

2020 Global Biopharma R&D Productivity And Growth Ranking



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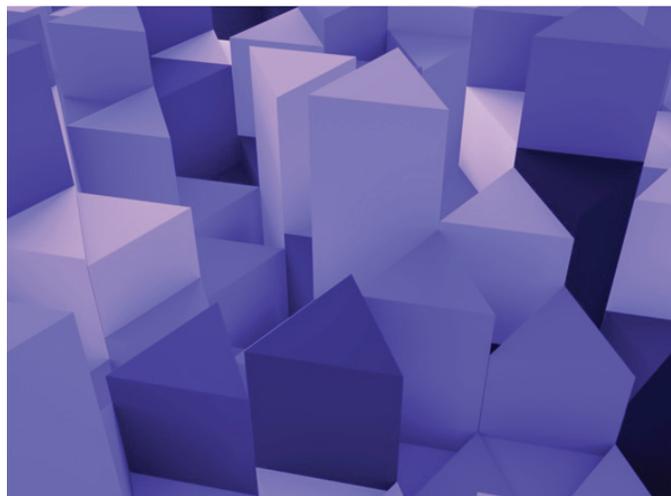
► By Erika Kuchen and Markus Thunecke

THE DECREASE IN OVERALL R&D PRODUCTIVITY continues – a trend that started in 2018. It would be too easy to attribute this fall in R&D productivity to COVID-19 alone.

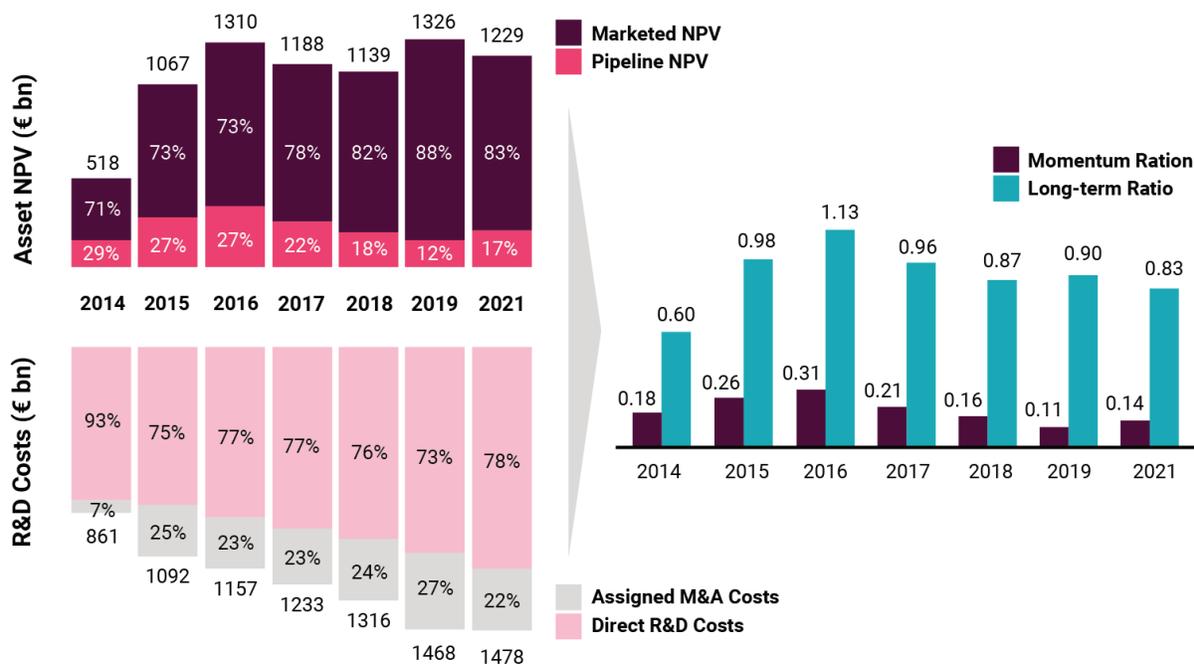
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With 2020 ending, Catenion is now in its seventh year of the annual survey of pharma R&D productivity. Compared to 2019 there was a slight drop in overall R&D productivity – a trend that has started in 2018. While the metric that captures the value of the pipeline vs. R&D spending plus cost of M&A has increased slightly compared with 2019, the long-term ratio that also counts mostly the value of products launched in the last five years on top of the pipeline has decreased in our sample of the top 30 biopharma companies based on pharmaceutical sales. It would be too easy to attribute the slight decrease in R&D productivity to COVID-19. Perhaps it played a role in slowing down recruitment and delaying some readouts, however, its overall impact on the biopharma space has been surprisingly low. In fact, the number of FDA approvals even increased from 48 in 2019 to 53 in 2020.

As every year, there are a number of companies that



performed extremely well, these are the top 10 players in the ranking. Only 3/10 qualify as big pharma based on the number of employees, namely AstraZeneca PLC, Novo Nordisk A/S and Roche Holding AG. The rest are mid-size companies. It is important to note that Catenion's definition of big pharma is not based on legacy size but on the current size in terms of number of employees (>40,000). Thus, while Eli Lilly and Company is often listed as a big pharma, its roughly 33k employees in 2019 classify it as a mid-sized player in the ranking. The corporate growth ranking, that measures both historical and forecast sales and profit, is even more skewed towards mid-size players. Out of big pharma, only Novo Nordisk made it into the top 10.



R&D productivity of the top 30 companies based on pharmaceutical sales. Productivity defined by the ratio of pipeline value versus R&D and M&A spending (momentum ratio), and pipeline + recently marketed value versus R&D and M&A spending (long-term ratio).

Source for all exhibits: Catenion

In industries that depend critically on science and creativity, size is a double-edged sword. In several functions there are economies of scale, such as commercialization or manufacturing. But in the most critical area of R&D, size can easily become a burden – due to increasing bureaucracy, silo mentality and the sheer impossibility of managing a huge portfolio of increasingly complex projects (think cell & gene therapy).

Oncology Still Dominating

Oncology is still the dominant area in terms of total NPV in the 2020 ranking with 43% of the total value, a second distant is systemic anti-infectives (11%), and CNS

(10%). However, due to the dominating PD-1 antibodies nivolumab and pembrolizumab fading out in our ranking, oncology is also the area that had the biggest year-to-year decrease in value. Both anti-PD-1s were launched in 2014, and all products launched >5 years ago are counted in our R&D productivity formula to a decreasing degree, emphasizing the need to replace products on a regular basis. The biggest increase in value was seen with immunomodulators (AbbVie Inc.'s JAKi upadacitinib has increased from \$13bn to \$31bn) and in dermatology, where Sanofi/Regeneron's anti IL-4/IL-13 dupilumab and Abbvie's anti IL-23 risankizumab have roughly doubled in value 2019-2020, to \$50bn and \$23bn, respectively.

China Has Arrived – The Story Of Jiangsu Hengrui

For the first time since our initial survey was done in 2014, a Chinese company has entered both the top 30 ranking and moved immediately to the top spot in the R&D Productivity and Corporate Growth Rankings. Hengrui had sales of \$4.6bn in 2020 and is best known for its anti PD-1 camrelizumab (\$9bn NPV, >\$2bn projected in peak sales) but it has built an impressive pipeline far beyond PD-1 to support a massive market cap of \$91bn. Reflecting the pipeline potential, analyst projections for the company predict \$12.6bn in sales for 2026 – a CAGR of 19%. Its two big pipeline products are a CDK4/6 inhibitor and a PARPi, both expected to become blockbuster drugs. Hengrui has both the largest R&D-budget (spending 16.7% of sales) and organization of any Chinese pharma company with ca. 3,400 scientists in 2019. Its pipeline contains close to 50 innovative NCEs/NBEs. Strategically the company

is still a typical representative of emerging Chinese biopharma as its pipeline is based on a first-in-China strategy for targets already well established in the Western hemisphere (but with global IP protection). Given that it started out as a less interesting generics player, this is already a huge success, the key challenge will be globalization beyond China to start competing with multinational biopharma leaders based on a best-in-class basis and then ultimately tackling completely novel areas through first-in-class innovation. Given the pace the company is showing it would not be a surprise if Hengrui arrived on the global scene in the near future. Some industry observers are pointing to Japan as an example of how companies initially focused exclusively on the local market have successfully globalized their effort. Takeda, Daiichi Sankyo or Astellas have become global players, although there is still a gap in terms of R&D productivity (they are in positions #23, #24 and #22 respectively).

Lilly In Top 5 For Second Year

R&D Productivity And Corporate Performance Ranking

R&D PRODUCTIVITY			
Final NPV Rank	Company	Momentum (Pipeline NPV)	Long-term (All NPV)
1	Jiangsu Hengrui Medicine	1	1
2	Eli Lilly	5	7
3	AstraZeneca	14	5
4	Vertex Pharmaceuticals	21	3
5	Novo Nordisk	25	2
6	Roche	11	8
6	Eisai	2	11
8	Ono Pharmaceutical	28	4
9	Biogen	4	13
10	Gilead Sciences	26	6

TOP 5

COMPANY PERFORMANCE			
Final Corp. Growth Rank	Company	Past Performance	Forecast Performance
1	Jiangsu Hengrui Medicine	2	1
2	Vertex Pharmaceuticals	3	4
3	Regeneron Pharmaceuticals	1	9
4	Ono Pharmaceutical	7	6
5	Eli Lilly	15	6
5	Novo Nordisk	12	9
7	AbbVie	5	17
7	Alexion Pharmaceuticals	4	18
9	Astellas Pharma	19	8
9	UCB	13	14

Lilly was a surprise last year when it appeared for the first time in the top 10 ranking and shooting straight to the #3 slot. This time Lilly has climbed even further up to the #2 spot in R&D productivity and the #5 slot in the Corporate Growth Ranking. Lilly's increasing effort to re-build its oncology pipeline (now 29% of total NPV) is beginning to pay and it is benefitting in a similar fashion as Novo Nordisk from the global diabetes epidemic (46% of Lilly's total NPV). The RET inhibitor selpercatinib that came to Lilly as part of the Loxo acquisition in 2017 has shown a large increase in value (to now \$4.9bn NPV, and blockbuster sales forecast for 2027).

Lilly's biggest value driver in its portfolio by far is the marketed GLP-1 agonist dulaglutide with an NPV of \$23bn (11% of Lilly's share price). This product is fading out in our ranking as it was launched more than five years ago, but Lilly has other large products with long patent runways such as the GLP-1/GIP dual agonist tirzepatide in Phase III (NPV of \$17bn and peak sales of >\$5bn). The biggest oncology drug is CDK4/6 inhibitor abemaciclib (\$16bn in NPV and peak sales of \$4.6bn).

Lilly has also been in an acquisitive mood since 2017 with 1-2 larger acquisitions per year. In January 2020, Lilly acquired Dermira for \$1.1bn adding Phase III anti-IL13 lebrikizumab for atopic dermatitis and in 2021 AAV gene therapy player Prevail was added with a mostly early stage neuro portfolio.

Is AstraZeneca's Pipeline Losing Steam?

AstraZeneca was last year's R&D productivity champion, reaping the rewards of an impressive turnaround. This year, however, shows how difficult it is to stay at the top as AZ has dropped to the #3 overall spot. Although AZ has 37 pipeline assets with NPV predictions, the combined NPV is insufficient to prevent AZ's further decline in momentum ranking to a midfield #14. Several assets have declined in value vs. 2019 and value driver trastuzumab deruxtecan was launched in 2020 and thus does not score in the pipeline ranking anymore. Mega-blockbuster osimertinib was launched in 2015 and is also counting less every year in the ranking (it has

a massive NPV of \$58bn, or 42% of AZ's share price). Oncology is still by far the biggest contributor to AZ's R&D productivity in our ranking.

The biggest news at the end of 2020 was the announcement that AZ intends to acquire Alexion for \$39bn (a premium of 43% on share price). Alexion was our Corporate Growth Champion of 2019 (#1 rank), and still came in at #7 in 2020. The issue was the slow R&D dynamics, in 2019 the company came in at #13, in 2020 it dropped further to #19. Activity investor Elliott Management had its way and succeeded in pushing the company into a sale. The case of Alexion also nicely illustrates how difficult it is to scale R&D productivity and build a long-term competitive advantage. Alexion had a fantastically successful journey from its establishment in New Haven, CT, in 1992 to the launch of mega-blockbuster eculizumab in 2007, and finally its announced sale to AZ on 12 December, 2020. From AZ's standpoint the deal brings additional strength and capabilities in rare immunology diseases and will reduce AZ's dependence on oncology.

New Entrant Vertex Comes In With Massive Value Concentration In Few Assets

Vertex Pharmaceuticals Incorporated has entered the ranking for the first time as it has now reached the size needed to be included. It claims a #4 spot in R&D productivity and a #2 in Corporate Growth, demonstrating that superior R&D performance ultimately translates into superior commercial performance (3 of the top 5 R&D productivity companies also appear in the top 5 Corporate Growth).

Vertex is still living off its success with the marketed triple combo CFTR modulator Trikafta (\$17.8 bn NPV, >1/3 of share price). As Trikafta launched in 2019 it still has lots of mileage in the tank (IP protection expected until 2027).

The problem of Vertex is how it can successfully move beyond its cystic fibrosis franchise, the pipeline contains a mixed bag of cystic fibrosis followers plus a few oncology assets, a lone pain drug and a few other

hopefuls. One of the most high-profile candidates for Vertex is based on a collaboration with CRISPR Therapeutics; a CRIPR-CAS9 gene editing (ex vivo) for thalassemia and sickle cell disease. But altogether the pipeline counts just for a #21 in the momentum ranking. As long as the IP on marketed products holds up Vertex will be fine, but a slowing down in R&D momentum or a failure to steer through the patent cliff years means trouble is on the (long-term) horizon. As the company has a growing free cash flow and war chest, larger acquisitions can be expected, something the company is still getting used to. In 2019 Vertex performed two mid-size deals by acquiring stem cell player Semma Therapeutics to focus on type 1 diabetes, for \$950mn in cash, and also gene editing player Exonics Therapeutics to focus on Duchenne muscular dystrophy for approximately \$1bn total deal value.

Novo's Evergreening Strategy Leads To Sixth Consecutive Showing In Top 5

Novo Nordisk is the only company in our ranking that has consistently been in the top 5 for the last six years. Although Novo is lacking pipeline momentum (#25) it is still profiting from its huge product launches over the last years and the global diabetes epidemic – altogether it is still sufficient to secure a spot in the top 5 in R&D Productivity and Corporate Growth. GLP-1 agonists Rybelsus (oral semaglutide) and Ozempic (s.c. semaglutide) combine for a whopping \$55bn and still have significant patent runway (2031). The pipeline looks rather dry with no assets of significant value (>\$1bn). Novo now has a window of several years to prepare for the future, but it will most likely require an evolution of its strategy that until now has relied mostly on internal growth. The 2020 acquisition of Corvidia for \$2.1bn in total deal value to access antibodies for chronic kidney disease and other cardiovascular indications, as well as glucose-responsive insulin focused Ziylo in 2018 for \$800mn in total deal value may illustrative the increasing openness for inorganic moves. But ultimately Novo will have to come up with much larger moves if the strategic intent is to prepare for the loss of exclusivity of its GLP-1 franchise.

The Difficulty Of Scaling R&D

Both Alexion Pharmaceuticals Inc. (#19) and Regeneron Pharmaceuticals, Inc. (#13) have dropped out of the top 5 in R&D productivity, their pipeline momentum is at the very bottom of the list. Both companies are still performing strongly in the Corporate Growth Ranking (#7 and #3, respectively) but also there they are expected to lose momentum (Future Growth Ranking #9 and #18, respectively). While the lacking growth prospects of Alexion have led to its sale to AstraZeneca, Regeneron will most likely rely on its superior discovery capabilities to innovate its way back to the top. So many companies before them have struggled to maintain R&D outperformance and to scale innovation over longer periods of time.

Biogen Pharma is another example as they had a great run over the last years but the company has found it difficult to replace its aging multiple sclerosis franchise with other high value neuro assets (#9 overall R&D productivity). Its Corporate Growth Ranking has already taken a severe hit (#24). Management itself spoke of a “reset year” in 2021. The key swing factor in the portfolio is Alzheimer's antibody aducanumab, which comes with a negative FDA advisory panel vote but analysts still expect an approval. The analyst consensus for aducanumab is \$4bn-5bn. Not bad for a drug whose overall clinical package did not convince the FDA's independent experts.

Orphan Drugs And Biomarkers

One of the reasons why so many biotechs and emerging biopharma companies focus on rare diseases or biomarker-driven areas is that these typically promise higher R&D productivity than more common diseases, in which large and heterogenous patient populations need to be treated with a one-size-fits all therapy. Our analysis shows that biomarker-driven development has taken a strong footing in drug development with >70% of assets of the top 30 companies relying on biomarkers in their development. But the range in the elite group of top 10 is still large with 91% for Hengrui versus 50% for Novo, showing that it is still possible to outperform even

with only moderate biomarker-driven stratification (but perhaps diabetes, where diagnosis is already based on biomarker readout is a positive exception).

For orphan diseases, we found that 25% of top company drugs are developed in the orphan space, vs. 17% for the bottom 10. Vertex is leading the charts here with development exclusive to the orphan space. However, true to their first-in-China motto, with only one orphan designation (for rivoceranib), Hengrui shows by far the lowest effort out of the top 30. Both orphan drugs and also those developed with a patient selection biomarker have substantially higher success rates in a recent survey by BIO. It is no wonder that executives in large pharma and biotech really like investing in both rare diseases and stratified drugs.

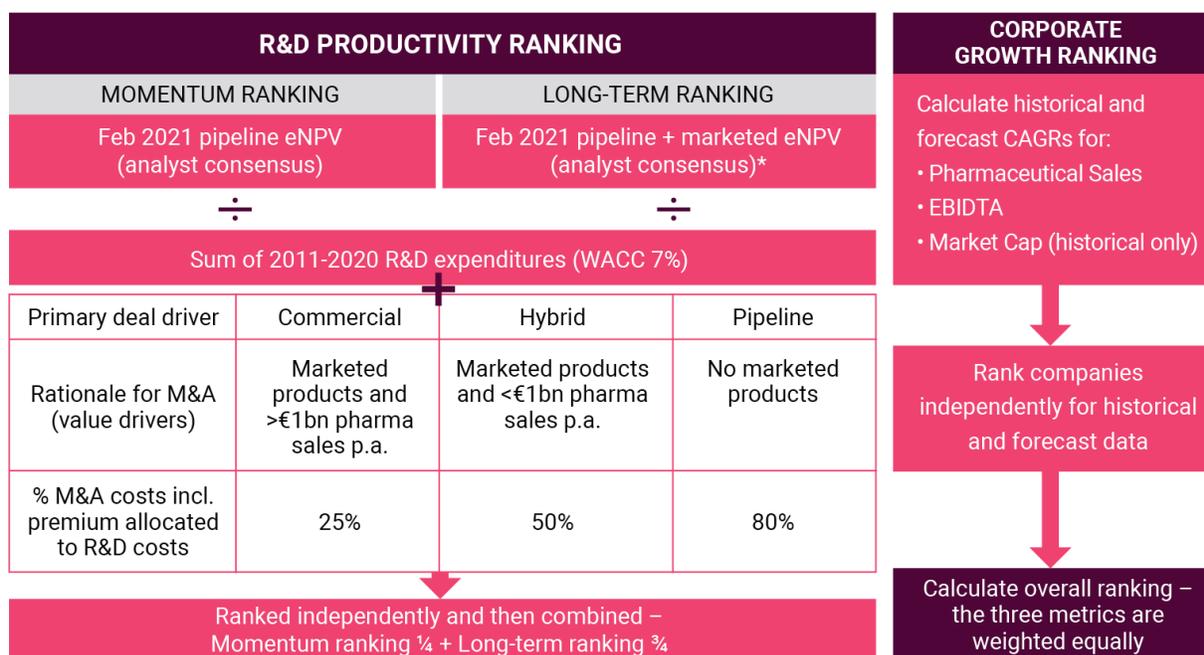
Will We See A Renaissance In Infectious Disease R&D?

2020 was clearly dominated by COVID-19, to which the industry responded with record-breaking innovation.

The vaccines of BioNTech and Moderna have surpassed even the most optimistic projections in terms of efficacy. Whether these efforts are enough to temper the numerous mutated variants of the SARS-Cov-2 virus remains to be seen, but the forecast for the class of mRNA vaccines for COVID-19 is of such magnitude that 2021/2022 could see the rise of two new large pharma companies with peak sales of >\$10bn each. The more interesting long-term question is whether this success will lead to a rise in infectious disease R&D to prepare against future pandemics and to come up with both vaccines and therapeutics? Or will the impact will be short-lived with the industry continuing its increasing focus on high-priced chronic or rare diseases?

Markus Thunecke, PhD (markus.thunecke@catenion.com), is a founding senior partner of Catenion, a biopharma focused strategy consulting firm. Erika Kuchen, PhD, is an associate at Catenion (erika.kuchen@catenion.com).

Methodology



*Products launched in the past 5 years plus tail-off

R&D Productivity Ranking

To evaluate the R&D productivity of the world's 30 largest public pharmaceutical companies, as judged by total pharmaceutical sales, the Catenion methodology takes an approach that focuses on value. We compared the total R&D spending from 2011-2020 including costs from M&A (see below) and a 7% cost of capital with the total net present value (eNPV) today of compounds marketed in the last five years and all pipeline products.

Using this data, two distinct rankings were calculated – a 'momentum' and a 'long-term' ranking. The momentum ranking aims to capture the forecasted value of a company generated by taking the current eNPV of its entire pipeline and dividing by the firms R&D and M&A costs, both adjusted for cost of capital, as described above. By contrast, the long-term ranking focuses on the value already generated by a company in the recent past, specifically the eNPV of products marketed in the last five years are added to the pipeline eNPV whilst those marketed six to eight years ago are also added but with the contribution tailing off by 33% per year. This is then divided by the total costs as per the momentum rank.

The overall R&D productivity rank was then generated by weighting the momentum rank $\frac{1}{4}$ vs. $\frac{3}{4}$ for the long-term rank.

Incorporating the costs of M&A

To fairly allocate M&A costs to the R&D costs, each deal was defined by its primary driver. If the acquired firm had pharma sales >€1 bn it was classified to be commercial and thus 25% of the total deal value was added to the R&D costs for that deal year. By contrast a deal involving a firm with no marketed products is, by definition, a pipeline driven deal, thus 80% of the deal costs were taken in account. In addition, if the total cumulative sales of the target company up until the deal date were <20% of the deal value then these were also considered to be a pipeline driven deal (e.g. AbbVie's acquisition of Pharmacyclics). Finally, if a firm had pharma sales <€1 bn it is considered a hybrid of the two deals and 50% of the M&A costs were considered.

Corporate Growth Ranking

To evaluate the corporate performance of each firm, the historical and forecasted CAGR for pharmaceutical sales, EBITDA and market cap (historical only) was calculated. Each company was ranked independently on each of the five metrics before they were combined with equal weighting to generate the overall corporate growth ranking.