
Productive Innovation Index 2015

White paper:

**Celebrating the top 30 pharmaceutical
companies most successful at
bringing innovations to market**

Productive Innovation Index 2015:

2015	Companies	Change	2014
1	Johnson & Johnson	0	1
2	Gilead Sciences, Inc.	16	18
3	Novartis AG	-1	2
4	Merck & Co., Inc.	2	6
5	Roche Ltd.	-2	3
6	Biogen Idec Inc.	7	13
7	Amgen Inc.	7	14
8	Celgene Corporation	8	16
9	Bayer AG	-2	7
10	Boehringer Ingelheim GmbH	0	10
11	Baxter International Inc.	9	20
12	GlaxoSmithKline plc	-7	5
13	Lilly and Company	4	17
14	AstraZeneca PLC	1	15
15	Bristol-Myers Squibb Company	-11	4
16	Takeda	5	21
17	Abbvie (inc Abbott)	-8	9
18	Novo Nordisk A/S	-7	11
19	Regeneron Pharmaceuticals, Inc.	10	29
20	Sanofi	-12	8
21	Eisai Co., Ltd.	4	25
22	Pfizer Inc.	-10	12
23	Actelion Ltd	3	26
24	Otsuka Holdings Co., Ltd.	-5	19
25	Teva	5	30
26	UCB S.A.	2	28
27	Shire Plc	-5	22
28	Merck KGaA	-4	24
29	Astellas Pharma Inc.	-6	23
30	Lundbeck A/S	-3	27

Overview:

Productive innovation in the pharma industry is at an all-time high. The FDA approved the highest number of drugs last year (44) since 1996. During the past two years, the industry has also witnessed a crop of new drugs that have quickly earned blockbuster status, best exemplified by Gilead's Sovaldi, which has become the fastest growing mega blockbuster of all time. So much for the prophecy that the blockbuster model is dead...

The Productive Innovation Index (PII), now in its fifth year, provides a systematic, objective assessment of how well the top 30 companies perform in bringing new medicines to market successfully.

With the 2015 ranking, we see a number of companies who were outside the top 10 last year make it into the upper rungs. These companies have been star performers – Gilead, Biogen, Amgen and Celgene have all climbed rapidly. Big Pharma delivered a so-so set of results. While J&J, Novartis, Roche and Bayer can count themselves as the best players in the Big Pharma bracket, for the likes of BMS, GSK, Sanofi and Pfizer, it has been a year to forget.

Some of what underpins the performance of the top 10 companies in this years' PII is provided in the commentary below:

1. Johnson & Johnson retains first place. J&J has bucked a trend among Big Pharma by delivering a very strong financial performance when it reported an increase in pharmaceutical worldwide sales of 14.9%. Revenues are up because of high double-digit growth from eight drugs across five disease franchises. The star performer has to be J&J's new Hepatitis C combination, Olysio/Sovriad, which posted over \$2bn in sales in 12 months. Much of the growth is also driven by other launches including Invokana, Imbruvica and Zytiga. Last year also saw a number of new approvals most notably in the form of Invega Sustenna and Rezolsta. J&J also has a solid late-stage pipeline of new drugs, principally across immunology and oncology among an impressive total number of programmes at phase III.
2. Gilead, one of the companies on our watch list last year, has made another significant climb up the PII rankings. Its standout performance sees it just shy of the top spot. The launch of Sovaldi was partly responsible. It was granted breakthrough designation, then launched at the end of 2013, and pulled in over \$10bn in revenue within its first year. Those who speculated it would flop because of limited reimbursement due to the \$84,000 treatment cost didn't appreciate the difference between clinical value and affordability. However, Sovaldi wasn't the only driver of success, when you consider Harvoni was only launched last October, and its sales already outstrip that of Sovaldi, with over 7,000 prescriptions per week, when you look at the same three months immediately post approval. Stribild has also put on a significant revenue growth spurt in 2014. The standings also reflect the FDA approval of the breakthrough designation drug, Zydelig, mid-way through 2014 for three haematological cancers, and CDC backing for Truvada, which is the only drug approved for HIV pre-exposure prophylaxis in high-risk individuals.
3. Novartis remains in the top three for the second year in a row - this year in recognition for its continued double-digit growth from Afinitor, Tasigna, Zortress and Gilenya and from an industry-leading late-stage pipeline. Its position was also helped when it secured a number of new approvals in 2014 including Zykadia for metastatic lung cancer; Xolair for hives; Cosentyx for psoriasis (with another two indications look set to follow in 2015 for psoriatic arthritis and ankylosing spondylitis, given the positivity of the late-stage data); Signifor LAR for acromegaly and Jakavi/Jakafi in polycythaemia vera. Bexsero also had a good year with a breakthrough designation, winning Prix Galien and finally getting FDA approval shortly before the time of writing this white paper. The potentially revolutionary CART-T (CTL-019) also impressed last year, receiving a breakthrough designation and from the perspective of positive mid-stage data in haematological tumours. What pegs Novartis back is a couple of regulatory refusals for serelaxin in heart failure, and withdrawal of the Tasigna application to the EMA for Philadelphia chromosome positive-CML.
4. Merck & Co has climbed two places to 4th in the latest rankings, after a year of transition in 2013. While the financial performance (worldwide sales down 4%) reveals the company is still suffering the effects of loss of patent coverage to key drugs, there were plenty of signs pointing towards recovery. After a hiatus of regulatory approvals it saw nods on a number of its filed drugs: Gardasil 9, Grastek, Zontivity and insomnia drug Belsomra. Most notably was the sprint to the finish line of Keytruda, which was approved by the FDA in September after being granted breakthrough status, and the first PD-1 therapeutic to market, beating Roche, AZ and BMS. Omarigliptin phase III data looked positive enough to allow Merck to begin to build a franchise

around the (plateauing) Januvia. Beyond the most prominent upsides, Merck & Co also boasted a phase II and III pipeline containing no fewer than 25 programmes. Merck had a couple of wobbles in 2014. The combination treatment containing MK-5172 and MK-8742 was granted breakthrough designation in March, but then had suboptimal 4-week data in November. The company also pulled the plug with vintafolide for ovarian cancer and delayed filing for odanacatib given the cardiovascular side effect signal seen in phase III.

5. Roche has fallen in the rankings slightly to sit at 5th place. The R&D powerhouse observed a slow down in revenue growth in pharmaceuticals (+4%), despite strong performances from Kadcyra, Perjeta, Actemra/RoActemra and Xolair. The principal reasons for the drop in PII ranking are the late-stage trial failures for onartuzumab in NSCLC, gantenerumab in prodromal AD, Kadcyra combined with Perjeta, and Kadcyra alone coming up short against Herceptin plus chemotherapy in the MARIANNE study. It was not all bad news. Avastin was approved by the FDA for cervical and ovarian cancers, which has helped to galvanise existing sales. The FDA also approved Esbriet for IPF, a rare lung disease. Gazyvaro was also granted EU approval for CLL. The summer saw very positive data on the cobimetinib/Zelboraf combination. Breakthrough designation status was granted for MPDL3280A, an anti PDL1 antibody, and Lucentis for diabetic retinopathy. Roche is one of the heaviest investors in R&D, is very active in the cancer immunotherapy space with over 30 combination studies running by the end of 2014, and has an overall pipeline boasting 60 new candidates.
6. Biogen Idec, featured on our watch list for the 2014 rankings and it has continued to go from strength-to-strength. A strong financial performance was delivered in the form of double-digit growth over last year and the company also launched four new products. Tecfidera has become recognised as the best MS launch in history, pulling in \$2.9bn. The European regulators approved it in February and Biogen further cemented its future leadership position in the space with an approval for Plegridy, and hitting primary and secondary endpoints in a phase III study with daclizumab. Biogen proved it's not just a one-trick pony when it secured FDA approval for Alprolix for haemophilia B and Eloctate, a drug for haemophilia A, beating other competitors, like Bayer, to market with a new generation of drugs and looking to overthrow Baxter's reign. Biogen also is progressing mid-stage candidates for spinal muscular atrophy, Alzheimer's disease, and acute optic neuritis amongst a dozen mid-to-late stage programmes.
7. Amgen hit a rocky patch prior to 2014, but this year's rankings see it pull off a strong recovery to land in at 7th place. The company had a modest 7% revenue growth supported by strong growth of Enbrel and Vectibix, and the newer products Prolia, Xgeva and Kyprolis. Amgen had FDA approvals for Vectibix in wt-KRAS colorectal cancer, scored a BTM and had a rapid FDA approval for blinatumomab for ALL. Amgen has a strong pipeline with 25 mid-to-late stage programmes on going at the time of writing, principally in oncology and immunology. Last year saw many of the late-stage drugs have positive phase III data, including its PCSK9 inhibitor, evolocumab, brodalumab - which showed superiority to Stelara in plaque psoriasis, Kyprolis in multiple myeloma and AMG-416 for secondary hyperparathyroidism. Amgen had mixed data for its T-Vec cancer vaccine in phase III, but pressed on with US and EU regulatory submissions, believing it has enough evidence to gain approval. The only flops were the failure of a phase III placebo-controlled study with ivabradine, and with trebananib in ovarian cancer.
8. Celgene is another company that has risen rapidly through our rankings, seeing it take a top 10 position with impressive revenue growth of 18%. Building on the great success and continued double-digit growth of Revlimid, Pomalyst and Abraxane, there have been other signs of success that suggest this newcomer to the top tier is not a fleeting visit. Expanding its reach outside of oncology, Celgene has made an immediate impact in the immunology arena. Otezla won FDA approvals for psoriatic arthritis and plaque psoriasis. However, Celgene did suffer one setback with Otezla, when a late-stage study in spinal arthritis failed. Celgene has an impressive mid-to-late stage pipeline across oncology, anaemia and immunology numbering some 30 programmes. The company is also investigating cell-based therapies, of which it has one candidate - PDA-002 in phase II.
9. Bayer fell a couple of places in 2015 despite strong growth from new launches Eylea, Xofigo, Stivarga and Adempas, and a number of new approvals. The only new drug launched by the company last year was Adempas for PAH, and it had already been granted FDA approval towards the end of 2013. However, it's been a great year for Eylea. Multiple regulatory authorities approved it for diabetic macular oedema and the NIH data presented in October showed superiority to Lucentis and Avastin in the same indication. BAY 94-9027 for haemophilia A racked up impressive data last year, but Biogen has already reached the market with their new drug. Nexavar fell over in a couple of phase III cancer studies, one in liver cancer in the adjuvant setting and another in breast cancer.

10. Boehringer Ingelheim (BI) rounds up the top 10 group for a second year running. It has developed its core business around COPD, cardiovascular disease and oncology, and 2014 saw positive advances across all these franchises, starting with strong growth from Giotrif in EGFR positive NSCLC and Trajenta for type 2 diabetes. Vargatef was granted a green light for NSCLC by the CHMP, and then there were FDA approvals for Jardiance (empaglifozin) for diabetes, Striverdi for COPD and Ofev (nintedanib) for IPF, which was also granted breakthrough designation in the same year. BI also presented positive phase III data for the combination of olodaterol and tiotropium for COPD. Volesertib, which received breakthrough designation in 2013, also impressed with phase II data in AML. The company also received breakthrough designation status for the Pradaxa antidote, idarucizumab, which is in phase III. Pradaxa may now pick up the pace and close the gap to Xarelto given FDA and European approvals for DVT and PE. The only negative of last year was when BI discontinued its hepatitis C programme for faldepravir.

Two companies that didn't make the PII top 10, but deserve recognition for their innovation, are Baxter (moving up from 20th to take 11th place) and Regeneron (moving up from 29th to secure 19th place).

While Baxter revenues grew by 11% in 2014, largely from older drugs, the company has gone a long way to maintaining its dominance in bleeding disorders, despite the best efforts of Bayer and Biogen, who are attempting to displace it. Obizur was approved in October by the FDA for bleeding episodes in adults with haemophilia A. Baxter also clocked up positive phase III data for BAX 855 for haemophilia A and BAX 111 for von Willebrands disease. Rixubia was also approved last year for haemophilia B in children. The company is now setting off to diversify and expand into haematology and oncology, and last year Baxter also launched Hyqvia for primary immunodeficiency in adults.

Regeneron is a company transformed since it refocused on Trap Fusion protein technology and fully humanised monoclonals. The launch of Eylea and Zaltrap are the by-products of those endeavours. During 2014, Regeneron impressed with Eylea's multiple approvals, US sales growth, breakthrough designation for diabetic macular oedema and new data. Regeneron also had positive late stage data for sarilumab for RA and mid-stage data for dupilumab for asthma and eczema. Regeneron's PCSK9 monoclonal, Praluent, is also set for a priority regulatory decision mid-way through 2015, so potentially the first of this new class of drug to market, if all goes to plan.

There are plenty of encouraging signs across the top 30 companies in the 2015 PII to suggest that the productivity challenges of a few years ago have abated, given the number of regulatory approvals and number of emerging blockbusters. Success is by no means assured and it will be fascinating to see how 2015 unfolds...

PII methodology:

Hypothesis:

If two companies each had the same NCE at the same stage of development (say end of phase I), which company would do the best job of commercialising the product?

i.e., which company adds most in the strategic sense (but not tactical., e.g. number of reps, details delivered, etc).

Constraints:

Cannot measure directly, therefore need to deploy surrogate measures.

Each measure or index must exist (somewhere), be gettable (either full or derivable), be useable (compare like with like, transferable).

Indices identified to date to rank top 30 pharma include:

1. Global sales/ market capitalisation – a measure of the funding available for commercialisation efforts:
 - a. Trend in historical sales and share movements
 - b. Projected/ analyst forecast sales and share movements
2. Regulatory efficiency: speed to market, end-of-phase I to launch, regulatory success ratio, etc.
3. Attrition rate in phase III - particularly failure on efficacy grounds vs placebo or standard of care
4. Value proposition, need for product:
 - a. Did products achieve reimbursement, NICE approval?
 - b. Did FDA grant expedited processing or breakthrough status?
 - c. Developing first in class NCEs or novel mechanisms of action
5. Sales vs ostensibly similar molecule; relative ranking
6. Gearing, sales and marketing spend vs turnover, etc.
7. Ratio of new product ideas vs 'me-toos'
8. 'Freshness index' - percentage of company sales generated by products launched in the last three to five years
9. Analyst ranking

In addition, IDEA Pharma monitors company websites, annual reports and industry sites to identify single or short-term events that would increase or decrease a company's PII ranking, e.g.

1. Changes in R&D strategy, research collaborations, etc.
2. Company restructuring to capitalise on areas of strength, optimisation of portfolios/ franchises
3. Innovative commercialisation or sales strategies (including social media)

Each of the above are collated by company and weighted to produce the PII.