	22.3	30.5	+5.3%	2.6%	2.5%	-0.1pp	+0
10.	Anti-coagulants	19.3	24.6	+4.1%	2.2%	2.0%	-0.2pp	+0

Top 11-15 continued over...

Rank	Therapy Area	WW Sales ($bn)		CAGR % Growth	WW Market Share		Chg. (+/-)	Rank Chg. (+/-)
		2018	2024		2018	2024		
11.	**Anti-hypertensives**	22.9	24.1	+0.9%	2.6%	2.0%	-0.7pp	-4
12.	**MS therapies**	22.7	21.1	-1.2%	2.6%	1.7%	-0.9pp	-4
13.	**Anti-fibrinolytics**	13.8	18.2	+4.7%	1.6%	1.5%	-0.1pp	+0
14.	**Anti-hyperlipidaemics**	9.6	17.7	+10.8%	1.1%	1.5%	+0.3pp	+4
15.	**Sera & gammaglobulins**	10.5	15.1	+6.2%	1.2%	1.2%	+0.0pp	+0
	Top 15	479	686	+6.2%	55.4%	56.2%	+0.7pp	
	Other	385	536	+5.7%	44.6%	43.8%	-0.7pp	
	Total WW Prescription & OTC Sales	**864**	**1,222**	+5.9%	100.0%	100.0%		
	Total 'Prescription & OTC Sales' includes:							
	WW Generic Sales	**75.2**	**99.8**	+4.8%	8.7%	8.2%	-0.5%	
	OTC Pharmaceuticals	**36.2**	**41.1**	+2.1%	4.2%	3.4%	-0.8%	

Note: Sales in 2018 based on company reported data. Sales forecasts to 2024 based on a consensus of leading equity analysts' estimates for product sales and segmental sales.

2024: Top 10 Selling Products in the World

Keytruda knocks Humira off the top spot; Revlimid falls out of top 3.

A $1.5bn increase in sales for Humira ensured AbbVie's blockbuster remained the top selling product worldwide in 2018. However, following a number of biosimilar launches in Europe and biosimilars set to hit the US in 2023, the 2024 EvaluatePharma® consensus forecast for Humira has decreased by $2.8bn compared to that given in last year's report. This decrease, coupled with a strong year for Keytruda in terms of product sales, positive data from ongoing clinical trials and further FDA approvals, will allow Keytruda to pip Humira to the post and take the number one spot for 2024 forecasted sales. As a result of this, Keytruda is forecasted to widen

the sales gap between its competitor Opdivo to over $5bn in 2024. Sitting just outside of the top 3 with predicted 2024 sales of $11.3bn, the checkpoint inhibitor Opdivo continues to have strong sales in the anti-neoplastic MAbs segment despite contrasting analyst views with regards to its trajectory as we move towards 2024. Falling out of the top 3 and down the rankings, worldwide sales of Revlimid are expected to fall with a CAGR of -3.2% between 2018 and 2024 to $8.1bn, with generic versions expected to hit the US market in 2022. Gilead's Biktarvy continues to outshine all other HIV medications and climbs a place to sit in the top 10 this year, boasting an impressive CAGR of +34.4% going into 2024 and sales of $7.0bn.

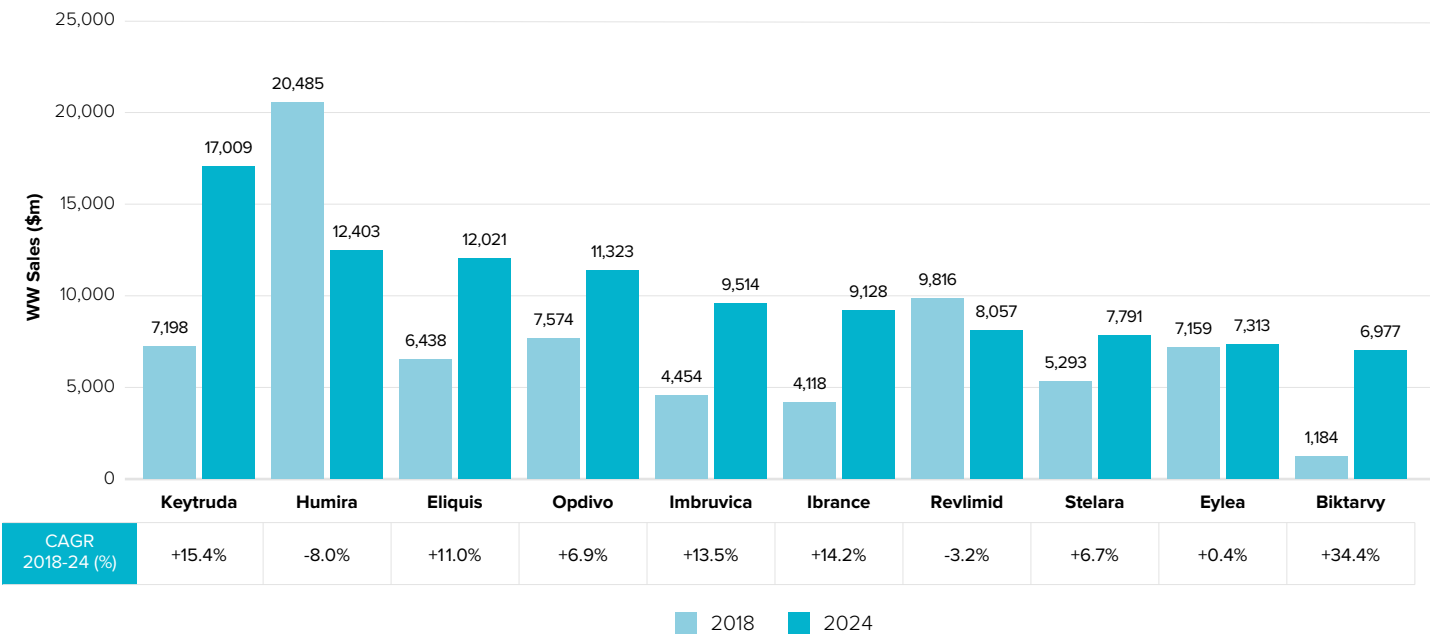## Table 13: Top 10 Selling Products WW in 2024

Source: EvaluatePharma, May 2019

Rank	Product	Generic Name	Company	Mechanism of Action	WW Product Sales ($m)			Market Status
					2018	2024	CAGR	
1.	**Keytruda**	pembrolizumab	Merck & Co + Otsuka Holdings	Programmed cell death protein 1 (PD1) antibody	7,198	17,009	+15.4%	Marketed
2.	**Humira**	adalimumab	AbbVie + Eisai	Tumour necrosis factor alpha (TNFa) antibody	20,485	12,403	-8.0%	Marketed
3.	**Eliquis**	apixaban	Bristol-Myers Squibb	Coagulation factor Xa inhibitor	6,438	12,021	+11.0%	Marketed
4.	**Opdivo**	nivolumab	Bristol-Myers Squibb + Ono Pharmaceutical	Programmed cell death protein 1 (PD1) antibody	7,574	11,323	+6.9%	Marketed
5.	**Imbruvica**	ibrutinib	AbbVie + Johnson & Johnson	Bruton's tyrosine kinase (BTK) inhibitor	4,454	9,514	+13.5%	Marketed
6.	**Ibrance**	palbociclib	Pfizer	Cyclin-dependent kinase 4 (CDK4) inhibitor; Cyclin-dependent kinase 6 (CDK6) inhibitor	4,118	9,128	+14.2%	Marketed
7.	**Revlimid**	lenalidomide	Celgene	Interleukin-6 (IL-6) antagonist; Natural killer (NK) cell stimulant; Natural killer T-cell (NKT) stimulant; Tumour necrosis factor alpha (TNFa) inhibitor; Vascular endothelial growth factor (VEGF) inhibitor	9,816	8,057	-3.2%	Marketed
8.	**Stelara**	ustekinumab	Johnson & Johnson + Mitsubishi Tanabe Pharma	Interleukin-12 (IL-12) antibody; Interleukin-23 (IL-23) receptor antibody	5,293	7,791	+6.7%	Marketed
9.	**Eylea**	aflibercept	Regeneron Pharmaceuticals + Bayer + Santen Pharmaceutical	Vascular endothelial growth factor receptor (VEGFR) antagonist	7,159	7,313	+0.4%	Marketed
10.	**Biktarvy**	bictegravir sodium; emtricitabine; tenofovir alafenamide fumarate	Gilead Sciences	HIV-1 integrase inhibitor; HIV-1 nucleoside reverse transcriptase inhibitor (NRTI)	1,184	6,977	+34.4%	Marketed
	Total				**73,719**	**101,536**	**+5.5%**	
	Total WW Individual Products Forecast in EvaluatePharma®				**676,147**	**989,099**	**+6.5%**	

Note: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Figure 9: Top 10 Selling Products WW in 2024

	Keytruda	Humira	Eliquis	Opdivo	Imbruvica	Ibrance	Revlimid	Stelara	Eylea	Biktarvy
2018	7,198	20,485	6,438	7,574	4,454	4,118	9,816	5,293	7,159	1,184
2024	17,009	12,403	12,021	11,323	9,514	9,128	8,057	7,791	7,313	6,977
CAGR 2018-24 (%)	+15.4%	-8.0%	+11.0%	+6.9%	+13.5%	+14.2%	-3.2%	+6.7%	+0.4%	+34.4%

Y-axis: WW Sales ($m)

Legend: 2018 2024

2024: Top 10 Selling Products in the USA

Humira to maintain top spot, Eliquis makes top 3.

Despite losing out on the top spot worldwide, Humira manages to hold on to the top spot within the US, owing to the product's continuing strength in the US market, where AbbVie has managed to secure US market exclusivity until 2023. This being said, the 2024 forecast is just over a $1bn less that the 2024 consensus forecast from last year. Meanwhile, Keytruda has seen an increase in its 2024 consensus forecast from last year with predicted sales to reach $8.7bn, driving itself into second place ahead of Bristol-Myers Squibb's lead product Eliquis. Outside of the top 3, Gilead's

market lead Biktarvy has climbed several spots this year, comfortably entering the top 10. Eli Lilly's market lead Trulicity has also climbed several ranks, securing itself a place in the top 10.

Forecasts are not so bright for Celgene's Revlimid. The product has seen a sharp decline in consensus forecast sales and, in contrast to last year's report where the product ranked 2nd, it now finds itself in 6th place. This downgrade is evidently due to the anticipation of generic competition entering the market. Similarly, other products such as Dupixent and Ocrevus have also seen a steep decline in sales, causing them to drop out of the top 10.

Table 14: Top 10 Selling Products in the USA in 2024

Source: EvaluatePharma, May 2019

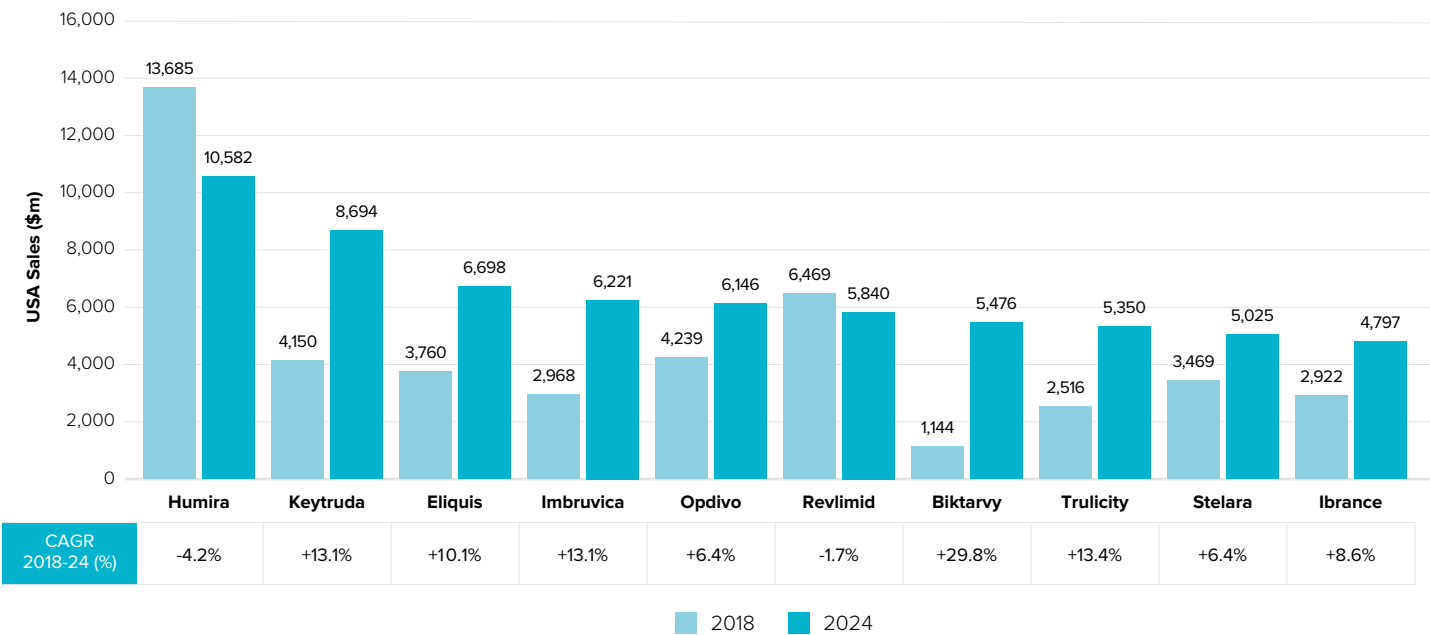| Rank	Product	Generic Name	Company	Mechanism of Action	USA Product Sales ($m)			US Market Status
					2018	2024	CAGR	
1.	**Humira**	adalimumab	AbbVie	Anti-tumour necrosis factor alpha (TNFa) MAb	13,685	10,582	-4.2%	Marketed
2.	**Keytruda**	pembrolizumab	Merck & Co	Programmed cell death protein 1 (PD1) antibody	4,150	8,694	+13.1%	Marketed
3.	**Eliquis**	apixaban	Bristol-Myers Squibb	Coagulation factor Xa inhibitor	3,760	6,698	+10.1%	Marketed
4.	**Imbruvica**	ibrutinib	AbbVie	Bruton's tyrosine kinase (BTK) inhibitor	2,968	6,221	+13.1%	Marketed
5.	**Opdivo**	nivolumab	Bristol-Myers Squibb	Programmed cell death protein 1 (PD1) antibody	4,239	6,146	+6.4%	Marketed
6.	**Revlimid**	lenalidomide	Celgene	Interleukin-6 (IL-6) antagonist; Natural killer (NK) cell stimulant; Natural killer T-cell (NKT) stimulant; Tumour necrosis factor alpha (TNFa) inhibitor; Vascular endothelial growth factor (VEGF) inhibitor	6,469	5,840	-1.7%	Marketed
7.	**Biktarvy**	bictegravir sodium; emtricitabine; tenofovir alafenamide fumarate	Gilead Sciences	HIV-1 integrase inhibitor; HIV-1 nucleoside reverse transcriptase inhibitor (NRTI)	1,144	5,476	+29.8%	Marketed
8.	**Trulicity**	dulaglutide	Eli Lilly	Glucagon-like peptide 1 (GLP-1) receptor agonist	2,516	5,350	+13.4%	Marketed
9.	**Stelara**	ustekinumab	Johnson & Johnson	Interleukin-12 (IL-12) antibody; Interleukin-23 (IL-23) receptor antibody	3,469	5,025	+6.4%	Marketed
10.	**Ibrance**	palbociclib	Pfizer	Cyclin-dependent kinase 4 (CDK4) inhibitor; Cyclin-dependent kinase 6 (CDK6) inhibitor	2,922	4,797	+8.6%	Marketed
	Total				**45,322**	**64,829**	**+6.1%**	
	Total USA Individual Products Forecast in EvaluatePharma®				**340,503**	**550,034**	**+8.3%**	

Note: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Figure 10: Top 10 selling products in the USA in 2024

Source: EvaluatePharma, May 2019

USA Sales ($m)

Product	Humira	Keytruda	Eliquis	Imbruvica	Opdivo	Revlimid	Biktarvy	Trulicity	Stelara	Ibrance
2018	13,685	4,150	3,760	2,968	4,239	6,469	1,144	2,516	3,469	2,922
2024	10,582	8,694	6,698	6,221	6,146	5,840	5,476	5,350	5,025	4,797
CAGR 2018-24 (%)	-4.2%	+13.1%	+10.1%	+13.1%	+6.4%	-1.7%	+29.8%	+13.4%	+6.4%	+8.6%

■ 2018　■ 2024

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