2015 DRUGS TO WATCH

THOMSON REUTERS MARKET INSIGHT REPORT

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DRUGS TO WATCH IN 2015

WHERE THE 2014 DRUGS-TO-WATCH ARE NOW

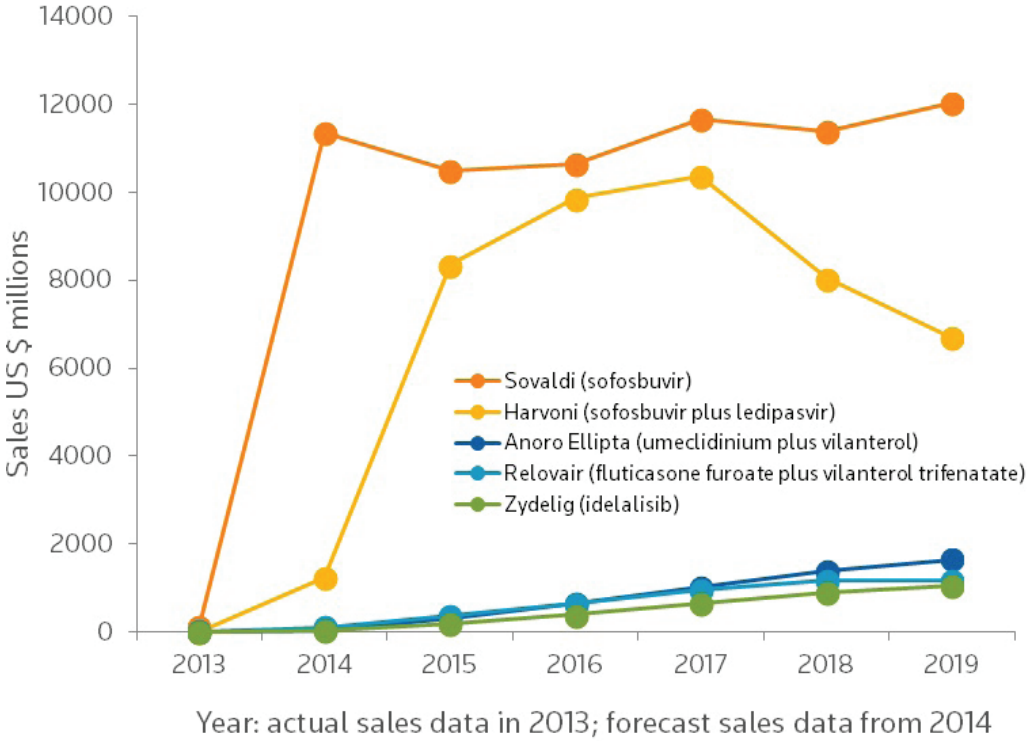
In January 2014, Thomson Reuters Cortellis Competitive Intelligence named three drugs to watch that were expected to enter the market that year and make sales of over $1 billion within five years. All three entered the market as anticipated, and although the Cortellis Consensus sales forecasts have fluctuated over the course of the year, all of the drugs are still forecast to be $1 billion-plus blockbusters.

Gilead Sciences' oral drug Sovaldi (sofosbuvir) for hepatitis C virus (HCV) infection was launched in the US at the very end of 2013, and in the EU in January 2014; a Japanese regulatory filing was submitted in June 2014. January 2014's Consensus sales forecasts for Sovaldi were $2.403 billion in 2014, rising to a peak of $9.121 billion in 2017 then declining to $7.518 billion by 2019. February 2015's forecast sales for the drug are dramatically higher, with a huge market-entry forecast of $11.352 billion in 2014 (see first graph). Full-year 2014 sales are yet to be reported, although sales for the first three quarters of the year total $8.551 billion. From 2014 onwards, Sovaldi's sales forecasts drop slightly to $10.507 billion in 2015, then climb to $12.022 billion in 2019. A lot of controversy has surrounded the market entry of this drug due to its high price tag of $84,000 per treatment course. Eliciting the same controversy is Gilead's Harvoni, an oral combination of sofosbuvir plus ledipasvir for HCV, which was approved and launched in the US in October 2014, priced at $94,500 per treatment course. Its forecast sales have also risen since January 2014, with current forecasts predicting peak sales of $10.367 billion in 2017.

GlaxoSmithKline/Theravance's Anoro Ellipta (umeclidinium plus vilanterol) entered the US market for chronic obstructive pulmonary disease (COPD) in April 2014, had been launched in the EU by July 2014, and became available in Japan in September 2014. The drug's 2019 sales forecasts have fallen significantly in the last year, from $3.081 billion predicted last January to current forecasts of $1.640 billion, but Anoro Ellipta is still expected to exceed the sales of its developers' previous blockbuster Relovair (fluticasone furoate plus vilanterol trifenatate), which are set to be $1.176 billion in 2019.

Another blockbuster predicted last year for Gilead was Zydelig (idelalisib) for chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin's lymphomas such as follicular B-cell non-Hodgkin lymphoma (FL) and small lymphocytic lymphoma (SLL). It was approved and launched in the US for these indications in July 2014, and received European approval for CLL and FL in September 2014; by January 2015 European marketing was underway. The sales forecasts for the drug have changed since January 2014, at which time sales of $1.218 billion were forecast for 2017, falling to $1.100 billion by 2019. Current forecasts show rising sales, albeit of only $649.4 million in 2017, increasing to $1.041 billion in 2019, thus just making it into the blockbuster category.

2014 DRUGS-TO-WATCH FORECAST SALES (US $ MILLIONS)



*Analysis based on data through early February 2015

WHAT TO WATCH IN 2015

Compared with 2014, there are more potential blockbusters expected to enter the market this year (see second graph). The majority of the drugs are forecast to have 2019 sales between $1 billion and $3 billion, although three drugs are set to exceed this, with the following 2019 sales forecasts: Bristol-Myers Squibb (BMS) and Ono Pharmaceutical's melanoma drug Opdivo (nivolumab) at $5.684 billion; Regeneron Pharmaceuticals and Sanofi's Praluent (alirocumab) for hypercholesterolemia at $4.414 billion; and Novartis' LCZ-696 (sacubitril and valsartan) for chronic heart failure at $3.731 billion. This year's other predicted blockbuster entrants (and their 2019 sales forecasts) are: Pfizer's Ibrance (palbociclib) for breast cancer ($2.756 billion); Vertex Pharmaceutical's lumacaftor plus ivacaftor for cystic fibrosis ($2.737 billion); AbbVie's Viekira Pak (veruprevir, ritonavir, ombitasvir and dasabuvir) for HCV ($2.500 billion); Amgen and Astellas Pharma's evolocumab for hypercholesterolemia/hyperlipidemia ($1.862 billion); Merck & Co.'s Gardasil 9 vaccine against human papillomavirus (HPV) infection ($1.637 billion); Otsuka Pharmaceutical and Lundbeck's brexpiprazole for schizophrenia and depression ($1.353 billion); Sanofi's Toujeo (new-formulation insulin glargine) for diabetes ($1.265 billion); and Novartis' Cosentyx (secukinumab) for psoriasis and psoriatic arthritis ($1.082 billion).

Key trends to watch in 2015 are the rise of immuno-oncology approaches for treating cancer, the race to be the next big cholesterol drug, the entry of a first-in-class heart failure drug, and the entry of more convenient all-oral regimes for HCV. Opdivo versus Keytruda is the race to watch in the immuno-oncology space, while Praluent and evolocumab battle it out in the cholesterol field, LCZ-696 aims to make its mark for heart failure, and Gilead, AbbVie and Merck compete to win space in the HCV market.

OPDIVO FOR MELANOMA AND NSCLC

Although the BMS and Ono Pharmaceutical drug Opdivo was launched in Japan in September 2014, it is in the US market that the drug is set to achieve blockbuster status, where it is expected to become available in early 2015. The PD-1 immune checkpoint inhibitor Opdivo was approved in the US in late December 2014, three months ahead of its March 2015 PDUFA date, for unresectable or metastatic melanoma with disease progression, and was launched in February 2015. Approval was based on data from the phase III CheckMate 037 trial, in which the overall response rate with Opdivo was 32% versus 11% for investigator's-choice of chemotherapy. An EU filing for melanoma was submitted in September 2014, and has been granted Accelerated Assessment. Additionally, a rolling BLA for non-small-cell lung cancer (NSCLC) was initiated in the US in April 2014; earlier in January 2015, a phase III NSCLC trial of Opdivo was stopped early as it had already met its endpoint of superior overall survival compared with control.

Forecast sales of Opdivo rise steadily from $652.1 million this year to $5.684 billion in 2019, of which $5.013 billion are from the non-Japanese markets, such as the US. There it will compete against Merck & Co.'s PD-1 inhibitor Keytruda (pembrolizumab), which sped onto the US market in 2014, gaining Accelerated Approval in September 2014 based on phase Ib data, and launching later that month. Keytruda sales are forecast to reach $3.466 billion in 2019. Like Opdivo, EU approval for melanoma is pending. In January 2015, Merck announced accelerated plans to file for US approval for NSCLC, with a filing expected in mid-2015. As the FDA granted Keytruda Breakthrough Therapy designation for this indication in October 2014, a 2015 launch for NSCLC is a possibility.

Ranking, by highest sales forecast for 2019	Drug	Disease	Pharmaceutical Company	2019 Forecast Sales (US $ billions)
1	**Opdivo** (nivolumab)	melanoma	Bristol-Myers Squibb (BMS) and Ono Pharmaceutical	5.684
2	**Praluent** (alirocumab)	hypercholesterolemia	Regeneron Pharmaceuticals and Sanofi	4.414
3	**LCZ-696** (sacubitril and valsartan)	chronic heart failure	Novartis	3.731
4	**Ibrance** (palbociclib)	breast cancer	Pfizer	2.756
5	**lumacaftor plus ivacaftor**	cystic fibrosis	Vertex Pharmaceutical	2.737
6	**Viekira Pak** (veruprevir, ritonavir, ombitasvir and dasabuvir)	hepatitis C	AbbVie	2.500
7	**evolocumab**	hypercholesterolemia/ hyperlipidemia	Amgen and Astellas Pharma	1.862
8	**Gardasil 9**	vaccine against human papillomavirus (HPV) infection	Merck & Co	1.637
9	**brexpiprazole**	schizophrenia and depression	Otsuka Pharmaceutical and Lundbeck	1.353
10	**Toujeo** (new-formulation insulin glargine)	diabetes	Sanofi	1.265
11	**Cosentyx** (secukinumab)	psoriasis and psoriatic arthritis	Novartis	1.082

*Analysis based on data through early February 2015

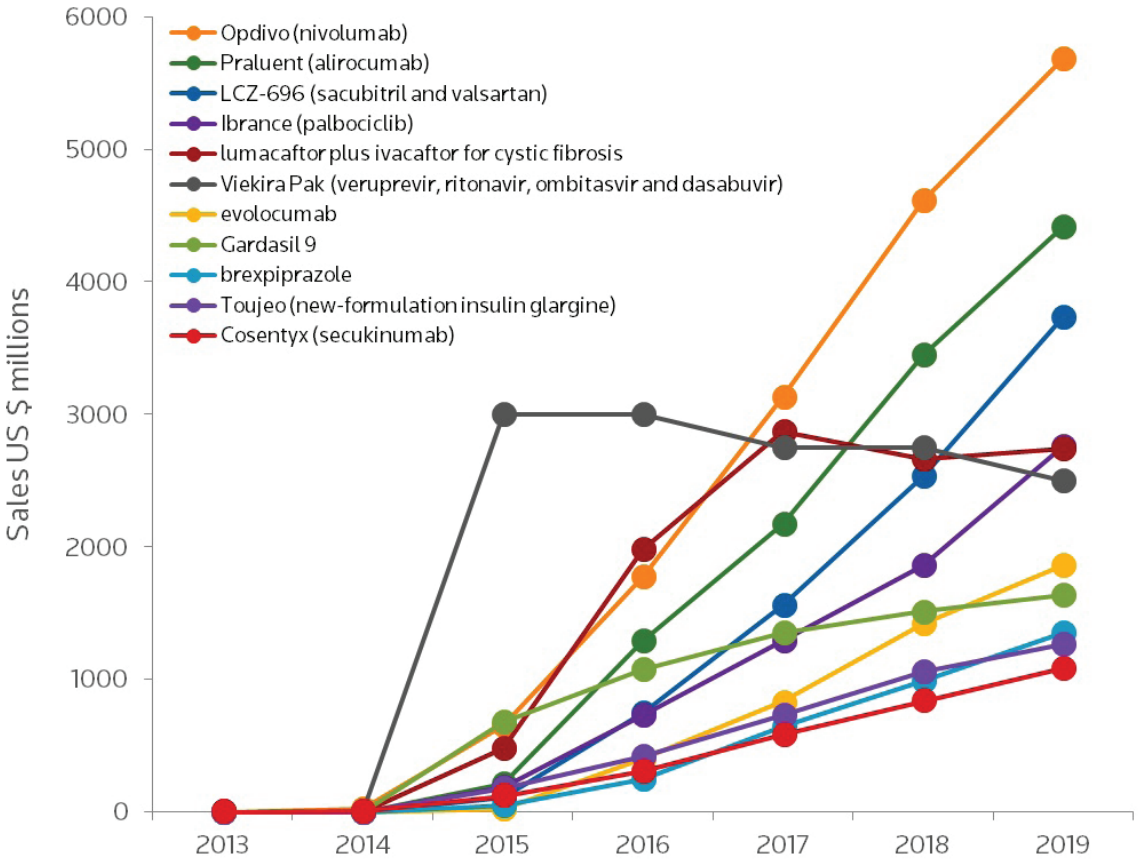
PRALUENT AND EVOLOCUMAB: TWO PCSK9 INHIBITORS FOR HYPERCHOLESTEROLEMIA

Sanofi/Regeneron and Amgen/Astellas's PCSK9 inhibitors, Praluent and evolocumab, are set to battle it out to be the next cholesterol-lowering blockbuster. Evolocumab took the initial lead in August 2014 when it was the first of the two to be filed for US approval. In November 2014, the filing was accepted for review with a PDUFA date of August 27, 2015; an EU filing for dyslipidemia is also pending approval, having been filed in September 2014. A number of phase III trials have demonstrated the ability of evolocumab to reduce cholesterol levels by week 12 of treatment. However, Praluent, which had been filed for US approval by the end of 2014, regained the lead in January 2015 when the filing was granted Priority Review with a PDUFA date of July 24, 2015. The drug also has the advantage of having shown a reduction in the rate of adverse cardiovascular outcomes such as cardiac death, heart attack and stroke in a phase III trial. An EU filing for Praluent was also accepted for review in January 2015. Forecast sales for 2019 are $4.414 billion for Praluent and $1.862 billion for evolocumab.

LCZ-696 FOR CHRONIC HEART FAILURE

This first-in-class agent represents a new treatment approach for heart failure by combining the enhancement of cardioprotective mechanisms via neprilysin inhibition, with the antihypertensive effects of angiotensin antagonism. It was filed for US and EU approval for chronic heart failure with reduced ejection fraction in the fourth quarter of 2014, with approval decisions anticipated in late 2015. In November 2014, the drug was granted European Accelerated Assessment, which will significantly shorten the EU review process. Filing was based on data from the PARADIGM-HF trial of LCZ-696 versus enalapril, which was halted early after data showed that patients receiving LCZ-696 lived longer without being hospitalized for heart failure than those who received standard-of-care enalapril. Data reported five months later, in August 2014, demonstrated that LCZ-696 was more effective than enalapril at reducing the risk of cardiovascular death (by 20%), the risk of hospitalization for heart failure (by 21%) and all cause-mortality (by 16%). Regulatory filings to expand the drug's indication to include chronic heart failure with preserved ejection fraction are planned for 2019 or later. Forecasts predict LCZ-696 sales of $110.9 million in 2015, rising to $3.731 billion in 2019.

2015 DRUGS-TO-WATCH FORECAST SALES (US $ MILLIONS)



Year: actual sales data in 2013; forecast sales data from 2014

IBRANCE FOR BREAST CANCER

Pfizer filed for US approval of its cyclin-dependent kinase 4 and 6 inhibitor Ibrance in August 2014 for postmenopausal women with ER+ HER2- advanced breast cancer not previously treated with systemic therapy; the filing received Accelerated Approval and the drug was launched in February 2015. In the phase II PALOMA-1 trial, on which the filing was based, Ibrance plus the aromatase inhibitor letrozole almost doubled progression-free survival compared with letrozole alone (20.2 versus 10.2 months). Overall survival was numerically but not significantly improved at an interim analysis, although a follow-up analysis was to be conducted once further survival events had been accrued. Assuming that phase III data are as good as the phase II trial results, Ibrance could become the treatment of choice in this therapy setting. Sales forecasts for the drug are $2.756 billion in 2019.

LUMACAFTOR PLUS IVACAFTOR FOR CYSTIC FIBROSIS

An NDA and MAA for the lumacaftor/ivacaftor coformulation were filed by Vertex in November 2014 for cystic fibrosis patients aged 12 years and older with homozygous F508del mutation in the CFTR gene. A request for Accelerated Assessment of the MAA was granted, and Vertex also requested Priority Review in the US; in January 2015, the FDA granted the request and set a PDUFA date of July 5, 2015. The filings were underpinned by results from the phase III TRAFFIC and TRANSPORT trials; pooled data reported in June 2014 from these two studies showed that the primary endpoint of mean absolute change from baseline in percent predicted FEV1 at the end of 24 weeks had been met. Forecasts predict 2019 sales of $2.737 billion for lumacaftor/ivacaftor, exceeding those of Vertex's Kalydeco (ivacaftor), which was launched in the US and EU in 2012, and which is expected to have sales of $1.175 billion in 2019.

VIEKIRA PAK FOR HEPATITIS C

AbbVie's Viekira Pak is an all-oral interferon-free regime for HCV, in which the NS3/4A protease inhibitor veruprevir, the boosting agent ritonavir, and the NS5A inhibitor ombitasvir are coformulated and are dosed alongside the NS5B polymerase inhibitor dasabuvir. Cure rates of 95 to 100% were seen in phase III trials, including treatment-naive and -experienced patients as well as patients with compensated cirrhosis. Based on these data, the regime received US approval in December 2014 for use with or without ribavirin for genotype 1 HCV. European approval was sought in May 2014; the filing was granted Accelerated Assessment and the drug was approved in January 2015 for use with or without ribavirin for genotype 1 HCV, and with ribavirin for genotype 4 HCV. European launch of the drug is expected in the first quarter of 2015. A Japanese filing is also expected this year.

The minimum four-pill-a-day Viekira Pak regime will face stiff competition from one-pill-per-day Harvoni; current forecasts predict 2019 sales of $2.500 billion for Viekira Pak, versus $6.697 billion for Harvoni. Price negotiations are set to feature significantly in the competition between the agents, with Viekira Pak to enter the market with a per-treatment-course price of $83,319, comparing favorably with the $94,500 cost of Harvoni. Furthermore, AbbVie showed it was willing to further discount the price: Express Scripts, the largest US pharmacy benefit manager, signed a deal in December 2014 with AbbVie to replace Harvoni with Viekira Pak in return for an undisclosed Viekira Pak price said to be somewhere in the region of the EU price tag of between $51,373 and $61,000 per treatment course. Subsequently, the pharmacy benefit manager CVS Health and the health insurer Anthem have signed deals with Gilead for preferential supply of Harvoni over Viekira Pak, with discounted prices presumed to form part of both deals. Both drugs are also likely to face additional competition from Merck & Co., which has announced plans to accelerate development of its HCV combination grazoprevir/elbasvir, with a US filing planned for the first half of 2015. Consensus forecasts predict that the first sales of grazoprevir/elbasvir will be in 2016, with sales of $2.167 billion expected in 2019.

GARDASIL 9 FOR PREVENTING HPV INFECTION

Quadrivalent Gardasil was launched in 2006 by Merck and Sanofi Pasteur as the first-to-market vaccine for preventing HPV infection and its associated cancers; sales rose from $234.8 million that year to $1.831 billion in 2013, but are forecast to decline to $1.236 billion by 2019. Gardasil 9 is Merck's nonavalent follow-on HPV vaccine that extends protection against HPV from four to nine HPV types. Clinical data have shown that Gardasil 9 is as effective as original Gardasil in preventing cancers caused by the four HCV types they have in common, and 97% effective in preventing cancers caused by the additional five HPV types. It is the only FDA-approved vaccine against these five HPV types, which are responsible for 20% of cervical cancers. US approval of Gardasil 9 was granted in December 2014, with launch planned for early February 2015. A European filing is under review. Sales forecasts for Gardasil 9 are set to reach $1.637 billion by 2019.

BREXPIPRAZOLE FOR SCHIZOPHRENIA AND DEPRESSION

Otsuka and Lundbeck's oral serotonin-dopamine activity modulator brexpiprazole was filed for US approval in July 2014 for treating schizophrenia and as adjunctive treatment for depression. The filing was based on data from three trials for schizophrenia and four for depression. In two phase III schizophrenia studies, 4 mg/day of the drug significantly improved symptoms compared with placebo. A 2 mg/day dose showed significant effects in one of these trials. In the third, phase II, schizophrenia study, clinically meaningful but non-statistically significant improvements were seen with brexpiprazole. Two phase III depression studies showed significant effects with 2- or 3-mg doses of the drug, and in one of the phase II trials, a 1.5-mg dose showed a significant effect. The second phase II trial supported the data of the other studies. The regulatory filing was accepted for review in September 2014, with a PDUFA date of July 11, 2015, and a European filing is planned for this year. Sales of the drug are predicted to be $1.353 billion in 2019.

TOUJEO FOR DIABETES

Sanofi created Toujeo as a smaller-volume formulation of its insulin glargine product Lantus for subcutaneous injection for type 1 and type 2 diabetes. Sanofi's filings for the drug were accepted for European and US review in May 2014 and July 2014, respectively, with regulatory decisions expected in those regions in the second and first quarters of 2015, respectively. A Japanese approval filing was submitted in July 2014. The filings are based on data from the phase III EDITION trials program, in which the drug demonstrated reductions in HbA1c from baseline.

Sales of Lantus were $7.590 billion in 2013, and are forecast to peak at $8.268 billion in 2014 then decline gradually to $6.630 billion by 2019. Forecast sales for Toujeo are not in the same league as this, although they are set to rise to $1.265 billion by 2019. Toujeo will face increasing competition from Lantus biosimilars, such as Eli Lilly and Boehringer Ingelheim's Basaglar (Abasria) which has been approved and is awaiting launch in the US, EU and Japan.

COSENTYX FOR PSORIASIS AND PSORIATIC ARTHRITIS

Novartis's anti-IL-17A monoclonal antibody Cosentyx was approved in Japan in December 2014 for psoriasis and psoriatic arthritis in adults not adequately responding to systemic therapies. In January 2015, it was approved in both the US and EU for moderate to severe plaque psoriasis, with further filings for psoriatic arthritis, ankylosing spondylitis and uveitis planned. Cosentyx met its primary endpoints in four phase III trials for moderate to severe plaque psoriasis, including showing head-to-head superiority over Enbrel (etanercept) in the FIXTURE study. The drug is expected to be the first of a number of anti-psoriatic IL-17 antagonists, such as Lilly's ixekizumab and Amgen/Kyowa Hakko Kirin/AstraZeneca's brodalumab, to gain approval for psoriasis. Cosentyx forecast sales rise from $120 million in 2015 to $1.082 billion in 2019.

SUMMARY

The next 12 months are set to see several potential blockbusters enter the market place – far more than in 2014. Whether this signifies anything about the state of pharmaceutical development or the endurability of the blockbuster model remains to be seen.