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September 2014
The Top 50 Drugs of 2014
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The Top 50 Drugs of 2014

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IN JUNE 2005, C&EN published a special report on the Top Pharmaceuticals judged to have had a major impact on human health and society. It was an exceptional team effort, and if you can’t quite put your hands on that issue it is well worth dipping back into our free digital archives to read some of those entries, from classics such as aspirin and ether to synthetic molecules that made their mark such as Rituxan and AZT.

For our third C&EN supplement of 2014, we considered the many storms that have swirled through the pharmaceutical landscape in recent years and decided it was about time to revisit this theme but update it, to look at current drugs. “The Top 50 Drugs of 2014” could be subtitled “Rebound of the Blockbuster,” for as contributing editor Malorye Allison Branca explains in her introduction, the recent launch of the molecule that graces our cover -- Sovaldi (sofosbuvir) from Gilead for the treatment of hepatitis C – exemplifies the rising optimism and financial upsides of the drug industry.

This is welcome news for an industry that endured a torrid period since 2005 – patent cliffs stripped billions of dollars in revenue and necessitated waves of severe job cuts and down-sizing, while safety concerns and recalls of many drugs punctuated otherwise lackluster annual approval rates.

Thankfully, there is no shortage of innovation fueling the pharma pipelines, even if it gets lost sometimes against the staggering cost and timelines to successfully bring a drug to market. That should be one takeaway from this supplement, which profiles not only 40 of the leading drugs on the market but also ten of the most promising molecules in the pipeline and speeding towards FDA approval. Hopefully this marks the beginnings of a renaissance in drug development, fueled by our rapidly growing understanding of protein target structures, signaling pathways, and genetic predispositions.

We thank the large number of companies for their advertising support for this supplement. Based on the reaction we’ve received so far, we plan to expand our supplement series in 2015. If you have suggestions for future topics we should cover, please let us know.

Many thanks to contributing editor Malorye Allison Branca, who compiled the Top 50 list and wrote this supplement, and the production team at C&EN.

For our final C&EN supplement in 2014 this December, we will tackle the exciting world of ‘Omnics – proteomics, metabolomics, lipidomics, glycomics, transcriptomics, and genomics. We expect to showcase a wide variety of exciting new technologies and applications.

Kevin Davies, PhD
Publisher, C&EN
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IT'S BEEN A COUPLE YEARS of startling firsts for the pharmaceutical and biotechnology industries.

A record number of drugs with blockbuster potential were approved in 2013. That remarkable group included Gilead’s Sovaldi (sofosbuvir), a hepatitis C treatment now set to rake in as much as $10 billion in its first year on the market (page 10). Sovaldi’s launch was stunning, given the prior first year sales record was just over $1.55 billion.

Productivity is up considerably, with 39 new molecular entities (NMEs) approved by the U.S. Food and Drug Administration (FDA) in 2012 – the most in 16 years. 2013 was another good year, with twenty-seven NMEs approved.

Prices too are rising. Sovaldi costs an eyebrow-raising $84,000 per year, while 11 of the 12 new cancer drugs approved by the FDA in 2012 were priced at over $100,000 per year.

Drug makers have plenty to be happy about. Innovation abounds and market conditions seem optimal. According to analysts, multiple compounds in development could earn $1 billion or more in a single year based on efficacy, disease prevalence and pricing. Some will earn much more.

Oncology is booming, particularly in the areas of immunology and targeted drugs. Thanks to new checkpoint modulators and cell therapy treatments, even patients with previously incurable cancers are surviving far longer than ever before (page 24, and 35).

Several new pills will be jousting with Sovaldi for domination of the hepatitis C market. All allow patients to avoid the dreaded interferon injections that are loaded with side effects but have been a mainstay of treatment for years.

More firsts are in the wings. Anti-LINGO-1 could be the first drug to reverse central nervous system (CNS) damage in multiple sclerosis (page 35). And gene therapy, long dogged by cycles of high hopes followed by deep despair, is finally showing signs of becoming more than a pipe dream thanks to start-up Bluebird’s LentiGlobin (page 35).

But is this sustainable? Prices and outcomes are clearly going to become a bigger issue in the US. And much of the growth in pharmaceutical markets over the next few years is going to happen in emerging markets, where generics will dominate.

Drug development is also a very uncertain business. Many highly touted drug candidates have crashed in late-stage trials. Others have done much better than expected once they reached the market. Initial sales estimates for Lipitor, for example, were in the $300 million per year range. But it eventually achieved peak sales of more than $13.5 billion – the highest of any drug ever launched.

Clinical trial results can also be better than expected. As this supplement went to press, fresh news came out comparing Novartis’ LCZ696 to the standard angiotensin-converting enzyme (ACE) inhibitor enalapril in heart failure. The new drug reportedly cuts the risk of cardiovascular death and hospital admission by a fifth. Given how stagnant heart failure drug development has been for decades, this is particularly encouraging. One Novartis spokesman told investors that LCZ696 could be “the most exciting launch the company has ever had.”

In this special C&EN supplement, we profile 40 of the top selling treatments currently on the market that have already achieved or are heading towards blockbuster status, along with 10 in earlier stages, but which we believe have great potential.

Malorye A. Branca
Contributing Editor, C&EN Supplements
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In the fastest blockbuster drug launch in history, Gilead’s Sovaldi (sofosbuvir) earned a startling $2 billion plus in its first quarter on the market. Sovaldi is the biggest winner so far among a wave of new direct-acting agents (DAAs) for hepatitis C. Launched in December 2013, the drug racked up $5 billion within six months and is well on its way to a spectacular launch year. The previous top drug launch was Vertex Pharmaceuticals’ Incivek (telaprevir), a protease inhibitor and one of the first DAAs approved by the U.S. Food & Drug Administration (FDA). It launched in 2011 and earned $1.56 billion during its first full year. Pfizer’s Lipitor (atorvastatin) is the top selling drug of all time, earning $13.7 billion at its peak.

Sovaldi is a once-daily, nucleotide analog polymerase inhibitor that greatly improves cure rates, but it has another critical advantage. Until now, treatment for hep C always required long term (sometimes as long as a year) combination treatment with interferon injections and the oral antiviral ribavirin. For many years, that combination was actually the only treatment for the disease. But low cure rates (about 50% for patients with the toughest cases) and side effects led many patients to stop treatment or avoid it entirely.

The introduction of pegylated interferon (PEG-intron) and then the protease inhibitors greatly improved cure rates. But patients were still stuck with long treatment times, debilitating side effects from interferon and the necessity of taking regular injections. Hep C is caused by several similar variants or subtypes (called genotypes) of the same virus. The genotype can influence a patient’s response to therapy. With Sovaldi, the majority of patients infected with viral genotypes 2 or 3 only need concomitant ribavirin to be completely cured. Those infected with genotype 1 or 4 take Sovaldi in combination with interferon plus ribavirin. However, patients with type 1 infections who are deemed interferon ineligible can still be prescribed the all-oral option.

Sovaldi has boosted cure rates to over 90%, and the drug is particularly effective in patients with Genotype 2 or 3. The drug also dramatically cuts treatment duration for many patients. As the sales figures suggest, it has quickly come into widespread use.
Blocking Replication
The NS5B polymerase enzyme is essential for replication of the Hep C virus. There are two main approaches taken to inhibit NS5B: nucleoside analog polymerase inhibitors (NPIs) such as Sovaldi and non-nucleoside inhibitors, which bind to allosteric sites on the polymerase and create a non-functional enzyme. NPIs such as Sovaldi mimic the natural substrates that bind the active site of NS5B and terminate viral RNA chain generation, thereby halting replication.

Gilead has priced Sovaldi at an eye-catching $84,000 for a course of treatment in the US -- that’s $1,000 per pill -- arguing that the benefits of curing the disease far outweigh the costs. The drug actually brings down the “cost-per-cure,” Gilead vice president Gregg Alton told the American Enterprise Institute, according to the Associated Press. Older treatments, he said, can cost between $150,000 to $200,000 for a cure.

However, some see the price as excessive. (The drug has been priced substantially lower in other countries. In Egypt, for example, it costs $900 per course.) Treating the estimated 3 million hep C patients in the US would cost a total of $300 billion. As a result, insurance companies are pushing back and urging companies with similar drugs in development to compete with Gilead on price.

Gilead acquired Sovaldi when it bought Pharmasset for the headline-grabbing price of $11 billion in fall 2011. Several other companies, including AbbVie, Bristol-Myers Squibb, and Merck have competing drugs in their pipelines (see page 26).

Pent-up demand for better hepatitis treatments has helped fuel Sovaldi’s surge. Globally, an estimated 170 million people are infected. Substantial numbers of US patients delayed treatment of any kind in anticipation of the drug’s launch.

Drug developers are now testing multiple new interferon-free combination DAA treatments. Gilead itself is pursuing approval of Sovaldi plus ledipasvir (an NS5A inhibitor). But the company is facing stiff competition and analysts are closely watching the results of recent trials to assess which will be the top hep C drug in the long run.
Biogen Idec’s Tecfidera (dimethyl fumarate, or DMF) drew headlines for a remarkable launch in the US in March 2013, earning $1.38 billion by April 2014. The drug far outperformed analyst’s expectations. A Bloomberg report quoted ISI Group analyst Mark Schoenebaum as saying “Tecfidera crushed it. This is really, truly, incredible.”

The pill is one of three that represent a dramatic step forward for treatment of multiple sclerosis (MS). Tecfidera, however, appears to be outperforming its competitors thanks to a winning combination of efficacy, safety and convenience.

Priced at $54,900 per year, the drug hit the market as a slightly cheaper alternative to its main rival Gilenya (fingolimod) from Novartis, the former market leader priced at about $60,000 per year. Another competitor -- Sanofi’s Aubagio (teriflunomide) -- costs about $48,000 per year in the US. Prior to the launch of these new pills, MS treatments all required injections or infusions.

While Novartis’ Gilenya, which was approved in 2010, appears to be more effective than Tecfidera or Aubagio, it also has more side effects. None of the current MS drugs cure the disease. Rather, these are all disease-modifying treatments that reduce the rates of relapses and improve patients’ overall function.

Analysts are predicting that Tecfidera will take the lion’s share of this new market for oral MS therapies, with peak sales probably reaching about $3.5 billion by 2017.

MS is a chronic inflammatory condition that damages nerve fibers in the brain and spinal cord by eroding the protective myelin sheath. The disease also has a spectrum of activity, from mild to very severe.

In an interesting example of repurposing, DMF is a fumaric acid ester that was once used as a protectant for sofas and other items. But it caused rashes and blisters in some people who came in contact with the chemical. In 1994, it was approved as a psoriasis treatment in Germany.

**Mice and MS**

Recently, scientists at the Max Planck Institute for Heart and Lung Research and the University of Lübeck published a paper in the *Journal of Clinical Investigation* suggesting a mechanism for how the drug works in MS. In their study, the German researchers used drugs to induce MS symptoms in mice. The animals treated with DMF had significantly less motor function problems than the control group. Moreover, mice genetically modified to lack expression of the HCA2 receptor experienced no observable benefit from DMF treatment.

HCA2 is a G protein-coupled membrane receptor found on cells that include white blood cells and neutrophil granulocytes. Animals treated with DMF, the researchers found, had much lower levels of granulocytes in their nervous system than those that did not receive the drug. Meanwhile, mice lacking the HCA2 receptor still had high levels of granulocytes regardless of whether they were treated with DMF.

Biogen Idec reports that while the drug’s exact mechanism of action is unknown, it is believed to work by activating the Nrf2 pathway – thought to be a major regulator of cytoprotective responses to oxidative and electrophilic stress. In lab models of autoimmune disease, Tecfidera activates this pathway.

The company released post-hoc Phase III data in April 2014 supporting Tecfidera’s efficacy in “a wide range of patients with relapsing-remitting multiple sclerosis (RRMS), as well as its favorable safety and tolerability profile in the real-world setting.”

Data from the DEFINE and CONFIRM Phase III studies, the company reported, show the drug is effective in RRMS patients with high disease activity. Further, data from the Phase IV MANAGE studies found that gastrointestinal side effects where mostly mild to moderate and generally manageable. Abdominal pain, diarrhea and nausea are some of the most common side effects from treatment with Tecfidera.
Approved in February 2013 and formerly known as T-DM1, Kadcyla is an antibody-drug conjugate (ADC) that has gained attention early as a potential breakthrough treatment for breast cancer. It combines a tumor killing “missile” (DM1) with Roche’s famous targeted cancer treatment – Herceptin (trastuzumab).

Analysts have predicted peak sales for the Roche/Genentech drug between $2-5 billion per year. But Kadcyla has also drawn attention for its price tag, which is about $94,000 per year for US patients.

Herceptin, which was one of the first targeted therapies ever developed, treats a subtype of breast cancer that is particularly aggressive and can develop resistance. Herceptin is a monoclonal antibody (MAB) that targets the anti-epidermal growth factor receptor 2 (HER2). Kadcyla has been described as “super Herceptin” because it combines the cytotoxic effects of chemotherapy with the specificity of an antibody. As the New York Times reported, Roche executives are hoping Kadcyla will actually help make Herceptin “obsolete” by the time the older drug goes off patent in 2019.

Roche partnered with ImmunoGen, a pioneer in antibody conjugate technology, to develop the drug. The missile in Kadcyla is emantasine (a derivative of maytansine), which is covalently bound via a thioether linker to the Herceptin MAB. The MAB binds to the surface of cells that express the HER2 receptor. Once the compound is internalized, the DM1 is released and binds to tubulin. Maytansine and its analogues are powerful inhibitors of cell division (mitosis), and are thought to act by suppressing microtubule dynamic stability.

Kadcyla is only effective in women whose tumors are positive for mutated HER2, and it is only approved for those patients whose cancers have spread despite receiving other treatments. Studies report it provides about six months of survival benefit compared to other approved drugs.

Based on the Phase III TH3RESA trial, the drug has recently been recommended as the standard of care for women with HER2-positive breast cancer that has progressed despite prior treatments, such as Herceptin and GlaxoSmithKline’s Tykerb (lapatinib).

Kadcyla appears to help even patients who have been heavily pre-treated. These data were consistent with an earlier trial, EMILIA, which compared T-DM1 with Roche’s Xeloda (capecitabine) and Tykerb in almost 1,000 patients who had progressed despite treatment with Herceptin and a taxane.

T-DM1 showed great promise early on, and Roche initially submitted for FDA approval of the drug in 2010 based on Phase II data. However, the agency demanded additional data, in part because all available treatment choices approved had not been used in the study population prior to treatment with Kadcyla.

Cost Benefit
As with Sovaldi, Kadcyla’s cost has garnered just as much attention as its efficacy. Because of its hefty price tag, the drug is not available through the United Kingdom’s National Health Service. While it is still recommended for women with HER2-positive breast cancer who have failed other drugs and chemotherapy, it is only available through the country’s Cancer Drugs Fund on a case-by-case basis.

Only one other ADC has been approved so far – Seattle Genetics’ Adcetris (brentuximab vedotin) for relapsed or refractory Hodgkin lymphoma. But Kadcyla’s success has inspired Roche to pursue additional MAB conjugates. The company is spending $200 million on a new manufacturing facility for ADCs in Basel, Switzerland, and has more than 20 such drugs in the Roche/Genentech pipeline, including nine currently in clinical trials.

Meanwhile, Immunogen has partnered with numerous other companies besides Roche, including Amgen, Bayer, Biotest, Lilly, Novartis and Sanofi, to develop additional ADCs using the company’s proprietary technology.
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The new blood cancer drug Imbruvica (ibrutinib) from Johnson & Johnson and Pharmacycics made a splash upon its launch in fall 2013 in the US. The drug was first approved for treatment of mantle cell lymphoma (MCL) but a few months later the indication was expanded to include chronic lymphocytic leukemia (CLL). Both of these are relatively rare and aggressive cancers, but the drug is being tested in several other indications as well.

Analysts expect Imbruvica to reap peak sales of at least $2 billion, possibly increasing to as much as $9 billion depending on how many additional indications it earns.

Pharmacycics acquired Imbruvica as part of a 2006 deal with Celera Genomics, the company famously founded by J. Craig Venter that spurred a rapid acceleration of the Human Genome Project. For the rights to several compounds, Pharmacycics paid Celera just $2 million up front and an equity payment of between 500,000 and 1 million shares of Pharmacycics common stock.

Imbruvica blocks an enzyme called Bruton’s tyrosine kinase (BTK), which is a member of the Tec family of kinases and a key component of B cell receptor (BCR) signaling and a regulator of cell proliferation and survival in various B cell malignancies. B cells are a type of lymphocyte, and play a key role in the immune system and related cancers.

The drug costs more than $90 per pill in the US, or about $130,000 per year for the required four pills per day in MCL. That fueled a launch that earned over $100 million in the drug’s first few months on the market, well above the $83 million analysts had forecast. A Forbes article described Imbruvica’s debut as possibly “the best blood cancer drug launch ever.”

Breakthrough Therapy

Notably, Imbruvica was approved under the FDA’s new “breakthrough therapy designation,” which was passed in July 2012. This new pathway allows the FDA to approve drugs for serious diseases based on data related to surrogate endpoints that can “reasonably predict a clinical benefit to patients.” As a result, the drug reached the market earlier than anticipated.

Breakthrough therapy designation aims to speed development and review of drugs for “serious or life-threatening conditions.” The designation requires “preliminary clinical evidence” that a drug provides substantial improvement over available therapy. Companies are expected to provide confirmatory data, however.

The drug’s preliminary approval and breakthrough designation was based on a phase II trial in MCL called PCYC-1104. Overall, 86% of the 111 participants in this study had what was deemed intermediate or high-risk MCL and most had received three prior therapies. More than 65% patients had their cancer shrink and in 21% the disease became undetectable.

The CLL breakthrough designation came in February 2014. By July, the FDA confirmed that Imbruvica’s clinical benefit in CLL had been verified, including among patients whose cancers carry a deletion in chromosome 17. CLL is a type of non-Hodgkin lymphoma, also associated with poor response to standard treatments. Clinical data showed that patients with the mutation saw a 75% reduction in the risk of death or cancer progression. About 40% of CLL patients who fail first line treatments have the chromosome-17 deletion.

Another study compared Imbruvica directly to GlaxoS-mithKline’s Arzerra (ofatumumab) in patients with CLL or small lymphocytic lymphoma (SLL). Imbruvica significantly improved progression-free survival and, more importantly, overall survival. After a year, overall survival among patients on Imbruvica was 90% compared to 81% among those who received Arzerra.
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Tivicay was developed after Pfizer and GlaxoSmithKline founded a new organization called ViiV to focus on creating new treatments for HIV. The goal, as Seeking Alpha has reported, was to “counterbalance the weight of market leader Gilead,” which is by far the most dominant firm in HIV drug development. ViiV started out with a nice array of older drugs, but got a big boost in 2012 when the Japanese pharma company Shionogi joined the collaboration and contributed its late-stage integrase inhibitor -- dolutegravir. In the summer of 2013, the drug underwent priority review and was approved by the FDA for sale as Tivicay.

The drug has important advantages over its competitors and is being hailed as a potential “best in class” blockbuster by 2016. Tivicay is priced at more than $14,000 per year in the US. Analysts anticipate annual sales of up to $2.1 billion by 2022.

Integrase inhibitors block the process by which HIV DNA is integrated into the genome of an infected CD4 cell. Once integration has occurred, the infected cell will produce new copies of the virus.

Because HIV can develop mutations that make it resistant to antivirals, such drugs are now typically given as combinations or cocktails of compounds, sometimes with different targets (e.g. integrases, proteases or reverse transcriptase). When drugs from multiple classes are used in combination, it is often referred to as Highly Active Antiretroviral Therapy (HAART).

Patients used to have to take all these drugs separately, but manufacturers have made great strides in combining HIV antivirals into single pills.

Once ViiV began conducting large-scale testing, the drug’s promise became clear. In a head-to-head study with Gilead’s Atripla (efavirenz/tenofovir/emtricitabine co-formulation), Tivicay plus Epzicom (abacavir/lamivudine) blocked all signs of HIV in 88% of patients after 48 weeks of treatment, compared to 81% for Atripla. The SINGLE study enrolled 833 patients who had not received prior antiviral therapy. The aim of the trial was just to prove the regimen with Tivicay was at least equal to Atripla, but Tivicay came out looking significantly better.

The regimen with Tivicay also suppressed HIV more rapidly than Atripla (28 versus 84 days, respectively). In addition, patients taking Tivicay developed integrase or reverse transcriptase drug resistance mutations. Researchers said that the Tivicay regimen was better tolerated and patients on Atripla were more likely to discontinue treatment.

**Combination Therapy**

Atripla is popular because it combines three agents in a single pill. It contains the non-nucleoside reverse transcriptase inhibitor Sustivar (efavirenz from Bristol-Myers Squibb) and Gilead’s Truvada (emtricitabine and tenofovir disoproxil fumarate), which itself is a fixed-dose product containing two anti-HIV medications – both nucleoside reverse transcriptase inhibitors. Epzicom is a single pill that contains two anti-HIV drugs from ViiV, abacavir and lamivudine. Abacavir is a nucleoside reverse transcriptase inhibitor and lamivudine is a synthetic nucleoside analog.

ViiV has conducted several other Phase III trials of Tivicay, including SPRING-2, VIKING-3 and SAILING. SPRING-2 was also in treatment-naïve patients, while the later two trials included patients who had used other anti-HIV drugs. Tivicay was found to be more effective than Johnson & Johnson’s protease inhibitor Prezista (darunavir). It also showed comparable efficacy to Merck & Co’s Isentress (raltegravir), considered the current standard of care among approved integrase inhibitors.

GSK is the majority owner of ViiV but gave up a portion of its equity to Shionogi in exchange for control of Tivicay. ViiV is devoted to HIV therapeutic development and marketing. Tivicay is its first development success, but the company currently has 11 other drugs on the market. The company plans to market Tivicay both as a single agent and in fixed-dose combinations, including one that combines Tivicay with Epzicom.
The first integrase inhibitor-based single tablet regimen, Stribild, was approved in 2012. It’s one pill that melds four HIV treatments – integrase inhibitor elvitegravir, a boosting agent (cobicistat), nucleoside reverse transcriptase inhibitor emtricitabine and reverse transcriptase inhibitor tenofovir.

Emtricitabine and tenofovir are already available together as Gilead’s Truvada. Combination therapies are the mainstay of HIV treatment now, and companies are pushing to identify the optimal mix of drugs to slow progression of the disease.

Stribild sold over $500 million in its first full year on the market, and some analysts anticipate it could top $3.5 billion by 2018.

The drug was approved based on studies of 1,408 adult patients in two double-blind clinical trials. Patients were randomly assigned to receive Stribild or Atripla, (which contains Truvada and efavirenz) once daily in the first trial. Or, they received either Stribild or Truvada plus atazanavir and ritonavir once daily in the second trial.

Between 88 percent and 90 percent of patients treated with Stribild had an undetectable amount of HIV in their blood, compared with 84 percent treated with just Atripla, and 87 percent treated with Truvada plus atazanavir and ritonavir.
GAZYVA (OBINUTUZUMAB)
Roche/Genentech and Biogen Idec, Leukemia

Gazyva was approved in November 2013 as a first line therapy for chronic lymphocytic leukemia (CLL). An intravenous infusion, this monoclonal antibody (MAB) is given in combination with chlorambucil. Peak sales are estimated at $1.5 to $2.5 billion annually.

Gazyva’s efficacy actually exceeds Roche’s pioneering CLL treatment, Rituxan (rituximab), which is one of the best selling drugs of all time and netted $7 billion at its peak. Like Rituxan, Gazyva selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells, but it was engineered to have higher binding affinity.

Gazyva was the first drug to receive FDA breakthrough therapy designation. Its approval was based on a study (CL111) of more than 350 patients. Patients who received Gazyva plus chlorambucil lived more than twice as long (23 months) compared to those on chlorambucil monotherapy. In the second stage of that study (CLL11) researchers carried out a head-to-head comparison between Gazyva and Rituxan. The patients who received Gazyva had significantly lower (61%) risk of disease worsening or death than those on Rituxan.

OTEZLA (APREMLAST)
Celgene, Psoriatic Arthritis

Otezla (apremilast) boasts limited side effects and oral delivery for psoriatic arthritis. A trial of almost 1,500 patients demonstrated efficacy that was on par with the standard-of-care injectables, dominated by AbbVie’s ultra-blockbuster Humira (adalimumab). Otezla became the first oral medication approved for this indication in March 2014.

Celgene is also seeking a broader approval in psoriasis, and that will have a big impact on the drug’s potential sales, which could reach $2 billion by 2017. The drug acts by blocking the enzyme phosphodiesterase 4.

Celgene is also studying the drug in other chronic inflammatory diseases and has multiple clinical trials ongoing. A study of Otezla in ankylosing spondylitis (a form of arthritis) is ongoing.

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BRINTELLIX (VORTIOXETINE)
Takeda Pharmaceutical Company Limited and Lundbeck, Antidepressant

Brintellix (vortioxetine) was approved by the US FDA in September 2013. It is an inhibitor of serotonin (5-HT) reuptake and is indicated for major depression. It is also an agonist of 5-HT1A receptors, a partial agonist of 5-HT1B receptors and an antagonist of 5-HT3, 5-HT1D and 5-HT7 receptors. It is considered the first and only compound with this particular combination of pharmacodynamic activity.

Shortly after the drug was launched, the drug makers released data that suggests Brintellix also helps patients think, concentrate and remember better. These improvements appear to be a direct effect of the drug, rather than due to a reduction in depressive symptoms. Last summer, Lundbeck reported it was recruiting more than 200 sales reps to help market the drug, which is expected to reap peak sales of $1.5 billion.
GlaxoSmithKline (GSK) has a number of new products that use the company’s Ellipta dry powder inhaler. The goal is for these to help replace the sales lost as asthma and COPD blockbuster Advair (fluticasone propionate and salmeterol) goes off patent. At least a couple have blockbuster potential. Approved in May 2013, Breo Ellipta is a combination of fluticasone furoate (an inhaled corticosteroid) and vilanterol (a long-acting beta2-adrenergic agonist, or LABA). It is indicated for long-term maintenance treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved for reduction of COPD exacerbations. The drug’s approval was based on studies involving more than 7,500 patients and is expected to generate more than $1.3 billion in 2018.

Anoro Ellipta (umeclidinium bromide and vilanterol trifenate) was approved in December 2013 as a once-daily, long-term maintenance treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The drug is a combination of two long-acting bronchodilators -- muscarinic antagonist umeclidinium bromide (an anticholinergic) and beta2 agonist vilanterol, which are delivered through the proprietary Ellipta inhaler. It was approved based on a study of more than 2,400 COPD patients and is expected to earn more than $1.2 billion in 2018.
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Few drugs have elicited as much excitement as the new cancer immunotherapies, in particular the so-called checkpoint inhibitors. Immuno-oncology has been a thankless field for decades, but giant leaps were made with the development of Bristol-Myers Squibb (BMS)’s Yervoy (ipilimumab), a CTLA-4 inhibitor, which was quickly followed up with the programmed death-1 (PD-1) and programmed death ligand-1 (PDL-1) inhibitors. Analysts are now predicting that within ten years, immunotherapy will grow to a $35-billion market and will be used to treat 60% of all cancers.

This wave of new drugs represents a novel approach -- inhibiting checkpoint molecules that normally act to protect the body from attacking itself. Cancerous cells can hijack these mechanisms, thereby avoiding detection by the immune system. Checkpoint inhibitors reverse that process, turning the immune system back on against the cancerous cells.

In a study published in 2010, Stephen Hodi and colleagues described the first trial showing an overall survival benefit from treatment with Yervoy. The study was in malignant melanoma, which was previously essentially untreatable.

In June 2012, two more reports made a splash: A study of anti-PD-1 antibody nivolumab (BMS) showed objective responses in 18% of patients with non-small-cell lung cancer, 28% of melanoma patients, and 27% of renal-cell cancer patients. The second study, from Brahmer et al., looked at an anti-PD-L1 antibody (also from BMS) in patients with several types of advanced cancer. Again, the drug worked in melanoma, renal cancer, and non-small-cell lung cancer.

What made those studies so important is that researchers have long believed that only a few cancers, particularly melanoma and renal cancer, have a strong immunological component. The fact that a checkpoint inhibitor could work -- and work so well -- in lung cancer was an eye opener. These drugs are now being studied in a much wider range of malignancies.
Then in June 2013, a study showed that two such drugs could work better than one. A trial of nivolumab plus Yervoy in 83 patients with advanced melanoma found 53% of patients had an objective response, all showing tumor reduction of 80% or greater. Another study, with Merck’s PD-1 inhibitor (lambrolizumab, or MK-34750), found an overall response rate of 38%. Some of the patients in the Merck study had received prior treatment with ipilimumab and relapsed on that regimen, but they also showed high response rates to the PD-1 inhibitor.

And there was more. A follow-up study on the initial Yervoy patients showed striking results: A full 21% of the melanoma patients lived at least three years (typically survival is no longer than one year), 17% were alive after 7 years, and no further deaths occurred after that. At the time of follow-up, some patients had lived ten years, which was previously inconceivable in this type of cancer.

In just a couple of years, the paradigm for cancer immunotherapy had been revolutionized. Suddenly, it was reasonable to test these drugs in any cancer, and the new goal was to push more patients, even with advanced disease, to that “plateau” of long-term survival that Yervoy had already shown was possible. It’s not clear what that will require yet, but researchers are investigating multiple combinations and trying to devise new ways to evaluate patients and select the optimal mix of therapies for a specific cancer.

Not surprisingly, several companies have amped up development of immunotherapies. Consulting firm Decision Resources (DR) has projected that no fewer than nine such drugs will be approved in the coming decade, but the top earners are all expected to be monoclonal-antibody based checkpoint inhibitors. These will capture a “staggering” 85% of the market, according to DR. These drugs include:

- Opdivo (nivolumab, a PD-1 inhibitor) from BMS. The company aims to submit to the FDA for a melanoma indication sometime in the third quarter of 2014. This is about a year ahead of expectations.
- Pembrolizumab (MK 3475 – a PD-1 inhibitor) from Merck & Co. Insiders say Merck expects approval for this drug in melanoma well ahead of the FDA’s late October 2014 deadline.
- MPDL-3280A (RG7446 - PDL-1 inhibitor) from Roche/Genentech. The drug has shown promise in lung cancer, and the company nabbed a breakthrough therapy designation for it in bladder cancer.
The market for oral hepatitis C drugs is poised for explosive growth (see Sovaldi, on page 10). Market research firm DataMonitor has estimated it will peak at $15.5 billion by 2020. Although several new entrants are headed for the market, a big question is how much of a lead Gilead will have thanks to being first to market with Sovaldi (sofosbuvir), the first in a wave of much more effective and convenient direct acting agents (DAAs).

Gilead exploded out of the gate with Sovaldi (an NS5B inhibitor) in December 2013. The drug is on track to surpass the previous record for a blockbuster launch by raking up $10 billion in sales its first year. Now, like its competitors, Gilead is exploring all-oral drug combinations.

There have also been calls for price wars. Insurers and patient advocates are concerned about Sovaldi’s high price — $84,000 per year in the US. But analysts don’t expect Gilead’s competitors to bow to pressure. Rather, as more patients are diagnosed and seek more convenient new therapies, commentators expect “the pie” to grow for all the hep C treatment developers.

The bottom line is that treating hepatitis C has long been a difficult and uncertain process. The long-standing combination of interferon and ribavirin has low cure rates and many side effects, takes too long, and is still expensive. Adding protease inhibitors helped but Sovaldi is a giant leap forward, and now the competitors are vying to see who can get the furthest above the 90% cure rate, especially in the hard-to-treat patients.

Lead contenders include Gilead’s oral combo of Sovaldi/ledipasvir: Sovaldi, a nucleoside analogue polymerase inhibitor of NS5B, is used in conjunction with a non-nucleoside inhibitor that targets NS5A (ledipasvir). These molecules are essential for HCV replication. Gilead filed for approval of the drug in patients with genotype 1 in February 2014. If approved, it will be the first all oral treatment for patients with this subtype of the virus. Type 1 is the most common subtype in the US. Sovaldi has an overall cure rate of about 94%, but the combination pill has been demonstrating near perfect cure rates.

AbbVie’s contender is a single pill that combines three antivirals (NS5A inhibitor ombitasvir, non-nucleoside polymerase inhibitor dasabuvir, and ABT-450/ritonavir, which combines an investigational protease inhibitor with one that is already approved). The drug was submitted for approval in April 2014 and was granted priority review. The cure rate is reportedly 96%.

Merck has reported a 98% cure rate after 12 weeks with its combination of a protease inhibitor (MK-5172) and an NS5A inhibitor (MK-8742). The company has also acquired hep C drug developer Idenix, with the intention of developing a single daily pill that works across all genotypes in just four to six weeks.

BMS filed an NDA with the FDA in April 2014 for its dual regimen daclatasvir and asunaprevir. The former is an NS5A inhibitor and the latter is a protease inhibitor. The combination was granted a breakthrough therapy designation and will be used in patients with genotype 1. The company will also test those drugs with other combinations. The cure rate reported for this combination so far is about 90%.

Finally, Achillion may be the dark horse in this race. The small biotech has an NS5B inhibitor (ACH-3422) and an NS5A inhibitor (ACH-3102). In August 2014, the company reported that a combination of ACH-3102 plus Sovaldi delivered a 100% cure rate in a clinical trial.
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The leading contender in a pack of next-generation heart disease drugs, evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Analysts predict winners in this race will rake in $2-3 billion per year each.

The drug significantly reduced low-density lipoprotein (LDL) cholesterol levels in recently reported Phase III studies. That news and other extensive data led market research firm Decision Resources to describe the drug as poised to become the “clinical gold standard” among statin add-on therapies for dyslipidemia. The drug is very effective and is expected to reduce rates of cardiovascular disease in patients.

PCSK9 inhibitors have an interesting back story. The target emerged from research into autosomal dominant hypercholesterolemia, which is a rare genetic disorder that leads to extremely high LDL levels and high rates of premature cardiovascular disease. Mutations in PCSK9 are one of the causes of hypercholesterolemia, although this is very rare and would probably not have ever been considered a likely drug target without subsequent pivotal genetic studies.

The work started with studies of regulatory pathways controlling the number and function of LDL receptors. Studies of proprotein convertases (proteins that activate other proteins) found that PCSK9 was encoded by a gene on chromosome 1. Researchers then identified a gain-of-function mutation in that gene as being responsible for familial hypercholesterolemia in a French family. That finding was confirmed by similar results in Norway. Then, work from the Dallas Heart Study showed that loss of function mutations in the PCSK9 gene were associated with very low cholesterol levels and markedly reduced cardiovascular disease rates in some African Americans. The fact
that people are actually living apparently healthy lives with these particular rare mutations was encouraging to drug developers creating PCSK9 inhibitors.

Those findings sparked a storm of pharmaceutical research and a race to approval, one that Amgen seems to be winning. In results of five Phase III studies presented at the American College of Cardiology scientific meeting last spring, Amgen revealed that evolocumab cut LDL levels by between 53% and 75% in trials that involved more than 4,000 patients.

In May 2014, the company announced that evolocumab also reduced LDL levels in patients on statins, regardless of the dose of statins they were taking. Then in June, they reported that the drug significantly reduced LDL in patients with a type of familial hypercholesterolemia.

Most importantly, none of Amgen’s studies have turned up any evidence that the drug causes neurocognitive side effects. That news is crucial, as both Amgen and Sanofi have reported that the FDA is looking into the possibility of such side effects from PCSK9 inhibitors. (Sanofi/Regeneron’s PCSK9 inhibitor is alirocumab). If evidence of such side effects do arise, it would greatly extend the drug’s development time and could even derail it completely.

Amgen is also trying to substantiate that the drug does indeed reduce cardiovascular events – a contentious topic in cardiology in terms of all drugs aimed at lowering lipid levels. The company is sponsoring a massive trial (FOURIER, with 22,500 patients) to document the drug’s effect on cardiac outcomes.

By all appearances, Amgen is ahead in this race. But in an interesting twist, Sanofi recently bought an FDA priority review voucher from BioMarin, which had won the voucher for a rare disease approval. That should shorten regulatory review time for alirocumab by four months. Amgen is planning to file for evolocumab in the third quarter of 2014, while Sanofi and Regeneron are aiming to submit before the end of the year.
Pfizer received Breakthrough Therapy designation for palbociclib from the FDA in April 2013 and announced in August 2014 that it had submitted an NDA for it in breast cancer. The NDA seeks approval for use in combination with Femara (letrozole) for treatment of postmenopausal women with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. The approval is for first line treatment and is based on results of the Phase II PALOMA-1 trial.

Palbociclib selectively inhibits cyclin-dependent kinases (CDKs) 4 and 6 to block tumor cell proliferation. The drug is thought to act by interfering with disrupted cell cycle control. CDKs 4 and 6 are serine/threonine kinases and upregulated in numerous cancers. If approved, this drug will be the first in its class.

PALOMA-1 was a Phase 2 trial designed to assess progression-free survival in post-menopausal women with ER+, HER2- advanced breast cancer receiving palbociclib as a first line treatment. The drug was given in combination with letrozole versus letrozole alone. Letrozole inhibits aromatase, which spurs productions of the estrogens – estradiol and estrone – that can encourage growth of breast tumors.

Final results of the trial were presented at the American Association for Cancer Research (AACR) Annual Meeting in 2014. The study found that palbociclib extended progression-free survival by approximately 50%. Progression free survival was 20.2 months for patients receiving palbociclib versus 10.2 months with letrozole alone. Overall survival trended in favor of the combination treatment but did not meet statistical significance at the time of analysis.

At the time, renowned UCLA breast cancer researcher Dennis Slamon told
Forbes: “These are as impressive results as I have ever seen. I do not say that lightly.” Slamon helped develop the blockbuster breast cancer drug Herceptin.

Analysts are predicting sales of around $2 billion per year, but some have suggested the drug could reach peak sales as high as $6 billion. The looming question is whether the FDA will approve the drug based on PALOMA-1 or whether it will require results from additional studies, which are expected by 2016. One important issue is whether the drug impacts survival. The survival benefit seen in PALOMA-1 so far was not statistically significant.

The FDA is sensitive to this issue in part because of experience with Genentech’s Avastin (bevacizumab), which received accelerated approval based on progression free survival (PFS), or a delay in cancer growth. Later, it was determined that not only did the drug have no survival advantage but also the PFS advantage was less than earlier studies suggested.

Palbociclib is regarded as Pfizer’s most valuable compound in late stage development. The company has also launched at least two Phase III studies of palbociclib in advanced/metastatic breast cancer. PALOMA-2 is evaluating palbociclib in combination with letrozole as a first-line treatment for postmenopausal patients with ER+, HER2-advanced breast cancer. PALOMA-3 is evaluating palbociclib in combination with fulvestrant in women with hormone receptor-positive (HR+), HER2-metastatic breast cancer whose disease has progressed after prior endocrine therapy. Additional, investigator-led studies of palbociclib in advanced/metastatic breast cancer and early breast cancer include the PEARL and PENELOPE-B studies.

Pfizer has a clear lead in this field but Novartis is mounting a challenge with another CDK 4 and 6 inhibitor, called LEE011, which is in development for several cancers including breast cancer. Eli Lilly also has a similar drug but it is still in early development.
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Like most pharmaceutical companies, Sanofi has looming patent expirations to worry about. One of those is for its best-selling Lantus, a recombinant-DNA based insulin analogue that brought in $7.7 billion in 2013 alone but which loses patent protection in February 2015.

The most prescribed type of insulin in the world, Lantus is a shining star in Sanofi’s portfolio. It is the only insulin approved for once-a-day use, controlling patients’ blood sugar for 24 hours. Not surprisingly, that’s a big attraction to patients and to the physicians eager to help them control their blood sugar. The loss of Lantus’s patent protection will be a huge blow to Sanofi.

The good news for the French pharma is that Toujeo (formerly U300) may be able to partially fill Lantus’ shoes.

Both Lantus and Toujeo are a type of insulin called glargine, which is a genetically engineered, longer-acting version of the drug (called “basal” insulin) than traditional forms of insulin. There is only one other form of basal insulin, Novo Nordisk’s Levemir (detemir), which lasts between 14 to 24 hours, but is not approved for once-a-day use.

Human insulin is comprised of two amino acid chains (A and B) with disulfide bonds between them. Glargine is created by switching out glycine-21 in the A-chain with asparagine and adding two arginine residues to the end of the B-chain. These changes cause a shift in the hormone’s isoelectric point, making it soluble at an acidic pH but less soluble at a neutral pH, as is found in the human body. The drug pools in the tissues and slowly moves into solution and the bloodstream. As a result, there is no pronounced peak in the amount of insulin in the bloodstream and the hormone is released gradually over the course of an entire day. These features are unique to glargine and helped propel Lantus to success.

In June, Sanofi reported pooled Phase III results for Toujeo. The analysis comprised several studies from the EDITION program – a series of global studies in a diverse population of patients. Results from the EDITION III trial showed that significantly fewer type 2 diabetes patients new to insulin therapy experienced low blood sugar overnight as compared to those taking Lantus. In the pooled analysis, night-time low blood sugar events were reduced by 31% in Toujeo users compared to those on Lantus. Results from EDITION III also showed that patients on Lantus or Toujeo had similar blood sugar level control (based on HbA1c levels) at six months. Further, the researchers saw a 25% risk reduction in low blood sugar events at any time of day or night across the six-month study period.

More than 9% of the US population (almost 30 million people) suffers from diabetes. The rate of this condition worldwide is expected to climb from 171 million in 2000 to 366 million in 2030. HbA1c levels are generally used to determine whether patients are at higher risk of diabetic complications, which can be debilitating and costly. As blood glucose peaks negatively affect HbA1c results, Lantus and Toujeo offer an important advantage.

In July, Sanofi reported that the FDA had accepted its NDA for Toujeo for review and the company expects to receive a decision in the first half of 2015. This is a pivotal decision for Sanofi as Merck, Eli Lilly and others are all poised to introduce generic versions of Lantus as soon as its patent expires. The looming question is whether Toujeo can demonstrate significant advantage compared to generic versions of Lantus. Sales of Toujeo are expected to reach about $1.5 billion per year.

TOUJEO
Sanofi, Diabetes
NERATINIB

Puma Biotechnology, Breast Cancer

Neratinib is a pan-ErbB tyrosine kinase inhibitor that Puma Biotechnology in-licensed from Pfizer in 2011. In July, Puma shared positive Phase III data and announced that it would start preparing a regulatory filing on the drug, which is expected to occur in the first half of 2015.

The drug is currently being tested as an adjuvant to blockbuster breast cancer drug Herceptin in HER2+ breast cancer patients. Patients who received neratinib plus Herceptin showed a 33% improvement in disease free survival over placebo. The trial enrolled almost 3,000 patients. They all underwent surgery and received adjuvant treatment with Herceptin. They were then randomized to receive extended adjuvant treatment with either neratinib or a placebo.

One concern about the drug has been various side effects, particularly diarrhea. Experts have suggested, however, that prophylaxis with Imodium will reduce that effect. Since the drug is being prescribed for a terminal cancer, the side effect is not considered too big a concern. Analysts are predicting peak sales for neratinib that range from $1 billion to as high as $6 billion.

ISONEP

Lpath, Wet AMD

Currently in Phase II for wet age-related macular degeneration (AMD), iSONEP is a monoclonal antibody targeted against sphingosine-1-phosphate (S1P). S1P is a bioactive lipid and key component of the sphingolipid signaling cascade. It acts on a complement of five G-Protein Coupled Receptors and promotes cell proliferation, migration and protection from cell death (apoptosis). It can also promote inflammation, pathogenic fibrosis and dysregulated angiogenesis.

Lpath is testing the drug in both a systemic formulation (ASONEP) and an ocular version (iSONEP), which targets wet AMD. This is an indication with great unmet need, as there are about more than 1.5 million patients with this condition in the US alone. Current therapies are not very effective and all target the growth factor VEGF. S1P is believed to contribute to both the early and late stages of AMD through various effects. Sales are expected to reach at least $650 million annually but could go as high as $2.4 billion.
ANTI-LINGO-1

Biogen Idec, Multiple Sclerosis

Anti-LINGO-1 is a monoclonal antibody in Phase II for multiple sclerosis (MS). It targets LINGO-1, a protein expressed selectively in the central nervous system (CNS) that affects axonal myelination and axonal regeneration. LINGO-1 is a leucine-rich repeat and Ig domain-containing, Nogo receptor interacting protein. Gene expression of this protein is upregulated in oligodendrocyte progenitor cells from the demyelinated white matter in samples from patients with multiple sclerosis.

Researchers at Biogen Idec discovered that blocking LINGO-1 helps promote myelin repair and recovery of the central nervous system (CNS) in models of MS. The company has completed two Phase I studies of the drug, including in healthy volunteers and MS patients. It's now advancing the drug into Phase II trials.

Considered a “high risk” candidate because it is a novel mechanism and still in early stages of development, this drug still has tremendous blockbuster potential if it becomes the first agent approved to actually repair the central nervous system.

CAR THERAPY

Bellicum, Juno, Kite, Novartis and others, Cancer

As with other cancer immunotherapies, efforts to engineer patients’ own immune cells have seemed like a long shot for quite a while. But the technique of adoptive cell transfer (ACT) has uncovered the immense potential of this field. In ACT the patients’ own T cells are collected, then genetically engineered to express proteins called chimeric antigen receptors (CARs) on the cell surface. These CARs help the T cells recognize a specific antigen on tumors. Billions of them can then be grown and given to the patient by infusion.

The turning point for this field may have been a 2011 study by Carl June (University of Pennsylvania) and coworkers. June’s team used customized T cells to eliminate the cancers in two out of three patients with advanced chronic lymphocytic leukemia. In December 2013, June and colleagues published another round of impressive data, demonstrating 19 complete remissions in 22 pediatric patients with lethal cases of acute lymphoblastic leukemia. Five of those patients later relapsed, but the findings were impressive enough to spur a rush to CAR therapy, led by several startups and Novartis.

While again, these products are all in very early stages, the promise of cure in lethal cancers offers significant blockbuster potential and further change in the oncology treatment paradigm.

LENTIGLOBIN GENE THERAPY

Bluebird, Thalassemia and Sickle Cell

Gene therapy has seen more downs than ups over the past decade, discouraging most companies from continuing to pursue it. But Bluebird Bio’s persistence is paying off. The company’s LentiGlobin treatment (lentiviral HPV569) inserts a fully functional human beta-globin gene into the patient’s own hematopoietic stem cells.

The company has tested the gene therapy in at least four patients with severe beta-thalassemia -- one of the most prevalent inherited diseases. Patients are typically dependent on routine transfusions from early childhood. All of the subjects are producing higher levels of beta-globin and one has been transfusion independent for more than 72 months since treatment.

Rare diseases have become a lucrative field as drug developers can justify higher prices for these drugs. A list of the “The World’s Most Expensive Drugs” published by Forbes in 2010 contained nine drugs, all costing more than $200,000 per year and most of them for rare genetic diseases.
1. Humira (adalimumab)

AbbVie, Rheumatoid arthritis, other immune diseases

Humira, a monoclonal antibody, is a tumor necrosis factor-alpha (TNF) inhibitor that was developed using phage display technology. It was launched in 2003 and is approved for certain types of arthritis, colitis and psoriasis. The drug had sales of just over $11 billion in 2013.

2. Enbrel (etanercept)

Amgen, Rheumatoid arthritis, other immune diseases

A recombinant fusion protein, Enbrel is indicated for several types of arthritis and psoriasis. Like Humira, Enbrel is a TNF inhibitor. It was developed by researchers at Immunex and launched in 1998. This soluble receptor fusion protein boasted sales of more than $8.75 billion in 2013.

3. Advair (fluticasone propionate and salmeterol)

GlaxoSmithKline, Asthma, chronic obstructive pulmonary disease

Advair is a corticosteroid and long-acting beta2-adrenergic agonist used to treat asthma and chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Launched in 2001, the drug brought in more than $8.3 billion in 2013 sales for GSK.

4. Remicade (infliximab)

Johnson & Johnson/Janssen, Rheumatoid arthritis and other immune diseases

Remicade is a chimeric monoclonal antibody against TNF that is approved for several types of arthritis, colitis and psoriasis. It was developed by Centocor Ortho Biotech, which later became Janssen Biotech. Remicade was launched in 1998 and had more than $8.3 billion in 2013 sales.

5. Rituxan (rituximab)

Roche/Genentech, Lymphoma, leukemia and rheumatoid arthritis

A CD20-targeting monoclonal antibody, Rituxan (rituximab) is approved for non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and rheumatoid arthritis. The drug was developed by IDEC Pharmaceuticals and, when launched in 1997, was the first monoclonal approved for a cancer indication. In 2013 it had more than $8 billion in sales.

6. Lantus (insulin glargine)

Sanofi, Diabetes

A recombinant human insulin analog, Lantus is the top-selling form of insulin in the world. Launched in 2000, the drug garnered more than $7.5 billion in 2013 sales.

7. Avastin (bevacizumab)

Roche, Cancer

An anti-VEGF monoclonal antibody, Avastin was the first angiogenesis inhibitor approved in the US. Launched in 2004, the drug had more than $6.5 billion in 2013 sales.

8. Herceptin (trastuzumab)

Roche/Genentech, Cancer

Launched in 1998, Herceptin was the first “targeted” cancer drug ever approved. The drug is used in patients with breast cancer whose tumors over-express the receptor HER2. Other cancers also over-express this protein so Herceptin may gain wider use. In 2013 it raked in more than $6.5 billion.

9. Crestor (rosuvastatin)

AstraZeneca, High cholesterol

A selective and competitive inhibitor of HMG-CoA reductase, Crestor is now the world’s top selling “bad cholesterol” lowering drug. Launched in 2003,
it had almost $6 billion in 2013 sales.

10. **Januvia (sitagliptin)**

**Merck & Co, Type 2 diabetes**

Launched in 2006, Januvia is a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. It’s believed to act by slowing the inactivation of incretin hormones and thereby stabilizing blood glucose levels. The drug made over $6 billion in 2013.

![Sitagliptin](image)

11. **Abilify (aripiprazole)**

**Otsuka, Schizophrenia, bipolar disorder, other mental health conditions**

Abilify was launched in 2002. It’s believed the drug mainly acts through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors. It earned more than $5.5 billion in 2013.

![Aripiprazole](image)

12. **Cymbalta (duloxetine Hcl)**

**Eli Lilly, Depression, anxiety and nerve pain**

A serotonin-norepinephrine reuptake inhibitor approved in 2004, Cymbalta earned over $5 billion in 2013.

![Duloxetine](image)

13. **Gleevec (imatinib mesylate)**

**Novartis, Cancer**

A small molecule kinase inhibitor, Gleevec is one of the first targeted therapies ever developed. Originally developed for leukemia, it is prescribed to cancer patients with the Philadelphia chromosome translocation. It was approved in 2001 and earned Novartis more than $4.5 billion in 2013.

![Imatinib mesylate](image)

14. **Lyrica (pregabalin)**

**Pfizer, Fibromyalgia, chronic pain**

First approved in 2004, Lyrica earned more than $4.5 billion in 2013. It is a 3-substituted analogue of gamma-aminobutyric acid (GABA).

![Pregabalin](image)
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15. Neulasta (pegfilgrastim)
Amgen, Cancer

Neulasta is a leukocyte growth factor prescribed to decrease incidence of infection in some cancer patients. A covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol, Neulasta earned over $4.25 billion in 2013. It was approved in 2002.

16. Copaxone (glatiramer)
Teva, Multiple Sclerosis

A mixture of synthetic polypeptides, Copaxone is an immuno-modulator used to treat multiple sclerosis. It is in the class of disease modifying drugs for this condition. Launched in 1997, the drug earned more than $4.25 billion in 2013.

17. Revlimid (lenalidomide)
Celgene, Cancer

A thalidomide analogue, Revlimid is used in patients with mantle cell lymphoma, multiple myeloma, and transfusion-dependent anemia. It was first approved in 2005 and earned more than $4.25 billion in 2013.

18. Lucentis (ranibizumab)
Roche/Genentech, Wet age-related macular degeneration and other eye conditions

Lucentis is a monoclonal antibody against vascular endothelial growth factor (VEGF) that is delivered directly into the eye. It is an angiogenesis inhibitor and was first approved in 2006 and earned more than $4.2 billion in 2013.

19. Spiriva (tiotropium bromide)
Boehringer Ingelheim, COPD

Launched in 2002, Spiriva is a long-acting, anti-muscarinic agent with affinity to receptors M1 to M5. The drug acts to keep airways open through sustained cholinergic blockade. It earned more than $4 billion in 2013.

20. Nexium (esomeprazole)
AstraZeneca, Gastroesophageal reflux disease (GERD)

Widely known as “the purple pill”, launched in 2001, Nexium is a proton pump inhibitor that reduces stomach acid. It quickly soared to the top of medications prescribed for GERD and garnered almost $4 billion in 2013 sales. AstraZeneca and Pfizer launched an OTC version of Nexium in May 2014, and generic versions are on the way.

21. Prevnar 13
Pfizer, Streptococcus pneumoniae

A bioengineered vaccine for pneumococcal pneumonia, Prevnar 13 was launched in 2010 and earned nearly $4 billion in 2013 sales.

22. Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate)
Gilead, HIV

Atripla is the first single pill combining a non-nucleoside reverse transcriptase inhibitor (efavirenz), a nucleoside reverse transcriptase inhibitor (emtricitabine), and nucleotide reverse transcriptase inhibitor (tenofovir). Approved in 2006, the drug earned more than $3.75 billion in 2013.

23. Diovan (valsartan)
Novartis, Hypertension, heart failure

Diovan is an angiotensin II receptor antagonist that acts on the AT1 receptor subtype. The drug earned over $3.5 billion in 2013, but faces competition from generic version approved in June 2014.

24. Symbicort (budesonide/formoterol)
AstraZeneca, COPD, asthma

Containing a long-acting beta2-adrenergic agonist (formoterol), Symbicort is a mainstay of COPD and asthma treatment and
earned just over $3.5 billion in 2013. But with key patents expiring, a generic version of the drug is looming.

25. Celebrex (celecoxib)
Pfizer, Pain

Celebrex is a COX-2 (cyclooxygenase-2) inhibitor that earned more than $3.3 billion in 2013. Generic versions from TEVA and Mylan are on the way.

26. Epogen/Procrit (epoetin alfa)
Amgen/Johnson & Johnson, Anemia

Recombinant erythropoietin stimulates erythropoiesis – the production of red blood cells. The drug was first launched in 1989 and earned over $3.3 billion in 2013.

27. Truvada (tenofovir/emtricitabine)
Gilead, HIV

The first drug that can prevent HIV infection, Truvada is also approved to treat people already infected with HIV. It is a combination pill containing a nucleoside reverse transcriptase inhibitor (emtricitabine), and a nucleotide reverse transcriptase inhibitor (tenofovir). Launched in 2012 and earned more than $3.2 billion in 2013.

28. Avonex (interferon beta-1a)
Biogen Idec, Multiple sclerosis

Launched in 1996, Avonex is used to treat relapsing forms of MS. It is a disease modifying drug (DMD) that slows the progression of MS and reduces the frequency and severity of attacks. The drug earned just over $3 billion in 2013. In summer of 2014, a longer-acting form of Avonex, Plegridy, was approved. It is also expected to be a blockbuster.

29. Micards (telmisartan)
Boehringer Ingelheim, Hypertension

First approved in 1998, Micards is an angiotensin receptor blocker. It earned just over $3 billion in 2013. The drug’s patent expired in January 2014 and generic versions have already been launched.

30. NovoRapid (insulin aspart)
Novo Nordisk, Diabetes

Launched in 2013, Novo Rapid is a prefilled insulin pump cartridge. The drug earned just over $3 billion in 2013.
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