
Productive Innovation Index 2016

White paper:

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

Productive Innovation Index 2016:

2016	Companies	Change	2015
1	Johnson & Johnson	-	1
2	Takeda	+14	16
3	Novo Nordisk	+15	18
4	Gilead	-2	2
5	AbbVie	+12	17
6	Biogen	-	6
7	Baxter	+4	11
8	Celgene	-	8
9	Otsuka	+15	24
10	AstraZeneca	+4	14
11	Regeneron	+8	19
12	Sanofi	+8	20
13	Amgen	-6	7
14	Roche	-9	5
15	Novartis	-12	3
16	Merck	-12	4
17	Eisai	+4	21
18	Bayer	-9	9
19	Bristol-Myers Squibb	-4	15
20	GlaxoSmithKline	-8	12
21	Astellas	+8	29
22	Pfizer	-	22
23	Lundbeck	+7	30
24	Shire	+3	27
25	Teva	-	25
26	Boehringer Ingelheim	-16	10
27	Eli Lilly	-14	13
28	Merck KGaA	-	28
29	Actelion	-6	23
30	UCB	-4	26

Overview:

It was a mixed year for pharma last year, with a notable high being the record number of NCEs approved by the Food and Drug Administration (FDA) (46). In a reverse of the trend seen in recent years, the top 25 companies by revenue originated 10.7% of the active drugs, slightly up on the 10.5% seen in 2015.

In terms of product number, big pharma's pipeline activity is clustered around oncology, dyslipidemia, hepatitis C and diabetes, and pressure to acquire the best assets will see a continuation of recent M&As, leading to what some describe as 2016 being the "year of merger mania".

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

Within the 2016 rankings, we see Johnson & Johnson retain the top spot for the fourth consecutive year, but following close behind are Takeda, Novo Nordisk, AbbVie and Otsuka that made significant leaps of 10+ places up the ranks to join the top 10. Amongst those making way for them were Roche, Novartis and Merck, all falling nine or more places downwards.

Some of what underpins the performance of the top 10 companies in this year's PII (and the three big fallers) is provided in the commentary below:

Once again, the Janssen Pharmaceutical Companies of **Johnson & Johnson** maintain the number one spot, albeit with the gap to the followers narrowing markedly and overall this was a mixed year for the company.

Immunology remains the main revenue driver at 30% of pharmaceutical sales, but competition and the future patent expiration for Remicade[®] will challenge the strong U.S. immunology growth and increased penetration of Simponi Aria[®]. Rather than rest on its laurels, the company continues to push the innovation bar in immunology with Stelara[®], that is awaiting U.S. and EU decisions for Crohn's disease indications, and two new filings expected this year in RA (sirukumab) and psoriasis (guselkumab).

After being one of the company's strongest launches to date, Zytiga[®] is facing increased competition – particularly in Europe in prostate cancer, but sales have been boosted by market growth across other regions. Elsewhere in oncology, sales of Imbruvica[®] grew due to new indications and strong patient uptake.

The company's cardiovascular and metabolism assets Xarelto[®] and Invokana[®] are growth drivers in high growth markets that are underpenetrated: seeing Xarelto[®] continue its novel oral anticoagulant U.S. market leadership through the end of 2015, and the U.S. filing in the same year for Invokamet[®] XR, a once-daily therapy combining fixed doses of canagliflozin and metformin hydrochloride extended release for the treatment of adults with type 2 diabetes.

With an industry leading 16 new medical entity launches since 2009 and plans to file 10 further new products by 2019, each with billion dollar plus potential, this is one company that leads by example.

Takeda continues to show strong sales growth, driven by the US and emerging markets (especially Russia and China), with gastroenterology delivering a 25% sales uplift on the previous year.

The company also continues its ability to balance creating efficiencies and pruning costs without compromising its commercial performance, resulting in a financially and commercially very "sound" operation.

Its strong position in multiple myeloma with Velcade[®] will be reinforced by December's approval of Ninlaro[®], the first once-weekly oral proteasome inhibitor, enabling the first all-oral triplet regimen that includes both a proteasome inhibitor and an immunomodulator for the treatment of relapsed and/or refractory multiple myeloma, a disease area of huge unmet need.

Takeda continued its aggressive global launch strategy with Entyvio[®] for ulcerative colitis and Crohn's disease (projected \$2 billion peak year sales), Takecab[®] for the treatment of acid-related diseases, Adcetris[®] for malignant lymphoma, Brintellix[®] for major depressive disorder and Zafetak[®] for type 2 diabetes (T2D).

Notably, Brintellix[®] had its label for major depressive disorder amended to improve cognitive function (approved in EU, FDA decision expected in March), the first to do so. Given that cognitive function is important in Alzheimer's disease, bi-polar disease and a whole range of other CNS disorders, this could lead to Brintellix[®] being the anti-depressant of choice across a huge number of patients.

Novo Nordisk chooses to operate in diabetes that remains a fiercely competitive therapy area, with three dominant players: Novo Nordisk, Eli Lilly, and Sanofi. The key emergent feature of the market is each individual player

attempting to fill any gaps within their diabetes portfolios, whilst leveraging existing access to physicians, and utilising strong sales and marketing forces.

Overall the T2D market will expand due to an increasing patient population and the rise in use of novel therapies at second and third lines with Novo Nordisk maintaining a (shrinking) lead.

Growth of insulin and glucagon-like peptide-1 (GLP-1) receptor agonists over the coming years, is leading the market to expand. Novo Nordisk will continue to lead the diabetes market, while Sanofi, Eli Lilly, and Merck will follow closely behind. The companies will aim to capture growth, driven by an increasing patient population and the rise in use of novel therapies at second and third lines.

Novo Nordisk's leading agents, Victoza[®] (GLP-1 agonist in T2D), and Levimir[®] (insulin used in type 1 diabetes (T1D) & T2D), both show strong growth currently and that 2015 approval of Tresiba[®] will add to the company's dominance in T1D.

Notably, it is forecast that Sanofi will supplant Novo Nordisk in 2020 to become the largest player in the Endocrine, Metabolic, and Genetic Disorders market (EM&GD).

Novo Nordisk is aware of its over-dependence on EM&GD and is attempting to leverage and expand its haematology franchise in particular, that currently stands at 11% of turnover.

Note that financial management plays an important part in Novo Nordisk's high ranking in that the percentage of sales spent on marketing, operating costs, etc., compared to its peer group, indicates a particularly well run and efficient organisation. Given that the basic question underlying the PII is "If I had an early phase asset, to whom would I license it for maximum return?" then this becomes an important consideration.

In purely sales terms, **Gilead** had a spectacular 2015 reporting \$32.2 billion sales compared to \$24.5 billion in 2014. Sovaldi[®], which had seen the most successful launch in pharma history, actually declined in sales (with increasing competition to come from AbbVie's Viekira Pak[®], Merck's elbasvir/grazoprevir). This, however, was offset by the uptake of Harvoni[®] that was launched in late 2014, and Sovaldi[®] and Harvoni[®] sales in Japan trebled to nearly \$4 billion.

Gilead is already charging ahead this year, planning to roll out a new hepatitis C combo pill that treats genotypes 1-6 of the virus with the FDA granting the medicine a speedy review (final decision expected by the end of June). In addition, pivotal phase III study results and NDAs are planned throughout 2016 across both liver disease and HIV/AIDS.

Focus on other therapeutic areas is lower key, but impressive data were published for Zydelig[®] in second-line chronic lymphocytic leukemia (CLL). A FDA indication was gained in pulmonary arterial hypertension for Letairis[®]. Phase II and III studies were announced across several inflammatory conditions.

The company is being cautious in terms of future sales projections, however, citing competition and increased payer pushback whilst highlighting that future growth will be driven by partnerships and acquisitions.

Given its short timespan to date and aggressive programme of launches, it is not surprising that Gilead's portfolio is characterised by new products. This is evaluated within the PII by the Freshness Index rankings: The Freshness Index 2010-15 is the percentage of 2015 sales generated by products launched from 2010 onwards, similarly for Freshness Index 2012-15. These are known as FI10-15 and FI12-15 respectively and Gilead's scores are nearly 69% for both. To put this into context, the average FI scores across all the PII companies are 29% and 16%.

At first glance, the acquisition of Pharmacyclics delivers on two fronts for **AbbVie**: it reduces the company's dependency on revenues from Humira[®] (the world's best selling drug), which is set to face biosimilar challenges and also expands its presence in oncology, specifically CLL and other haematological cancers.

This may prove to be complex and expensive, particularly as Johnson & Johnson already owns 50 percent of the drug Imbruvica[®], into which much of Pharmacyclics' value is effectively tied.

As stated, AbbVie's oncology pipeline strengthened with the purchase of Pharmacyclics and the company has now received three FDA Breakthrough Therapy Designations for venetoclax across CLL and acute lymphoblastic leukaemia (ALL), plus a Priority Review in multiple myeloma for Empliciti[®].

AbbVie still has faith in Humira[®] and is continuing the process of generating additional indications, and also building on its already 90-country wide coverage by pushing more and more into emerging markets.

It has also strengthened its position in Parkinson's disease with the approval of Duopa[®]; with a novel delivery system aimed at late stage patients who currently have limited treatment options.

The company's Viekira Pak[®] continues to carve out Hepatitis C subpopulations and was recently granted a priority FDA review in patients with compensated cirrhosis.

AbbVie's host of positive data in late stage studies across oncology and immunology, for both novel and launched compounds, indicates that its policy of novel launches and maximising penetration of existing brands will continue.

Biogen's Tecfidera[®], which launched in the US in early 2013, is set to overtake Novartis' Gilenya[®] as the leading product in multiple sclerosis (MS) due to a balance of efficacy and tolerability that makes it an ideal first-line

treatment option. Tecfidera® carries no contraindications, and the only monitoring requirement is for a recent complete blood count test. This positions Tecfidera® favourably against Gilenya® and Tysabri®, which carry notable safety uncertainties and onerous monitoring regimens.

Already dominant in treating MS with Tecfidera®, Tysabri® and interferons, Biogen is now looking at reversing or repairing MS changes with an innovative phase II study of anti-LINGO-1, an antibody intended to stimulate regrowth of the myelin sheath.

The company's commitment to CNS continues with phase III assets in Alzheimer's disease, MS and spinal muscular atrophy (SMA), and earlier stage studies in Parkinson's disease and amyotrophic lateral sclerosis (ALS). The oncology franchise, current at \$1.3 billion, looks to expand particularly by expanding the indication range of obinutuzumab.

Biogen's commitment to replenishing and supplementing its portfolio is reflected in its Freshness Index rankings. Biogen's FI10-15 and FI12-15 respectively scores near 43% for each (versus average scores of 29% and 16% across all the PII companies).

Baxter's decision to spin off its biological sciences division into Baxalta clearly created a company with an attractive portfolio and pipeline as evidenced by Shire's \$30+ billion bid for it.

Baxter itself continues to set the trend in providing support and services above and beyond the core drug offering, particularly in parenteral nutrition and renal dialysis.

Although light in approval/launch terms, Baxter made significant announcements regarding late stage assets in two areas of high unmet medical need: pacritinib®* in myelofibrosis and BAX817 in patients not responding to standard treatments for haemophilia. Like Gilead and Biogen, Baxter is committed to replenishing its portfolio regularly. In fact, its scores of nearly 70% each are the highest across the rankings for both FI10-15 and FI12-15.

*Note: In mid-February 2016, the FDA decided that the adverse events and deaths recorded in pacritinib®'s pivotal programme of the myelofibrosis drug pacritinib® were of a scale to impose a full clinical hold on the trial, halt dosing and retract the newly completed drug application. This will be reflected in the 2017 PII rankings.

The US market remains **Celgene's** focus (US: global = 2:1 for key product sales) with total net product sales growing 24% over 2014. Despite its time on the market (US launch 2005), Revlimid® continued its steady growth to \$6 billion and beyond, driven by increased duration of therapy and its added indication in newly diagnosed multiple myeloma. Pomalyst®/Imnovid® is being kept to refractory third-line cases to protect Revlimid®, but still generated \$300 million in Q4 alone.

European approval of Abraxane® will add to its current blockbuster sales status and the antipsoriasis drug Otezla®, demonstrated the efficacy in patients who switch over from Pfizer and Amgen's injectable competitor Enbrel®.

Celgene spent 34% of turnover on R&D (bettered only by Regeneron in the PII table), focusing on haematology/oncology and inflammation/immunology. In addition to developing new data for its marketed products, it is collaborating with AstraZeneca on an extensive clinical development programme with durvalumab, in a range of hematologic malignancies and has also initiated a pivotal phase III study in active Crohn's disease for GED-0301.

Otsuka continues to maintain focus on its two key therapeutic areas – CNS and oncology.

Abilify Maintena® (once-monthly injection in schizophrenia) generated significant growth in sales in the U.S. aided in part by expanding the routes of administration available. In addition, Rexulti® received approval from the FDA in July 2015 simultaneously for both schizophrenia and adjunctive therapy in major depressive disorder. In pipeline terms, assets in phase III and Onzetra® seeking FDA approval in migraine (approved in January 2016), indicates that CNS will remain the company's core focus.

In terms of oncology, all of Otsuka's current late phase assets are slated for Japanese approval only. After Lonsurf®'s FDA approval in September 2015, for refractory/intolerant recurrent colorectal cancer, all other EU/US solid tumour therapies are in phase II at the latest – although there are both blood tumour and cancer pain assets in phases II & III across all markets.

AstraZeneca has sought to maximise the emerging markets perhaps more than any other company with China representing 11% of its global turnover. This is now AZ's second largest market and a key growth platform.

The company had the fourth biggest pipelines in terms of drug numbers and was active in regulatory terms with a significant label update for Brilinta®, accompanied by submission acceptances and accelerated reviews in cancer, respiratory diseases and lupus. In particular, the oncology portfolio maintained its momentum with four Priority Review and Fast Track designations as well as supportive data at key congresses.

Even though durvalumab's failure in phase III, as a checkpoint inhibitor monotherapy in lung cancer, was seen as a setback, the company still sees it as a cornerstone of immune-oncology when used in novel combinations.

The recent acquisition of ZS Pharma gives AZ access to the potential blockbuster hyperkalaemia treatment ZS-9 (with the possibility that it could build out the franchise further by buying Receptos).

AstraZeneca is suffering from a new round of patent losses, and that will only worsen even after facing generic competition to its former top-seller, Nexium, with the next two years seeing it lose protection on two key assets, first with Crestor[®] and then Seroquel XR[®].

The rankings are also notable for three very large (top 10 in sales terms) companies which tumbled out of the PII top 10: Roche, Novartis and Merck.

Whilst **Roche** did not have a bad year, it certainly was not as impressive as previous ones. A modest sales growth driven by Avastin[®] and Herceptin[®] (both of which will face generic/ biosimilar competition) and Perjeta[®], all of which sit in oncology. Generic competition also faced Valcyte[®]/ Cymevene[®] and Xeloda[®], and Pegasys[®] declined due to increased competition. Whilst many companies would have been pleased with the approvals and breakthrough designations obtained by Roche, comparison to previous years' performance pushes them down the table.

Novartis reported flat sales and the acquisition of GSK's oncology assets has yet to make an impact on cash flow. Gilenya[®] continues to give ground in MS to Biogen's Tecfidera[®] due its FDA-mandated restrictions and monitoring, coupled with increasing concerns around progressive multifocal leukoencephalopathy (PML). The overturning of a key US patent also diminishes Gilenya[®]'s future projections.

Considerable emphasis was placed on Entresto[®] in congestive heart failure, but its impact has been blunted by formulary National Drug Code (NDC) blocks for six months post-launch.

Generic competition hit Novartis to the tune of \$2.8 billion in 2015 (largely for Exelon Patch[®], Diovan[®] monotherapy and Vivelle-Dot[®] in the US) and this is expected to rise to \$3.2 billion in the coming year, particularly regarding Glivec.

A \$3 billion decline in annual sales for **Merck** also coincided with a lacklustre regulatory year with one (minor) FDA approval and little in the way of groundbreaking phase III data.

Keytruda[®], which has current FDA approvals in melanoma and non-small cell lung cancer, appears key to future attempts to reverse this with the company announcing that it plans over 100 studies involving Keytruda[®] in combination with other drugs.

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.