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Global Biopharma R&D Productivity And Growth Rankings

Catenion, a biopharma-focused R&D strategy consulting firm, has analyzed the performance of the top-30 biopharma companies in 2018 and outlined major concerns for the future of innovation in drug development.

BY GRAHAM SCHOLEFIELD AND MARKUS THUNECKE

In 2017, R&D productivity of the top-30 pharmaceutical companies had decreased for the first time since 2014, according to Catenion's annual review of the sector. This trend continued into 2018, albeit with a lower magnitude as overall R&D productivity dropped by around 10% (vs. about 15% last year).

Yet again, the major driver is a decline in the metric that looks at pipeline value versus cumulative R&D spending (momentum ranking), whereas the decrease in the metric that includes products launched within the last five years (long-term ranking) is relatively small by comparison.

Is this continuing industry-wide decline in R&D productivity a bellwether for things to come? Interrogating the drivers shows that total R&D costs (including those assigned from M&A) have increased this year in a similar manner to all prior years, at a CAGR of around 9%. However, unlike 2017, the decline of total asset expected net present values (eNPVs) of the top-30 pharmaceutical companies was relatively modest at almost 4% (vs. 9% last year). This explains the more modest decrease in overall R&D productivity. Perhaps the most telling trend is the contribution of pipeline drugs' eNPVs to the total NPV; this was about 29% back in 2014 but now has plummeted to around 18%.

The instinctual reaction to this drop would be that there has been a lot of high-value pipeline failures. However, with some notable exceptions – such as **Roche**'s lampalizumab for dry age-related macular degeneration (AMD) – this is not the major driver, rather the industry has launched a number of high-value drugs, which have not been replaced by equally high-value candidates in their pipelines. Indeed, the total number of compounds in clinical development has dropped by around 44% over the past two years. This year the total value of launches by the top-30 pharma companies was around €77 billion ($88.7 billion) in today's NPV, led by **Gilead Sciences Inc.**'s HIV drug combo *Biktarvy* (bictegravir, emtricitabine, and tenofovir alafenamide) with a launch worth almost €17 billion and halving the pipeline value of the entire systemic anti-infective field as a consequence.

Other examples include **Novo Nordisk**'s semaglutide for type 2 diabetes (about €8.4 billion), **Shire PLC**'s lanadelumab for hereditary angioedema (around €7.4 billion) and **Johnson & Johnson**'s apalutamide for prostate cancer (roughly €5.5 billion). Overall, just €20 billion of this launch value has been replaced in the companies' pipelines, leaving a €57 billion hole that has to be filled over the coming years.

AstraZeneca Leads Big Pharma

The seminal finding of Catenion's initial R&D productivity analysis was that mid-sized pharma dominated the top-10 firms; this continues today with them taking seven of the top-10 places (*see Exhibit 1*).

The top-five spots contain three firms from last year's analysis, with **Biogen Inc.** retaining the top spot and Novo Nordisk keeping third place, while **Regeneron Pharmaceuticals Inc.** moved back up to fifth at **AbbVie**'s expense. Nevertheless, the gap between mid- and big-sized pharma continues to close, with the standout example being **AstraZeneca PLC.** Back in 2014, AZ languished in 20th position but today is in the second-place spot. What is the driver of this radical turnaround story?

Significant insights can be gleaned through a series of papers published by the company over the past couple of years. In 2011, AstraZeneca transformed its R&D strategy, devising a new 5R Framework whereby all decision-making is built around improving the discovery and development of new drug candidates focusing on the "right" target, tissue, safety, patient and culture (*see Exhibit 2*). This last element, culture, is often overlooked during company strategic reorientations but is arguably the most important component. In this case, AstraZeneca designed internal incentives to reward quality drug candidates versus just sheer quantity of candidates as well as published internal case studies and statistics where higher quality (new assays, focused effort, etc.) facilitated reaching project goals, giving other project teams the confidence to take quality-led approaches.

Ultimately, this meant R&D efforts became front-loaded to reduce the money at risk in later development phases leading to about a 75% drop in the number of molecules in late-stage research and a two- to three-fold increase in target ID projects. Since then, key performance indicators (KPIs) such as cost to percentage of completion (PoC), cycle times, high impact publications and investor

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Exhibit 1

Mid-Size Companies Are Still Top Performers In Both R&D And Overall Company Rankings

R&D PRODUCTIVITY

Final NPV Rank	Company	Momentum (Pipeline NPV)	Long-term (All NPV)
1	Biogen	1	2
2	AstraZeneca	5	4
3	Novo Nordisk	11	5
4	Gilead Sciences	21	3
4	Regeneron	27	1
6	Amgen	12	7
7	AbbVie	3	11
8	Bristol-Myers Squibb	20	6
9	Celgene	2	13
10	Eli Lilly	16	10

TOP 5

COMPANY PERFORMANCE

Final Corp. Growth Rank	Company	Past Performance	Forecast Performance
1	Regeneron	2	1
2	Celgene	3	7
3	Allergan	1	13
4	Otsuka Holdings	13	2
5	Novo Nordisk	5	12
6	Johnson & Johnson	10	10
6	AbbVie	11	9
6	Bristol-Myers Squibb	16	4
9	Biogen	4	18
10	Eli Lilly	18	6

SOURCE: Catenion

sentiment have dramatically improved.

The major driver for AstraZeneca's higher position in Catenion's productivity ranking is a dramatic increase in the NPV of osimertinib (to €27 billion), its highly specific EGFR inhibitor that won approval for first-line LoT EGFR+ NSCLC in 2018 and first entered clinical trials in 2013. This was complemented by the launch of two new drugs, benralizumab (IL-5 mAb) and acalabrutinib (BTK inhibitor), and the increase in value of durvalumab (PD-L1 mAb), likely due to the strong data in stage 3 NSCLC.

Contrasting Fortunes For Other Big Pharma

By contrast other big pharmas have been less successful in boosting their R&D productivity. **Bristol-Myers Squibb Co.** has been slowly slipping down the rankings since 2014 and this year is no different. This was driven by a general devaluation of its marketed drugs, principally the immuno-oncology franchise of nivolumab (PD-1 mAb) and ipilimumab (CTLA mAb), as well as a halving of its pipeline eNPV. The latter was due to the collapse in value of its LAG3 and IDOi compounds, due to poor results from the class, leading to a very poor pipeline rank similar to previous years. The recent announcement of its buyout of **Celgene Corp.** for $74 billion, one of the largest deals ever in biopharma, is likely a response to its dire pipeline situation.

However, a significant chunk of Celgene's pipeline value is attributed to highly complex cellular therapy candidates (JCAR017 and bb2121) which, as Novartis' *Kymriah* (tisagenlecleucel) has demonstrated, have significant commercial hurdles to overcome despite the outstanding efficacy. The majority of the remaining value lies with ozanimod (S1P1 agonist) in multiple-sclerosis, a field with which BMS has little experience. Thus, it remains to be seen if BMS can successfully extract value from the deal beyond just milking the *Revlimid* (lenalidomide) franchise and realizing cost synergies. Overall, BMS' situation represents the general trend in immuno-oncology this year, where almost all of the much-valued checkpoint combination trials have failed to deliver.

Another big pharma to suffer is Johnson & Johnson, which dropped out of the

top 10 to 11th position this year. This was driven by a large reduction in its pipeline NPV due to the launch of apalutamide for prostate cancer and by there being, outside of esketamine, nothing of substantial value remaining in the pipeline. The question thus becomes, how will the company re-build its late-stage pipeline? Considering that the majority of J&J's big value drives in its recent history came through M&A or BD&L – for example, infliximab (roughly €20 bililon NPV, from the acquisition of **Centocor**) and daratumumab (about €24 billion NPV, licensed from **Genmab**) as well as its $30 billion acquisition of **Actelion** last year – it seems likely that deal-making will be the mechanism.

Scaling The Model: Where Do Biogen, Gilead And Regeneron Go Now?

In previous years Catenion has discussed the difficulties of successfully scaling the outperformer model, specifically the need to grow the organization as a result of top-line growth without losing the creative spark that made it so successful in the first place. This is now what Biogen, Gilead and Regeneron face over the coming years while Celgene took the usual "exit" through its planned acquisition by BMS.

Biogen remains in the top spot in this year's ranking after launching four drugs since 2013, which still have an NPV of about €20 billion today. However, the competition in multiple sclerosis is increasingly fierce, putting pressure on the company's key oral drug, *Tecfidera* (dimethyl fumerate). In addition, its pipeline has a startling risk concentration around aducanumab, the beta amyloid targeting mAb in Phase III solely for Alzheimer's disease, which harbors around 80% of its pipeline NPV. The controversy around this drug cannot be understated, and can be broken down into three key points:

- scores of compounds targeting beta amyloid have failed in the disease;
- very little evidence of clinical activity has been seen in early clinical trials of Biogen's compound; and
- Biogen recently expanded the trial size, likely an indicator of lack of confidence in the outcome. If aducanumab failed today, Biogen's pipeline momentum ranking would drop from first to 14th.

Gilead has slipped down the rankings to the fourth spot from second last year. This was entirely due to the launch of its HIV drug combo Biktarvy, which moved around €17 billion NPV out of the pipeline momentum ranking. By contrast Regeneron moved back up two spots, albeit entirely due to companies moving around them. What is common for both companies is that their pipelines are very thin on the ground with just one candidate with an eNPV of more than €1 billion between them, Gilead's filgotinib (JAK1 inhibitor), despite a total market capitalization of around €110 billion.

However, with launches worth around €78 billion in today's NPV between them over the past four years, they are unlikely to be under huge pressure to fill that void right away, especially for Gilead with its **Kite Pharma Inc.** acquisition last year. Nevertheless, even the best companies have to make sure that they do not become complacent as today's success is usually the result of the R&D efforts of five to 10 years ago, and if they do not fix the pipeline of today they will have created a huge problem for the future.

Exhibit 2

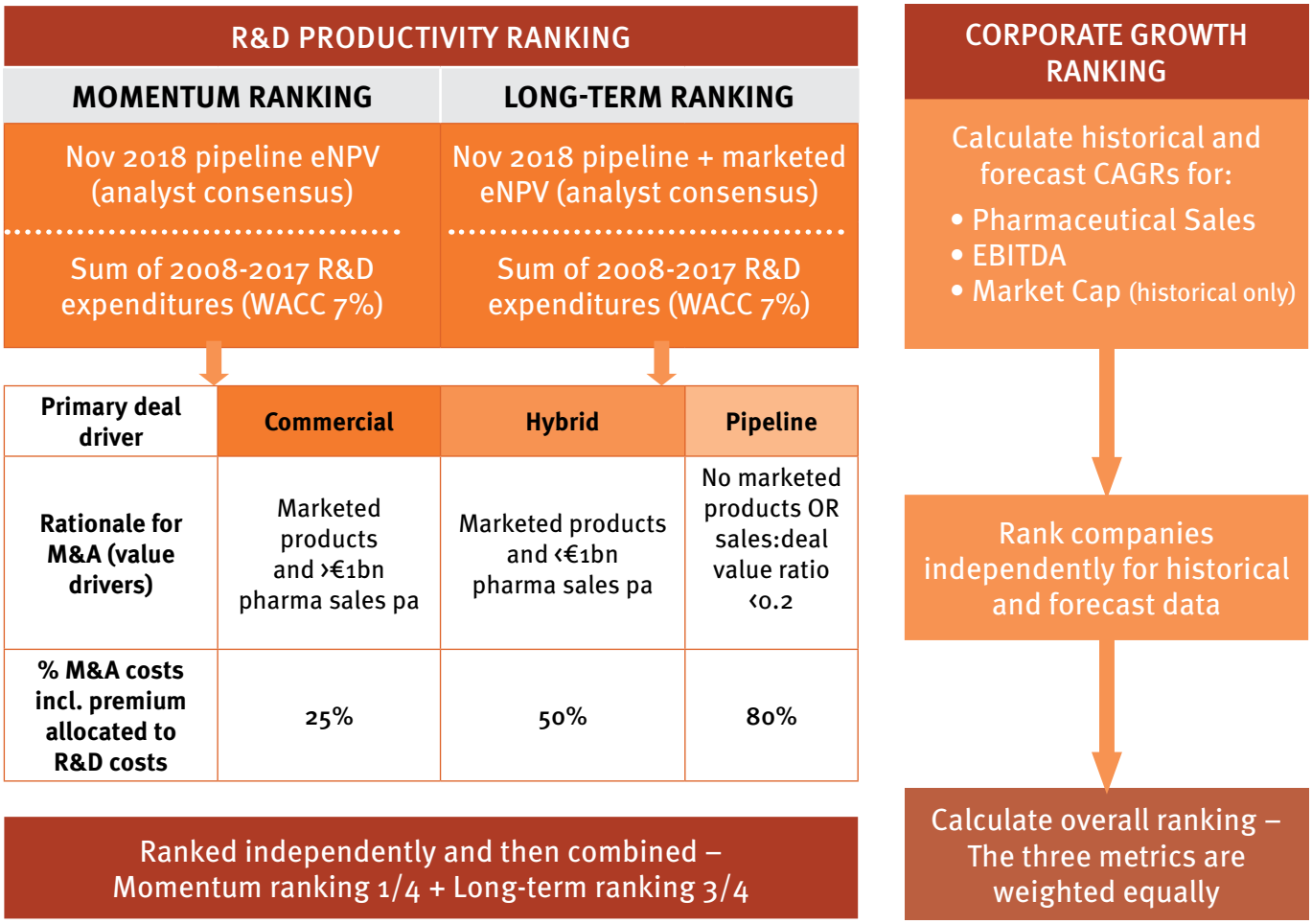
For Each Of The Five 'Rs', AstraZeneca Has Taken Discrete Steps To Improve And Maximize Compound Quality

ASTRAZENECA'S 5R APPROACH

1 THE RIGHT TARGET	2 THE RIGHT TISSUE	3 THE RIGHT SAFETY	4 THE RIGHT PATIENT	5 THE RIGHT CULTURE
• Cutting back-up programs • Shifting to higher causality targets (kinases versus ion channels) • Using complex phenotyping as basis for target ID • Running screens in parallel instead of sequential • Gaining access to biobanks and genomics • Sharing HTS libraries with competitors	**PK** Model based approaches to incorporate ADME as well as additional in-silico, in vitro and preCdata into human PK predictions **PD** Implementation of a novel 'Model-based drug discovery' MBDDxsystem with key focus on PD biomarkers	Implementation of drug discovery model with integrated early toxicology (from Lundbeck) Implementation of novel Models to identify key safety risks early • Liver: 3D liver microtissues • Cardiac: Human iPSC-derived cardiomyocytes • Organoids and microphysio-logical systems	Prioritizing assets with a personalized healthcare approach in place Investing into partnerships and technologies for companion diagnostics • Abbott • Sutter health • Qiagen • Roche • Sarah Cannon Research Institute • Foundation one	Conscious shift from high-volume to project quality and depth of understanding as driver of success Fostering a culture of quantitative science and decision making with the implementation of pre-defined efficacy and safety target Prioritizing science over commercial potential

SOURCE: AstraZeneca

Exhibit 3
High-Level Overview Of Ranking Methodology



Methodology:
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 2008-2017 including costs from M&A and a 7% cost of capital with the total expected net present value (eNPV) today of compounds marketed in the last five years and all pipeline products.

Using these data, two distinct rankings were calculated – a "momentum" and a "long-term" ranking. The momentum ranking aims to capture the value a company is forecasted to generate by taking the current eNPV of its entire pipeline and dividing by the firm's 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 a company has already generated in the recent past – specifically, the eNPV of products marketed in the last five years are added to the pipeline eNPV, whereas 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.

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 more than €1 billion, then it was said to be commercial and thus 25% of the total deal value was added to the R&D costs for that 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 addition, if the total cumulative sales of the target company up until the deal date were less than 20% of the deal value, then the deal was also considered to be a pipeline-driven deal (e.g., AbbVie's acquisition of **Pharmacyclics**). Finally, if a firm had pharma sales less than €1 billion, then it was considered a hybrid of the two deals and thus 50% of the M&A cost were used.

Corporate Growth Ranking

To evaluate the corporate performance of each firm, the historical and forecasted CAGRs for pharmaceutical sales, EBITDA and market cap (historical only) were 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.

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