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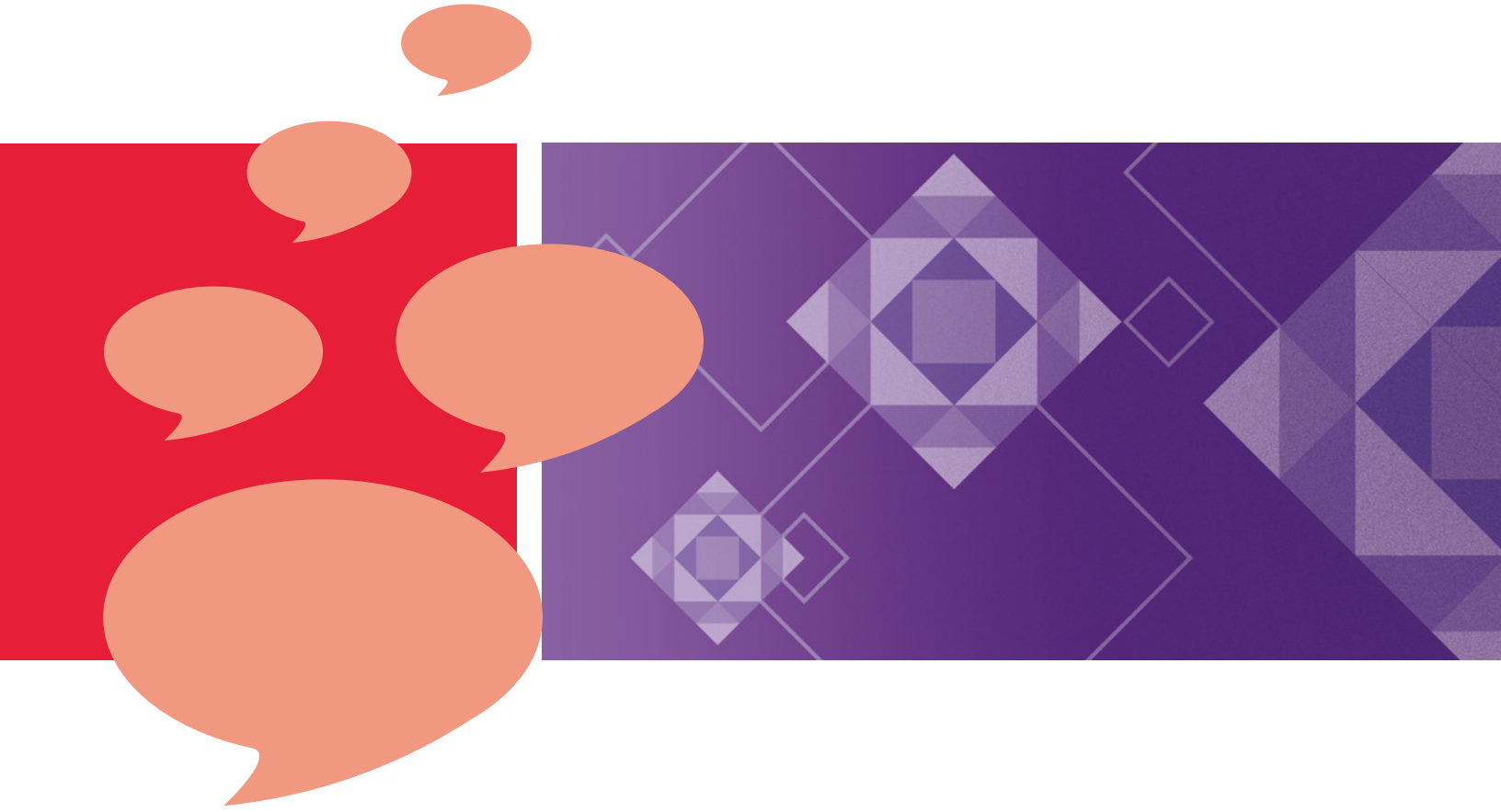
PHARMA & BIOTECH 2015 PREVIEW



EvaluatePharma®

For those seeking proof of the pharma sector's ability to innovate, 2015 promises much evidence.

A dozen products due to be launched next year are forecast to reach blockbuster sales by 2020, including new drug classes in huge disease areas such as cardiovascular and respiratory diseases. Cancer will also have a big year as the promise of immuno-oncology therapies like the checkpoint inhibitors are further tested in both the market and in the clinic.

At the other end of the market, the lack of any really substantial patent expiries will be another boost to the industry's top line – the potential loss of exclusivity of Teva's Copaxone and the confirmed departure of Otsuka's Abilify notwithstanding. *EvaluatePharma* data show that, overall, the pharma industry is set to replace sales lost to patent expiries more than three times over next year. This is a far cry from the desperate year of 2011, when generics bit hard and big drug approvals were hard to find.

Since then, investor sentiment towards the pharma sector has improved greatly. Soaring drug stock indices make this clear, and given the tailwinds mentioned above it is hard to see a major retrenchment happening in the markets in 2015. One ominous-looking cloud is reimbursement, particularly in the US, where payers are increasingly flexing their muscles in an attempt to restrain drug prices.

It also seems unlikely that the M&A frenzy will continue, at least to the same level, sapped by the desertion of political will to tolerate tax-driven takeovers. Deals worth more than $200bn were announced in 2014, the most since 2000, which saw two huge mega-mergers.

But as long as stock markets remain in a jubilant mood deals will still happen at a fair lick, and the financing climate in particular should remain friendly.

Overall, 2015 is shaping up to be a robust year for the drug industry.

The big launches of 2015

Should the dozen future blockbusters on the cards for approval next year reach the market, 2015 will overshadow even the impressive class of 2013. That year saw the arrival of huge products like Sovaldi, Tecfidera, Imbruvica and Kadcyla.

The value of 2015 launches will be helped along by penetration into massive yet already well-trodden sectors like cardiovascular and respiratory disease, along with diabetes and schizophrenia. Drugs treating high cholesterol and heart failure are set to dominate the year's new products, with combined 2020 sales forecast at $8bn.

The analysis below is based on a consensus of equity analysts' expectations, collected by *EvaluatePharma*.

Top five biotech and small molecule launches of 2015

					Annual Sales WW ($m)	
	Product	**Therapy area (pharma class)**	**Company**	**Phase**	**2015**	**2020**
Biotechnology	Alirocumab	LDL lowering (anti-PCSK9 MAb)	Sanofi	Phase III	44	2,179
	Evolocumab	LDL lowering (anti-PCSK9 MAb)	Amgen/Astellas	Filed	77	1,947
	Toujeo	Diabetes (long-acting insulin)	Sanofi	Filed	139	1,692
	Mepolizumab	Severe asthma (anti-IL-5 MAb)	GlaxoSmithKline	Filed	28	1,161
	Cosentyx	Psoriasis (anti-IL-17A MAb)	Novartis	Filed	133	1,099
Conventional	VX-809 + ivacaftor	Cystic fibrosis (CFTR corrector)	Vertex Pharmaceuticals	Filed	575	4,744
	LCZ696	Heart failure (AT1 & ARNI)	Novartis	Phase III	251	3,875
	Palbociclib	Breast cancer (CDK 4 & 6 inhibitor)	Pfizer	Filed	281	3,078
	Selexipag	PAH (prostacyclin agonist)	Actelion	Phase III	18	1,245
	Brexpiprazole	Schizophrenia (5-HT1A & D2 & 5-HT2)	Otsuka Holdings	Filed	95	1,141
Biggest US launch…	Opdivo	Cancer antibody (anti-PD-1 MAb)	Bristol-Myers Squibb	Filed (US, EU)	658	7,122

Source: EvaluatePharma® December 2014

The most keenly awaited launches of the year should come from the competing cholesterol-lowering drugs alirocumab from Sanofi and evolocumab from Amgen. These potent antibodies target PCSK9, a protein that modulates low-density lipoprotein cholesterol (LDL-C) metabolism in the liver. They are reckoned as a potential option for patients with inherited forms of heart disease as well as those who cannot effectively lower LDL-C on cheaper statins.

The PCSK9s' ability to address that latter market will have a significant bearing on their eventual outlook, especially as payers will want to look closely at maximising statin dosing and substantiating intolerance before authorising use of what are likely to be very expensive products.

Remaining in the cardiovascular sector, Novartis's heart disease project LCZ696 is forecast as the biggest individual drug launch of the year in that space. The combination pill has shown a strong benefit in preventing cardiovascular death or hospitalisation in heart failure patients and would be the first new drug to be launched in the indication in years. As it has not been submitted in either the US or Europe, it may be a stretch to get the regulators' OK in 2015, although the European Medicines Agency's recent award of accelerated assessment raises the possibility that it will make a year-end deadline.

The respiratory sector will come a close second to cardiovascular, with launches of Vertex Pharmaceuticals' cystic fibrosis combination, Actelion's pulmonary arterial hypertension pill selexipag and GlaxoSmithKline's eosinophilic asthma drug mepolizumab.

Vertex's VX-809 + ivacaftor, the latter the generic name of the marketed cystic fibrosis drug Kalydeco, is slated to be the biggest single product of 2015's rich field. The pairing should allow Vertex to tap a bigger market, as Kalydeco alone has a target population of only about 3,000 patients who have a G551D mutation. Approval of VX-809 would expand it to those patients with two copies of the F508del mutation, which includes about 22,000 patients in North America, Europe and Australia.

Actelion has gone from strength to strength in building a pulmonary hypertension franchise, and selexipag has a good chance of adding significantly to this with its strong morbidity/mortality benefit. Glaxo, on the other hand, may have more of a challenge in meeting the blockbuster expectations for mepolizumab – the UK group has stumbled in trying to extend its reach in asthma beyond Advair, and certainly payers will be looking to minimise the number of patients taking a biological for a lung disorder.

The same will be true of Toujeo, Sanofi's follow-on to the venerable long-acting insulin Lantus. With Eli Lilly's biosimilar Lantus expected to debut next year, Toujeo's trajectory will be closely watched to see if its $1.7bn sales forecast is likely to be achieved in 2020.

As with mepolizumab, Toujeo and the PCSK9 agents, Novartis's Cosentyx, an antibody for moderate and severe plaque psoriasis, will have payers applying fairly restrictive reimbursement criteria. A positive recommendation from European regulators bodes well for its approval in both the EU and US.

This analysis includes a forecast for Bristol-Myers Squibb's immuno-oncology project Opdivo. An approval for partner Ono in Japan makes this technically a marketed product, but its FDA decision by the end of March will be one of the big events of 2015.

The top sellers of 2015… and beyond

The progress of next year's next-big-things will be closely watched for regulatory hold-ups and success on launch. Those already on the market, meanwhile, will be monitored for their ability to meet expectations, and a look at what analysts expect next year's top sellers to look like yields a list of familiar names. Few should deliver surprises.

Top 10 forecast worldwide sellers in 2015

Product	Company	Therapy area (pharma class)	Annual Sales WW ($bn) 2015	2020	Launch
Sovaldi + Harvoni	Gilead Sciences	Hepatitis C (NS5B & NS5A polymerase inhibitors)	15.3	12.5	2013
Humira	AbbVie	Anti-rheumatic (anti-TNF Mab)	14.1	13.5	2003
Lantus	Sanofi	Diabetes (Insulin analogue)	8.0	5.7	2000
Rituxan	Roche	Cancer antibody (anti-CD20 Mab)	7.6	5.5	1997
Avastin	Roche	Cancer antibody (anti-VEGF Mab)	7.2	6.3	2004
Herceptin	Roche	Cancer antibody (anti-HER2 Mab)	6.6	5.3	1998
Seretide/Advair	GlaxoSmithKline	Bronchodilator (LABA & ICS)	6.3	3.0	1998
Remicade	Johnson & Johnson	Anti-rheumatic (anti-TNF Mab)	6.0	5.9	1998
Revlimid	Celgene	Blood cancers (immunomodulator)	5.7	8.0	2006
Crestor	AstraZeneca	Anti-hyperlipidaemic (statin)	5.2	1.6	2003

Source: EvaluatePharma® December 2014

Only Sovaldi, Gilead's potent new hepatitis C antiviral that reached the market a mere 12 months ago, can be classed as a new launch. Its phenomenally quick uptake has taken it straight to the top spot.

A quirk of analyst forecasting means that this number is slightly disingenuous as it also includes sales of Gilead's second oral anti-viral, the combination Harvoni. Many banks only provide forecasts for the franchise as a whole, and it seems likely that sales of Sovaldi as a stand-alone product will come in below Humira next year.

Either way, the huge success of these hep C products, which promise a quick and painless cure for many sufferers of the virus, is undisputable. And should AbbVie object to Humira's second place it can always comfort itself with thoughts of longevity. Analysts expect sales of Sovaldi and Harvoni to peak in 2016 – the result of the clearing of the "warehouse" of patients and competition from elsewhere – after only three years on the market. Humira is projected to peak in 2017, 14 years after its launch, and reclaim the top spot by 2020.

After Sovaldi the most recently launched drug in the top 10 next year is Celgene's Revlimid, approved to treat a range of blood malignancies. Growing use in its dominant indication, multiple myeloma, is

projected to drive sales growth to the extent that consensus for 2020 shows it as the third biggest-selling drug that year.

The resilience of this franchise could also depend on novel immuno-oncology approaches like the anti-PD-1 antibodies disappointing in haematological cancers. Looking forward to 2020 shows that a number of these big franchises are expected to make way for new arrivals in the approaching years. For example very swift uptake is forecast for Opdivo, currently seen as the most promising anti-PD-1 antibody; Astellas and Medivation's prostate cancer drug Xtandi is seen capturing a significantly bigger share of the market; and Biogen Idec's oral MS therapy Tecfidera continues to go from strength to strength.

Top 10 forecast worldwide sellers in 2020

Product	Company	Therapy area (pharma class)	Annual Sales WW ($bn) 2015	2020	Launch	2015 rank
Humira	AbbVie	Anti-rheumatic (anti-TNF Mab)	14.1	13.5	2003	1
Sovaldi + Harvoni	Gilead Sciences	Hepatitis C (NS5B & NS5A polymerase inhibitors)	15.3	12.5	2013	2
Revlimid	Celgene	Blood cancers (immunomodulator)	5.7	8.0	2006	9
Opdivo	Bristol-Myers Squibb	Cancer antibody (anti-PD-1 Mab)	0.6	6.5	2015	249
Tecfidera	Biogen Idec	Multiple sclerosis (Nrf2 pathway activator)	3.9	6.5	2013	21
Avastin	Roche	Cancer antibody (anti-VEGF Mab)	7.2	6.3	2004	5
Remicade	Johnson & Johnson	Anti-rheumatic (anti-TNF Mab)	6.0	5.9	1998	8
Soliris	Alexion Pharmaceuticals	Haematological conditions (anti-C5 Mab)	2.7	5.8	2007	32
Lantus	Sanofi	Diabetes (insulin analogue)	8.0	5.7	2000	3
Xtandi	Astellas Pharma	Cancer (androgen receptor antagonist)	1.8	5.5	2012	63

Source: EvaluatePharma® December 2014

Most valuable indications

Many of the features of the biggest-selling drug analysis above are reflected in a look at the most valuable indications.

It is notable, however, that next year's most valuable indication by far – type 2 diabetes – only has one product in the top 10, Sanofi's long-acting insulin Lantus. With a number of novel drug classes – including the DPP-IV inhibitors and the GLP-1 antagonists – having reached the market in the last decade, this is an indication in which the drugs will retain valuable exclusivity periods for some time. Add to this a rising incidence in type II diabetes and it is clear that this disease area will remain lucrative for drug makers for some time, though it is a highly competitive space facing increasing pricing pressures.

Top 10 indications in 2015

	Annual WW Sales (Indication) ($bn)		
	2015	2020	CAGR
Type II diabetes (maturity onset)	41.43	59.17	7%
Hypertension	24.20	22.93	(1%)
Rheumatoid arthritis	23.52	28.68	4%
HIV treatment	21.28	22.60	1%
Hepatitis C treatment	21.20	21.75	1%
Multiple sclerosis	20.88	26.54	5%
Asthma	16.09	16.45	0%
Hyperlipidaemia	15.44	15.08	(0%)
Breast cancer	13.39	24.52	13%
COAD/COPD	11.77	16.16	7%

Source: EvaluatePharma® December 2014

The opposite is true for hypertension, where a number of big classes have lost patent protection – Novartis's Diovan is a recent high-profile example. Rheumatoid arthritis will retain its value as an indication largely thanks to the sustainability of the expensive biologics used to treat this disease. Despite having been around for some time the dim prospect for competition from biosimilars, particularly in the US, means that this is expected to remain a lucrative disease area for the companies involved.

Finally, hyperlipidaemia would be showing a substantial decline in the coming years, reflecting the loss of patent protection for the statin class, were it not for the projected success of the anti-PCSK9s.

Five fast growing indications (2015 sales >$1bn)

	Annual WW Sales (Indication) ($bn)		
	2015	2020	CAGR
Melanoma	2.7	8.8	27%
Chronic lymphocytic leukaemia	2.6	8.5	27%
Non-small cell lung cancer	7.3	23.7	26%
Stroke prophylaxis, secondary to AF	6.2	11.9	14%
Non-Hodgkin lymphoma	7.3	13.9	14%

Source: EvaluatePharma® December 2014

Looking forward, the projected fastest-growing indications of next year also reflect the rise of various high-profile and novel drug classes.

Growing use of the anti-PD-1 antibodies Opdivo and Keytruda are largely responsible for projected growth in melanoma and lung cancer.

Elsewhere, the treatment of chronic lymphocytic leukaemia is being transformed by the arrival of the BTK inhibitor Imbruvica, while the expected arrival of AbbVie's venetoclax a year or so down the line promises further treatment advances.

Imbruvica is also projected to make its mark in non-Hodgkin lymphoma, although Gilead's Zydelig, a PI3K inhibitor, was approved here in 2014.

Preventing stroke in patients with atrial fibrillation is already a highly valuable indication, thanks to the oral anticoagulants Xarelto, Pradaxa and Eliquis that have reached market in the last five years or so. Analysts expect their use to broaden substantially.

A focus on earlier data: immuno-oncology is set to dominate attention

The advance of immuno-oncology over the past couple of years has been notable not just for the responses generated in previously untreatable patients, but also for the speed of progress. The previous analysis run even 12 months ago, for example, would probably not have seen such growth expectations for lung cancer and melanoma indications.

This field of research will remain a key focus in 2015, and should the checkpoint inhibitors and other immuno-oncology approaches make inroads into other tumour types – data in bladder and ovarian cancers have shown promise – fast growth could soon be forecast for other indications.

But much focus will also be on earlier-stage research, where new targets are emerging that could provide new areas worthy of investment.

OX40, for example, is already a keenly watched mechanism which, in contrast to checkpoint inhibition, belongs to a group of immune system targets which cause immune system activation. The most advanced OX40 asset appears to be AstraZeneca's MEDI-6469, in phase II, while Roche recently said very early data on its RG7888 combined with PD-L1 therapy might emerge next year.

Other targets here include CD137 (also known as 4-1BB), where Pfizer and Bristol are developing PF-05082566 and urelumab respectively.

Another closely followed target is LAG-3, which like PD-1/PD-L1 and CTLA-4 is a checkpoint that allows tumour cells evade immune response. Bristol, Immutep, GlaxoSmithKline, Agenus and Tesaro are working in this space.

Another hot area is innate immune system checkpoints – specifically those expressed on natural killer cells, like KIR and NKG2A. The French firm Innate Pharma claims near exclusivity here, and 2015 should see the readout of a phase II trial of its anti-KIR MAb lirilumab, based on which its partner Bristol will decide whether to file.

Most importantly, perhaps, there is combination therapy. The clear aim here is to target patients who at present do not seem to be responding to monotherapy, and also to reduce the dose of each component to try and combat some notorious immunological side effects.

Thus, while 2015 will give the first clinical insight into follow-on approaches, the way in which they might fit into treatment could take longer to pin down.

Next year will of course yield important data for a number of other therapy areas. For example Novo Nordisk is waiting to find out whether interim data from its huge outcome study on the insulin follow-on Tresiba are good enough to satisfy US regulators, it should also unveil the first phase III data on its once-weekly follow-on to blockbuster Victoza, semaglutide. UCB is due to announce the results from the pivotal programme testing its lupus antibody, epratuzumab; given past failures in this space a win would be considered a huge deal.

Earlier stage but still closely-watched data are due from Biogen Idec, from a phase II study on a novel MS mechanism, an anti-Lingo-1 antibody that purports to promote remyelination and could represent a step change in treatments. Gilead is also expected to release mid-stage data on its anti-LOXL2 antibody simtuzumab in both idiopathic pulmonary fibrosis and liver fibrosis conditions including NASH; both these indications are attracting much attention and any signal that the company plans to move forward in these areas would be an interesting development.

But with cancer continuing to attract the most investment, progress in this space, and in particular new techniques to harness the immune system, is likely to dominate the R&D news next year.

Fresh outlook

The promise of a dozen new blockbusters has turned the pharma sector's outlook on its head. From 2011, when new sales barely offset those lost to patent expiry, 2015 will see sales grow close to four times that of patent losses. This positive balance is forecast to become even more impressive through 2020, to more than fivefold.

The industry's freshness - sales at risk and new growth ($bn)

	2011	2015	2020
Total sales at risk	34	38	25
Actual sales lost or forecast to be lost	19	18	12
Sales replaced	19	64	64
Total WW Rx & OTC sales	763	819	1,069
% of lost sales replaced	104%	349%	538%

Source: EvaluatePharma® December 2014

This protection of the industry's top line is being aided by an ever-bigger proportion of drug sales coming from biologics, which remain largely shielded from the generic threats that stalk small molecules. This will not remain the case forever, of course, and any further guidance from the FDA on interchangeability as well as late-stage data on biosimilar projects from the likes of Amgen will be key events for this issue next year.

The relatively insignificant patent expiries awaiting in 2015 – both to the companies involved and the industry as a whole – reflects how much more resilient the sector looks at the moment, compared with a few years ago.

Otsuka's Abilify will represent the biggest casualty next year, although the ongoing contest over Teva's Copaxone will be closely watched – the twists and turns that the battle between the Israeli drug maker and generic manufacturers has taken means the outcome is still up in the air.

The main US patent expired in May 2014, but Momenta and partner Sandoz and Natco and partner Mylan are still awaiting final approvals of their copycat versions of the original 20mg version from the FDA. When a green light is given they have to decide whether to launch "at risk" while Teva has lawsuits ongoing to prevent them.

A vital Supreme Court decision over a 2015 patent could come early next year, and help determine when the franchise might face competition.

Five big patent expiries to watch

			Annual US sales ($m)		
Product	**Company**	**US patent date**	**2014**	**2015**	**2016**
Copaxone	Teva	May 2014	2,747	2,091	1,814
Abilify	Otsuka	Apr 2015	3,779	1,789	334
Avodart	GlaxoSmithKline	Nov 2015	477	403	70
Tracleer	Actelion	Nov 2015	553	398	157
Zyvox	Pfizer	May 2015	689	364	110

Source: EvaluatePharma® December 2014

If 2015 lives up to today's heady expectations, it will be a remarkable year that the sector will long remember. Indeed, these frothy aspirations may themselves be the biggest threat to the sector next year. When hopes are unrealistically high, sometimes the only way is down.

However, with a healthy pipeline of drug approvals ahead and a friendly financing climate in place, the stage is set for a buoyant 2015. Traditionally exuberant sell-side analysts have at times struggled to keep up with investor enthusiasm for even the riskiest assets in 2014, and the coming 12 months shows no sign of this changing.

Regulatory setbacks are always possible, of course, as is clinical failure, and not all of these highly promising compounds will deliver. And with payers increasingly signalling that new drug prices are unacceptable, the commercialisation risks that confront those that do reach the market are perhaps more heightened than for a long time.

The industry's innovative efforts must be matched by commercial execution,otherwise its claims of improved R&D productivity will fail to ring true.

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