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Biopharma R&D Productivity And Growth 2016: Innovation Performance Improves

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CATENION UPDATES ITS ANNUAL LIST OF the year's top pharma R&D performers, based on R&D productivity and growth. This year Regeneron shoots to the top and Gilead drops to third place.

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Has R&D productivity increased since last year's analysis? Who are the new entrants into the elite top five group, and who has dropped out? Have the positive innovation dynamics of recent years continued? (*Also see "Value-Based R&D Pharma Productivity 2015: Oncology And Hep C Drive Top Performers" – In Vivo, December 2015.*)

Our annual survey suggests that the fundamental innovation performance of our sample of top 30 companies has improved considerably since we published the first survey in 2014. (*Also see "Value-Based Pharma R&D Productivity: Is There A Sweet Spot?" – In Vivo, June 2014.*) The overall R&D productivity in our sample has increased by 46% from 2014 to 2016 with oncology driving just under half of that rise. This trend holds true both for the metric that looks at pipeline value versus spending (momentum ranking) and for the metric that includes products launched within the last five years (long-term ranking). (*For a detailed description of our methodology, see sidebar, "Methodology: R&D Productivity Ranking."*) Not surprisingly, PD-1 and PD-L1 monoclonal antibodies (mAbs) account for almost 12% of the overall growth, followed by anti-PCSK-9s in cardiovascular and the VEGFr inhibitors in ophthalmology. The biggest loser in value is the monotherapy hepatitis C nucleoside analogue class (e.g., *Sovaldi*); however, this has been offset by fixed-dose combos (e.g., *Harvoni*).

We wanted to be sure that the increase we saw using our value-based method was not just based on broader analyst coverage of assets or analysts simply being more bullish about individual assets, but rather reflected a truly improved outlook in terms of quality and prospects. We have checked the number of assets covered by analysts, and have reviewed the increase in the share prices of these companies, the number of NME approvals and compounds granted breakthrough designations. All data points were consistent with a fundamental improvement in innovation performance.

As our method relies on consensus views of future performance, the impact of external events such as health care reform and drug pricing pressures can still change the picture in the end. Drug pricing in the all-important US market has been a matter of much debate both before and after the recent presidential election. While most of the companies in our top 30 survey are first and foremost in the business of creating value through meaningful innovation for patients, some have focused on more dubious business models by exploiting inefficiencies in pricing and niche marketplace dynamics – for that reason we have excluded **Valeant Pharmaceuticals International Inc.** from our ranking.

Mid-size Companies Still More Productive

On average, mid-size companies continue to dominate the top-five outperformers in both R&D productivity and corporate growth rankings (four of five companies). (*See Exhibits 1 and 2.*) This shows once again that having a deep disease focus and a still manageable size can go a long way in biopharma R&D. (*For another take on mid-size pharma R&D productivity, see "When It Comes To Pharma R&D ROI, Mid Pharma Companies Outperform" – In Vivo, October 2016.*)

With the blockbuster success of **Gilead Sciences Inc.**, **Bristol-Myers Squibb Co.** and others, it was necessary to revise our definition of big pharma from pharmaceutical sales of more than €15 billion to having more than 40,000 employees to ensure this group reflects "traditional" big pharma as was the intention when we started our survey in 2014.

Exhibit 1

2016 R&D Productivity And Corporate Growth Ranking, Top 10 Companies

By and large, mid-sized companies are the top performers in both R&D and overall company rankings

R&D PRODUCTIVITY				COMPANY PERFORMANCE			
Final NPV Rank	Company	Momentum (Pipeline NPV)	Long-term (All NPV)	Final Corp. Growth Rank	Company	Past Performance	Forecasted Performance
1	Regeneron Pharma	2	1	1	Regeneron Pharma	2	1
2	Biogen	1	3	2	Celgene	4	3
3	Gilead Sciences	9	2	2	Shire	5	2
4	Celgene	3	5	4	Novo Nordisk	7	8
5	Novo Nordisk	4	6	5	Allergan	1	15
6	AbbVie	5	10	6	Biogen	6	11
7	Roche	10	9	7	Chugai Pharma	14	4
8	Astellas Pharma	17	7	8	AbbVie	17	4
9	Johnson & Johnson	15	8	9	Bayer	10	13
9	Bristol-Myers Squibb	27	4	10	Bristol-Myers Squibb	20	4

TOP 5

NOTE: Pink=big pharma >40k employees in 2015
SOURCE: Catenion

The relative distance between the outperformers and the rest in absolute terms is still significant, but the difference has become roughly 20% smaller since 2014, showing that the average performance is increasing. Interestingly, big pharma is at the head of the pack with an average rank increasing from 18 in 2014 to 15.3 today and as with last year, a few big pharma companies made it into the top 10 – **Novo Nordisk AS** ranks fifth, and **Roche** seventh, whereas **Johnson & Johnson** shares ninth place with BMS. It seems that several traditional large pharmas may be successfully revamping their struggling R&D organizations, often through clever sourcing of external innovation (in fact, most key value drivers in our top 10 big pharma group stem from external sources or acquisitions). (*Also*

Exhibit 2

Rank Movement Driver Analysis, 2016 Versus 2015

Detailed rationales for companies that have moved ≥2 places in the rankings since the last analysis

R&D PRODUCTIVITY						
Final NPV Rank	**Company**	**Momentum (Pipeline NPV)**	**Long-term (All NPV)**	**2015 Rank**	**Final Rank Movement**	**Major Driver Of The Movement**
1	Regeneron Pharma	2	1	New Entrant		See article
2	Biogen	1	3	2	0	-
3	Gilead Sciences	9	2	1	-2	Cumulative R&D & deal spend has increased 26% while the NPV of their pipeline has decreased 71% to €13.1 bn, primarily because of analyst revaluation of their Hep franchises.
4	Celgene	3	5	5	1	-
5	Novo Nordisk	4	6	3	-2	NPV has increased 252% driven by Semaglutide and faster-acting insulin Aspart which have doubled and tripled respectively. Novo has slipped in the rankings simply because Regeneron and Celgene out-performed them.
6	AbbVie	5	10	3	-3	AbbVie increased its total NPV by 142% primarily due to the launch of Ventoclax and the acquisition of Stemcentrx (for Rovalpituzumab tesirine). This came at the cost of €8.1 bn and thus overall the companies above have outperformed them.

Exhibit 2

Rank Movement Driver Analysis, 2016 Versus 2015 (*continued*)

Detailed rationales for companies that have moved ≥2 places in the rankings since the last analysis

R&D PRODUCTIVITY						
Final NPV Rank	**Company**	**Momentum (Pipeline NPV)**	**Long-term (All NPV)**	**2015 Rank**	**Final Rank Movement**	**Major Driver Of The Movement**
7	Roche	10	9	10	3	The launches of Cobimetinib, Alectinib, Venetoclax, Atezolizumab have almost tripled the total NPV of Roche's marketed products, with the latter contributing 75% of that increase. Despite the 'loss' of Atezolizumab from the pipeline, the NPV of Ocrelizumab has increased 5-fold and the newly valued Emicizumab also makes a significant contribution (~17%). Overall Roche's total pipeline NPV remains virtually unchanged from last year.
8	**Astellas Pharma**	17	7	20	15	The main driver is the NPV of their marketed drugs which has increased 35%, driven by Enzalutamide and Mirabegron.
9	Johnson & Johnson	15	8	11	2	J&J has more than doubled the NPV of its pipeline because Sirukumab, Guselkumab and Apalutamide are valued 4-8 fold higher than last year. Also, the launch of daratumumab has increased the NPV of marketed products by 35%.
9	**Bristol-Myers Squibb**	27	4	8	-1	-

NOTE: Pink=big pharma >40k employees in 2015
SOURCE: Catenion

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 2005 to 2015 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 NPV of its entire pipeline and dividing it 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 NPV before being divided by the total cost as per the momentum rank.

The overall R&D productivity rank was then generated by weighting the momentum rank ¼ versus ¾ 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 greater 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 was, 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 also was considered to be a pipeline-driven deal (e.g., **AbbVie Inc.**'s acquisition of **Pharmacyclics Inc.**). Finally, if a firm had pharma sales of less than €1 billion, then it was considered a hybrid of the two deals and thus 50% of the M&A cost was used.

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) 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.

see "External R&D Is Up, But Which Companies Are Reaping The Most Benefit?" – Scrip, October 5, 2016.)

Shooting Star Regeneron

In 2015, **Regeneron Pharmaceuticals Inc.** became one of the 30 largest biopharma companies, and more importantly, its R&D productivity and corporate growth performance catapulted this new entrant to the top of both our R&D and corporate growth rankings. To many industry observers this is not a big surprise as the company's leadership duo of Leonard Schleifer, MD, PhD, and George Yancopoulos, MD, PhD, has steadily built the firm following a similar path outlined by **Genentech Inc.** under Art Levinson, PhD, or **Merck & Co. Inc.** under Roy Vagelos, MD. It is no coincidence that the latter is chairman of Regeneron's board. Its model for success is based on strong, visionary leadership and a culture of scientific and technological excellence. (*Also see "What Can The Biopharmaceutical Industry Learn From Apple Inc.?" – In Vivo, January 2014.*) Regeneron's slogan, "Make great medicine. And then do it again and again." has become a reality as the company has not only launched best-in-class *Eylea* (aflibercept) for wet age-related macular degeneration (AMD) and diabetic macular edema (DME), but has also created a pipeline containing several potential mega-blockbusters such as dupilumab (anti IL-4 for asthma/atopic dermatitis), sarilumab (anti-IL-6R for RA) and alirocumab (anti PCSK-9 for severe dyslipidemia). Although there have been some setbacks recently (clinical hold for anti-NGF, complete response letter for dupilumab), the long-term prospects look promising, fueled by an ever increasing pipeline of differentiated NBEs, many of which are still fully owned by Regeneron and not part of the large alliance with **Sanofi**.

This type of alliance must be every biopharma CEO's dream as it has created great stability for Regeneron: providing funding for research ($160 million annually for a certain period) and development (Sanofi paying for a large majority of costs), while also providing commercial opportunities (Regeneron gets 50% of US and 35% to 45% of ex-US profits, retains co-promote rights in the US and other major markets). In addition, there is a real commitment as Sanofi took around a 20% equity stake.

Gilead Losing Momentum, BMS Dominated By Checkpoints With Little To Follow

While new entrant Regeneron moved **AbbVie Inc.** out of our top five, the other companies have defended their positions (Gilead, **Biogen Inc.**, **Celgene Corp.** and Novo Nordisk). Gilead as the former number 1 has lost considerable momentum as it has dropped to third place – this is explained by its increasing R&D and deal spending at twice the average rate, and a devaluation of its pipeline with both HepC and HepB forecasts and NPV going down considerably compared with last year (ninth in momentum ranking). The other new entrants in the top 10 are **Astellas Pharma Inc.** (eighth) and J&J (ninth, shared with Bristol-Myers Squibb).

Some may wonder why Bristol-Myers Squibb has been slipping down the productivity rankings since 2014 and only just barely made it into the top 10 today, even though it has the industry's most valuable drug with nivolumab. The short answer is that the company's advanced pipeline, which is considered for our ranking, contains no high-value assets (it is 27th in the momentum ranking). The numerous nivolumab combo trials require development capacities and spending but are counted as life-cycle management of a marketed drug – therefore the long-term R&D ranking of BMS (fourth) is very good, but not sufficient to overcome the poor momentum ranking.

By contrast, when we look at Roche, we can see that in addition to launching four new drugs since our last update, including the highly valuable atezolizumab, the firm also has several high-value drugs in its late-stage pipeline including ocrelizumab (anti-CD20) and emicizumab (coagulation stimulator). This demonstrates how the methodology rewards continuous innovation.

Japanese Pharma At A Crossroads

Japan's Astellas has greatly improved its overall position and is now number 8 in the R&D ranking, driven by the success of marketed drug enzalutamide in prostate cancer, with which it shares rights with **Pfizer Inc./Medivation Inc.** There has also been some notable progress in its pipeline; but when factoring in R&D spending it still only leads to an average pipeline performance (17th). It may take a while before the improved R&D productivity of Astellas fully translates into corporate growth, where the company is number 18 in the ranking.

From an overall corporate growth perspective, the best-performing Japanese company is **Chugai Pharmaceutical Co. Ltd.** (seventh). Chugai obviously also benefits from having access to Roche's portfolio for Japan, in spite of an only average R&D performance (15th).

Nevertheless, overall the Japanese companies cluster toward the bottom part of the ranking (five of seven companies in both R&D and corporate growth rankings). It seems that Japanese pharma is really in a transition phase moving from historical strengths in small-molecule drug discovery in cardiometabolic markets to NBEs, oncology and accessing innovation externally. Globalization of their commercial and R&D footprint as well as management structures is still a top priority for most players, who face little to stagnant growth in their home market. Recently, the first western CEO, Christophe Weber, took the helm at **Takeda Pharmaceutical Co. Ltd.**, a rare but noteworthy exception, and perhaps a sign that Japanese pharma is serious about challenging and changing established views and corporate models.

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