Drugs to Watch 2016

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Where the 2015 Drugs to Watch Are Now

In January 2015, Thomson Reuters Cortellis for Competitive Intelligence named 11 drugs to watch that were predicted to enter the market that year and make over US $1 billion within 5 years.

The drugs ranked by highest sales forecasts for 2019 were: Bristol-Myers Squibb (BMS) and Ono Pharmaceutical's melanoma drug Opdivo (nivolumab); Regeneron Pharmaceuticals and Sanofi's Praluent (alirocumab) for hypercholesterolemia; Novartis' Entresto (LCZ-696; sacubitril and valsartan) for chronic heart failure; Pfizer's breast cancer drug Ibrance (palbociclib); Vertex Pharmaceutical's Orkambi (lumacaftor plus ivacaftor) for cystic fibrosis; AbbVie's Viekira Pak (paritaprevir, ritonavir, ombitasvir and dasabuvir) for hepatitis C virus (HCV) infection; Amgen and Astellas Pharma's hypercholesterolemia/hyperlipidemia drug Repatha (evolocumab); Merck & Co's Gardasil 9 vaccine against human papillomavirus (HPV) infection; Otsuka Pharmaceutical and Lundbeck's schizophrenia and depression drug Rexulti (brexpiprazole); Sanofi's Toujeo (new formulation of insulin glargine) for diabetes; and Novartis' Cosentyx (secukinumab) for psoriasis and psoriatic arthritis. All 11 drugs entered the market as anticipated, and although the Cortellis Consensus sale forecasts have fluctuated over the course of the year, all of the drugs (with the exception of Gardasil 9, for which forecasts were not available as of January 2016) are still forecast to be $1 billion-plus blockbusters. An in-depth discussion of the fortunes of the 2015 drugs to watch is provided in the 2015—A Blockbuster year report.

Drugs to Watch 2016

There are seven emerging therapeutics that are poised to enter the market in 2016 and achieve blockbuster sales status by 2020. The majority are anticipated to yield annual revenues of $1 billion to $2 billion, although two are set to exceed this.

In the $2 billion-plus annual revenue bracket are drugs treating chronic liver disease and HIV-1 infection. Ranked by highest sales forecasts for 2020, the potential blockbuster drugs are Intercept Pharmaceuticals and Sumitomo Dainippon Pharma's obeticholic acid ($2.621 billion) for chronic liver disease; Gilead Sciences and Japan Tobacco's anti-HIV-1 infection combination emtricitabine + tenofovir alafenamide (F/TAF; $2.006 billion); Gilead Sciences and Janssen R&D's tenofovir alafenamide + emtricitabine + rilpivirine (R/F/TAF; $1.572 billion) also for HIV-1 infection; Merck & Co's anti-HCV infection drug MK-5172A (grazoprevir + elbasvir; $1.537 billion); Abbvie's chronic lymphocytic leukemia (CLL) agent venetoclax ($1.477 billion); ACADIA Pharmaceuticals' Nuplazid (pimavanserin; $1.409 billion) for Parkinson's disease psychosis (PDP); and Nippon Shinyaku Co and Actelion's Uptravi (selexipag; $1.268 billion) for pulmonary arterial hypertension (PAH). A summary of the drugs to watch in 2016 and their associated forecast sales data are provided in Table 1 and Figure 1.

This year's forecast reveals several key trends in the pharmaceutical industry: the increasing focus on rare diseases, the continued development of more convenient fixed-dose combination (FDC) regimens, and the conflict between price and access to medicines.

Trends

Key trends in the pharmaceutical industry for 2016 and beyond, as exemplified by several of the potential blockbuster drugs described herein, are the increasing focus on rare diseases, the continued development of more convenient fixed-dose combination (FDC) regimens, and access to medicines and affordability.

With declining R&D productivity, the pharmaceutical industry is increasingly turning to treatments for rare diseases, also referred to as orphan diseases, which are generally classified as affecting fewer than 200,000 people in the US and no more than 5 in 10,000 people in the EU. There are approximately 7,000 'rare' diseases and disorders that affect around 350,000,000 individuals globally. Both Intercept/

Table 1: 2016 Drugs to Watch Forecast Sales Rankings

Ranking *(by highest sales forecasts for 2020)*	Drug	Disease	Pharmaceutical Company	2020 Forecast Sales *(US $ billions)*
1	Obeticholic acid	Chronic liver diseases, primarily primary biliary cirrhosis	Intercept Pharmaceuticals and Sumitomo Dainippon Pharma	2.621
2	Emtricitabine + tenofovir alafenamide (F/TAF)	HIV-1 infection	Gilead Sciences and Japan Tobacco	2.006
3	Tenofovir alafenamide + emtricitabine + rilpivirine (R/F/TAF)	HIV-1 infection	Gilead Sciences and Janssen R&D	1.572
4	MK-5172A (grazoprevir + elbasvir)	HCV infection	Merck & Co	1.537
5	Venetoclax	Chronic lymphocytic leukemia	Abbvie	1.477
6	Nuplazid (pimavanserin)	Parkinson's disease psychosis	ACADIA Pharmaceuticals	1.409
7	Uptravi (selexipag)	Pulmonary arterial hypertension	Nippon Shinyaku Co and Actelion	1.268

Analysis based on data accessed on January 08, 2016
Source: Thomson Reuters Cortellis

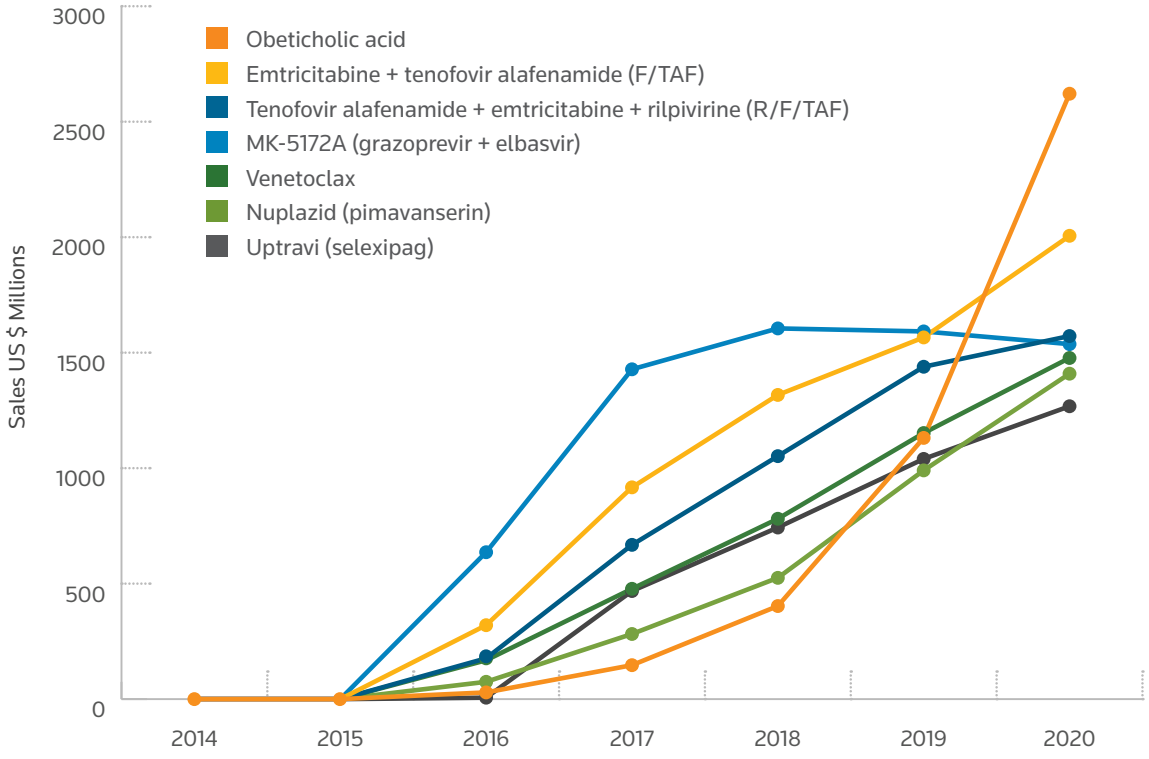
Sumitomo Dainippon Pharma and AbbVie are aiming to enter the orphan market in 2016 with their candidate potential blockbusters drugs obeticholic acid (OCA) and venetoclax, respectively.

Traditionally, the development of orphan drugs has not been an area of focus for the pharmaceutical industry, given the limited number of patient populations for each disease and the challenges caused by the often scant knowledge regarding cause, pathophysiology and epidemiology. However, this trend has been changing steadily as the revenue potential of orphan drugs becomes more evident.

In 2015, the FDA approved more orphan drugs for rare diseases than any previous year: 21 (47%) of the novel drugs approved by the FDA in 2015 were classified as orphan drugs, compared with 17 (41%) in 2014, 9 (33%) in 2013, 13 (33%) in 2012 and 11 (37%) in 2011. This shift has been stimulated by a range of commercial drivers, including reduced timelines for clinical development and a higher probability of approval, a longer period of marketing exclusivity, tax credits and user fee waivers, premium pricing, faster uptake and lower marketing costs. It is anticipated that such incentives will continue to promote the shift toward a drug development business model that incorporates orphan diseases.

Gilead's FDC products, such as the TDF/TAF-based products described in this article, have allowed the company to gain significant shares in the HCV and HIV markets. Such products are becoming increasingly important in the management of complex diseases, such as HIV infection, diabetes and cardiovascular disease. FDCs can also confer a range of advantages to both the developing company and patient. These products can provide lifecycle extension strategies and product differentiation, as well as increased efficacy with the added benefit of reduced pill burden to improve patient convenience and compliance. The FDA has further incentivized the development of FDC products by making them eligible to five years of market-based exclusivity upon regulatory approval. Prior to October 2014, such products were ineligible for this protection.

Figure 1: 2016 Drugs to Watch Forecast Sales (US $ Millions)



Year: actual sales data in 2014; forecast sales data from 2015

Source: Thomson Reuters Cortellis

A key trend in 2016, as exemplified by the potential blockbuster drugs described herein, is the continued development of more convenient fixed-dose, all-oral regimens for HCV and HIV. The growing conflict between access to drugs and affordability is also likely to intensify in 2016.

Price Fixing

A congressional committee is investigating the high prices of innovative new branded therapeutics in the US. As that nation's presidential election looms, the increased political focus on drug pricing is expected to continue.

Several companies have come under fire regarding their pricing strategies, most notably Gilead, which has experienced intense scrutiny for the pricing of its HCV treatments Sovaldi and Harvoni. The growing conflict between access to medicines and affordability is not only seen in the US. It is a worldwide issue, with Europe's health agencies struggling to pay for expensive new drugs.

One new initiative that Novartis is testing with its heart failure drug Entresto is a success-driven pricing model, where the price is set based on an assumption that the number of hospital admissions and therefore treatment costs will fall below a certain level. It will be interesting to see if other companies follow suit. Such drives to improve value for money, as well as to increase affordability and access, may impact potential sales revenues of new drugs entering the market in 2016. This year may also witness the first and only drug to be approved in the US for PDP and the first new treatment for PBC to reach the market in more than two decades.

Obeticholic Acid for Chronic Liver Disease

Intercept and Asian licensee Sumitomo Dainippon Pharma are developing the farnesoid X receptor agonist OCA for the potential oral treatment of chronic liver diseases. A rolling NDA submission was initiated in

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December 2014 for primary biliary cirrhosis (PBC) in patients with inadequate response to ursodeoxycholic acid (UDCA) or as monotherapy in adults unable to tolerate UDCA.

In August 2015, the NDA was granted Priority Review with a Prescription Drug User Fee Act (PDUFA) date set for February 29, 2016. However, in December 2015, the FDA extended the PDUFA date by 3 months to May 29, 2016, following the submission of extra clinical data in response to an FDA request. A marketing authorization application (MAA) was accepted for review in Europe for PBC in June 2015.

In PBC, clinically meaningful biochemical improvements were seen in the phase III POISE study in patients not responding to UDCA: 47% of patients had ALP levels <1.67 times the upper limit of normal at 6 months and total bilirubin within normal limits within 12 months, versus 10% of placebo patients. However, PBC is a rare liver disease that results from autoimmune destruction of the bile ducts in the liver, and estimates of annual incidence and prevalence range from 2 to 24 cases per million and 19 to 240 cases per million, respectively.

OCA has also demonstrated good efficacy in phase II studies in nonalcoholic steatohepatitis (NASH), and it is the larger NASH market that is anticipated to be the most lucrative. NASH is estimated to affect 2 to 3% of the population and the worldwide market is expected to expand rapidly due to an increasing incidence of predisposing factors, such as metabolic disease, obesity and insulin resistance. Currently, there is no approved treatment for NASH.

The Breakthrough designation awarded to OCA for this indication raises the hope that the registration path for NASH will be possible without an outcomes trial. Intercept stated that the phase III REGENERATE study, which is scheduled to complete in 2021, will form the basis of regulatory filings for NASH.

If approved, OCA could become the first new treatment for PBC in more than two decades. Forecasts predict sales of OCA of $29 million in 2016, rising to $2.621 billion in 2020. Competitor UDCA is the only drug currently approved for PBC and it is now generic.

Potential longer-term competition for PBC comes from investigational agents GSK-2330672, A-4250, MBX-8025, NGM-282 and SHP-625. Genfit's PPAR alpha and delta agonist GFT-505 (elafibranor) is in phase II studies and is expected to be OCA's main near-term competitor in the oral NASH market. Gilead's allosteric humanized mAb simtuzumab, which inhibits lysyl oxidase-like 2 (LOXL2), is an infusion that may also feature in the NASH market. Simtuzumab is in phase II development and may be useful in reversing the fibrosis associated with liver cirrhosis.

Fixed-Dose Combinations for HIV Infection

Gilead's nucleoside reverse transcriptase inhibitor tenofovir alafenamide fumarate (TAF; GS-7340), a follow-on to the company's tenofovir disoproxil fumarate (TDF), is currently being developed as a component of several FDC regimens, including the potential blockbuster regimens emtricitabine (a nucleoside reverse transcriptase inhibitor) + tenofovir alafenamide (F/TAF) and tenofovir alafenamide + emtricitabine + rilpivirine (a non-nucleoside reverse transcriptase inhibitor; R/F/TAF), for the potential treatment of HIV-1 infection.

The F/TAF regimen was filed for US and EU approval in April and May 2015, respectively, for the treatment of HIV-1 infection in adults and pediatric patients age 12 years and older, in combination with other HIV antiretroviral agents. A PDUFA date of April 07, 2016, has been set in the US. Regulatory filings in the US and EU for the R/F/TAF regimen were submitted in July and August 2015, respectively. A Priority Review voucher acquired from Knight Therapeutics was submitted along with the US filing to expedite the review and a PDUFA date of March 01, 2016, has been set.

The filings for the F/TAF and R/F/TAF regimens are based on data from phase III clinical studies evaluating the safety and efficacy of the TAF-based regimen Genvoya (emtricitabine/cobicistat/elvitegravir/tenofovir alafenamide or E/C/F/TAF), which demonstrated non-inferior efficacy and improved renal and bone mineral density (BMD) measurements compared with the TDF-based regimen Stribild (comprising E/C/F/TDF). Genvoya was effective in a range of patients with HIV, including treatment-naïve adults and adolescents, virologically suppressed adults who switched regimens and adults with mild-to-moderate renal impairment. Additionally, F/TAF also demonstrated non-inferior efficacy to the widely used E/TDF combination drug Truvada in a head-to-head phase III trial, but with less impact on BMD and renal parameters, highlighting its potential to become a safer replacement for Truvada.

The improved longevity of HIV-infected patients and widening of the antiretroviral eligibility criteria are expanding the size of the already large HIV market, providing significant revenue-generating opportunities. Market-leader Gilead has a dominant position within the

HIV market given its convenient, once-daily combination products with reduced pill burden, such as the TDF-based regimens Atripla (emtricitabine/efavirenz/TDF), Truvada, Stribild and Complera/Eviplera (emtricitabine/rilpivirine/TDF). In 2014, Atripla, Truvada, Stribild and Complera generated combined sales of $9.235 billion. However, expiry of patent coverage for TDF begins in July 2017 and Teva has entered into an agreement in principle to launch its generic version of the drug in December 2017.

The entry of generic versions of TDF will make all-generic regimens a possibility in the short term, and their availability will impact sales of Gilead's four TDF-based regimens, with combined sales predicted to decrease to $8.589 billion in 2020. TAF has the potential to protect Gilead's HIV franchise from generic TDF competition, as the patents covering TAF extend to 2025 in the US and 2027 in the EU. The company's Genvoya was the first TAF-based regimen to enter the market in December 2015 and additional F/TAF-based regimens for HIV treatment are currently in development.

If approved, the TAF-based regimens F/TAF and R/F/TAF will face competition from other TAF-based regimens as well as from GlaxoSmithKline/ViiV's Triumeq, the first non-Gilead single-tablet regimen that has been helping to increase ViiV's share of the HIV market since its launch in September 2014. Triumeq is expected to generate sales of $4.020 billion in 2020. Forecasts predict respective F/TAF and R/F/TAF sales of $320 million and $176 million in 2016, rising to $2.006 billion and $1.572 billion in 2020.

MK-5172A for Hepatitis C Virus Infection

Merck & Co's MK-5172A is an oral fixed-dose tablet formulation of the pan-genomic NS3/4A inhibitor grazoprevir (MK-5172) and the NS5A inhibitor elbasvir (MK-8742). Cure rates of between 92% and 100% were seen in phase III trials, including in treatment-naïve and experienced patients, as well as in patients with compensated cirrhosis and those with advanced chronic kidney disease stage 4 or 5. Based on these data, regulatory filings in the US for HCV genotypes 1, 4 or 6 infection and in the EU for HCV genotypes 1, 3, 4 or 6 infection were submitted in May and July 2015, respectively.

The NDA has been accepted for priority review by the FDA and a PDUFA date of January 28, 2016, has been set. Merck had previously received FDA Breakthrough Therapy designation for treating patients with chronic HCV genotype 1 infection in October 2013, although this designation was rescinded in January 2015 based on recent approval of treatments for HCV genotype 1 infection.

Merck experienced a further setback in December 2015 when the European Medical Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) stated that the MAA, which had previously been accepted for an accelerated assessment, would now be assessed under the standard process; a decision in the EU is expected in mid-2016 according to Merck.

Interferon-free regimens are expected to become the standard of care as the elimination of side effects associated with interferon improves quality of life significantly. MK-5172A will face tough competition from recent interferon-free market entrants, including Gilead's once-daily pill Harvoni (sofosbuvir/ledipasvir) and Abbvie's twice-daily four pill offering Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets).

However, Merck could experience some respite, as sales forecasts of Viekira Pak have been clipped by an FDA warning released in October 2015 highlighting a potential risk of serious liver injury for certain patients. Merck could therefore gain a competitive advantage over Viekira Pak if the company is able to position MK-5172A as a safer option.

Nevertheless, gaining market share from Harvoni could be challenging, as Harvoni has first-to-market advantage and a best-in-class profile. Current forecasts predict 2020 sales of $9.335 billion for Harvoni versus $1.749 billion for Viekira Pak, while MK-5172A is anticipated to achieve sales of $636 million in 2016, rising to $1.537 billion in 2020. Both Gilead and Abbvie have come under intense scrutiny regarding the high price of these drugs, which were listed for around $90,000 per treatment course. Discounted pricing with pharmacy-benefit managers, insurers and other payers has featured significantly in the competition between these two agents. An aggressive pricing strategy for MK-5172A versus the Gilead and AbbVie regimens could drive growth as competition intensifies within the market for interferon-free, all-oral regimens to treat HCV.

Venetoclax for Chronic Lymphocytic Leukemia

Second-generation BH3-mimetic venetoclax (ABT-199) is being developed by AbbVie, in collaboration with Genentech, as a potential oral treatment for cancer, primarily CLL. In September 2012, venetoclax received Orphan designation for the treatment of CLL and in

May 2015 the FDA granted the agent Breakthrough Therapy designation for the treatment of patients with relapsed or refractory CLL with 17p deletion. An NDA was submitted to the FDA for venetoclax for relapsed or refractory CLL with 17p deletion in November 2015 and by December 2015, an MAA had also been filed in the EU.

Venetoclax was one of the leading agents at the 2015 annual meeting of the American Society of Hematology, with over 40 presentations on the drug in multiple indications. Enthusiasm for venetoclax was generated, at least in part, by data reported from the pivotal phase II M13-982 trial in patients with relapsed/refractory CLL who have del17p. An overall response rate of 79.4% was observed, with 12-month progression-free survival and overall survival rates of 72.0 and 86.7%, respectively. The M13-982 trial formed the basis of the regulatory filings for venetoclax. Venetoclax is also being tested in combination with other drugs and earlier in the course of CLL, as well as in other hematological cancers, including non-Hodgkin's lymphoma, diffuse large B-cell lymphoma and follicular lymphoma. The drug is also being evaluated in a phase I trial in combination with tamoxifen in patients with metastatic breast cancer.

del17p is associated with highly aggressive disease and resistance to chemotherapy. This abnormality is present in 3% to 10% of previously untreated cases and approximately 30% to 50% of relapsed or refractory cases of CLL. Moreover, individuals with del17p CLL have a median life expectancy of less than 5 years and a high unmet need in this disease therefore remains.

Significant competition in CLL will come from Imbruvica (ibrutinib) and Zydelig (idelalisib), which were approved in 2014. These agents are transforming the landscape of CLL due to their very high response rates, and approvals in both relapsed and refractory patients and as first-line treatments in the presence of del17p. Forecasts predict 2020 sales of $6.467 billion for Imbruvica, exceeding those of Zydelig, which is expected to achieve sales of $722 million in 2020. Sales of venetoclax are forecast to be $168 million in 2016, rising to $1.477 billion in 2020.

Nuplazid for Parkinson's Disease Psychosis

In November 2015, the FDA accepted an NDA for ACADIA's Nuplazid for Parkinson's disease (PD) psychosis (PDP), which was granted priority review. Psychosis is a common morbidity in PD and up to 40% of patients may develop psychotic symptoms. While currently marketed antipsychotics have activity at the dopamine D2 receptor and interfere with dopiminergic therapy, Nuplazid is a highly selective serotonin inverse agonist that targets 5-HT2A receptors without worsening of motor symptoms. This agent therefore represents a potential new class of psychosis therapy and is expected to be the first and only drug approved in the US for PDP. The FDA granted breakthrough therapy designation for the PDP drug in September 2014 and at that time a regulatory submission was expected by the end of that year. However, the filing was delayed to allow manufacturing operations to be prepared; a PDUFA date of May 01, 2016, has been scheduled.

The NDA submission included data from the pivotal phase III ACP-103-020 study, which demonstrated a 5.79-point improvement in psychosis (SAPS-PD scale) for Nuplazid versus a 2.73 point improvement for a placebo in patients with PD. Moreover, there was no worsening of motor function and significant improvements in night-time sleep, daytime wakefulness and caregiver burden were also reported.

Nuplazid is also being evaluated in other psychosis settings, including Alzheimer's disease psychosis and schizophrenia. According to the World Health Organization, approximately 47.5 million people worldwide have dementia, and this number is expected to double every 20 years as the population ages. Alzheimer's disease accounts for 60% to 80% of dementia cases and around 25% to 50% of patients may develop psychosis. In addition, it is estimated that up to 51 million people worldwide may be suffering from schizophrenia at any one time.

Additional approvals in these indications would therefore widen the addressable market considerably. ACADIA plans to launch the product in the US and if commercialization in select markets outside of the US is sought, the company intends to establish strategic alliances to facilitate this. Nuplazid forecast sales rise from $74 million in 2016 to $1.409 billion in 2020.

Uptravi for Pulmonary Arterial Hypertension

Nippon Shinyaku and licensee Actelion's non-prostanoid prostacyclin receptor agonist Uptravi received approval in the US in December 2015 for PAH to delay disease progression and reduce the risk of hospitalization. The product entered the US market in the first week of January 2016.

Actelion holds a dominant place within the PAH market and Uptravi is being positioned as an additional treatment option after the initiation of a baseline treatment, such as the company's Opsumit, and ahead of its late-stage disease drug Valetri. Uptravi produced impressive results in the largest outcomes trial ever conducted in PAH (the GRIPHON study), where 1,156 patients were treated for up to 4.2 years. In this study, in which more than 80% of the patients were already receiving PAH-specific therapies, the risk of a morbidity/mortality event was reduced by 39%, versus the placebo.

Uptravi faces tough competition in PAH, including from Bayer HealthCare's soluble guanylate cyclase stimulator Adempas, a first-in-class drug that augments cyclic guanosine monophosphate (cGMP) biosynthesis and is approved for PAH and chronic thromboembolic pulmonary hypertension (CTEPH, Group 4). Additionally, direct competitor United Therapeutics' Orenitram is the only FDA-approved, orally administered prostacyclin analog. United Therapeutics is likely to drive sales of this more convenient oral prostacyclin analog over its established offerings iv/sc Remodulin and inhaled Tyvaso, taking away potential market share from Uptravi.

Adempas and Orenitram are predicted to generate sales of $939 million and $499 million, respectively, in 2020. Actelion is expecting to charge an annual per-patient price of $160,000 to $170,000 in the US for Uptravi before rebates, which according to Actelion's CEO Otto Schwarz is priced below that of inhaled prostacyclin therapies currently on the market, including United Therapeutic's Tyvaso.

Revenue from Uptravi should help to maintain sales of Actelion's PAH portfolio following the loss of patent protection and generic entry in 2015 for the company's blockbuster drug Tracleer (bosentan). Revenue from Tracleer is predicted to plummet from peak sales of $1.722 billion in 2011 to $246 million in 2020. In contrast, Uptravi sales are forecast to increase from $189 million in 2016 to $1.268 billion in 2020.

Summary

A review of the drugs to watch in 2016 suggests that the year ahead will be a very interesting and challenging one for the pharmaceutical industry.

Trends that look set to continue include an increasing interest in rare diseases and the development of FDCs as companies realize the revenue potential of both areas. Significant breakthroughs in the treatment of PBC, del17p CLL and PDP are possible. Other highlights include the development of more convenient fixed-dose, all-oral regimens for HCV and HIV. Additionally, Gilead's TAF-based follow-on drugs F/TAF and R/F/TAF for HIV infection and Nippon Shinyaku/Actelion's Uptravi for PAH will be central to the lifecycle management of the companies' drug portfolios following patent expiry of key therapeutics. However, the ongoing dilemma of how to recoup development costs with the need for affordable new therapeutics will continue to impact the pharmaceutical industry, raising the possibility of new pricing models and more aggressive pricing strategies in 2016.

This year may also witness the first and only drug to be approved in the US for PDP and the first new treatment for PBC to reach the market in more than two decades.

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