POSTER DRUG Gilead's Sovaldi (sofosbuvir) offers a cure for hepatitis C at a price of $84,000 per course of treatment.

MIXED SIGNALS

Amid healthy sales and bountiful approvals, a **PRICING CONUNDRUM** impedes patient access to medicines in 2014

RICK MULLIN, C&EN NEW YORK CITY

WITHIN A WEEK of publication of C&EN's 2013 Pharmaceutical Year in Review, a new drug called Sovaldi was introduced. Like others before, it came with a backstory and kicked off a new adventure for the firm that developed it and the patients, physicians, and payers that populate the market. In the case of Sovaldi, a highly effective treatment for hepatitis C, the narrative illuminates the key issues and dilemmas characterizing the drug industry in 2014.

The active ingredient in Sovaldi, sofosbuvir, was discovered by Pharmasset, a Princeton, N.J.-based biotech firm with fewer than 100 employees. Seeing potential, Gilead Sciences acquired Pharmasset in 2011 for a surprising $11 billion. The bet, although big, has already paid off: Sovaldi sales were $8.5 billion in the first nine months of this year.

For Gilead, a fast-growing drug company with a portfolio of successful therapies in areas such as HIV/AIDS and oncology, Sovaldi exemplified the kind of product

TODD SMITH/DIGITAL WORLD BIOLOGY

most highly prized in drug discovery and development: one that has a novel and positive impact on an intractable disease.

By midyear, however, a Senate committee had convened to inquire into the cost of the drug—a whopping $84,000 per course of treatment.

Sovaldi's path from innovation to financial success to frustration for patients highlights the perilous trajectory of treatments advanced by an industry that has massively reorganized product development and market orientation in recent years without fundamentally changing its business model.

Rattled by the dry-up of drug pipelines and the loss of patent exclusivity on the last generation of billion-dollar sellers, drug companies have turned to the development of therapies for unmet medical needs that often target small patient populations.

But the industry has carried over a pricing regimen that's focused on recouping, and then some, the high cost of developing a successful new drug—close to $3 billion, according to a report released last month by the Tufts Center for the Study of Drug Development. Companies launch drugs at sometimes astronomically high prices, claiming that they actually save the health care system money when costs are calculated over a decade or more.

But drugs need to be paid for upfront. And while it is not the most expensive drug on the market, Sovaldi's price tag put it at center stage in an examination of pricing in 2014. This included a July report prepared for the Pharmaceutical Care Management Association, a group of pharmacy benefit management firms, by actuarial services firm Milliman estimates that new hepatitis C drugs, including Sovaldi, will increase Medicare Part D spending by between $3 billion and $6 billion annually, causing premiums to rise by as much as 8.6%.

Having achieved a true breakthrough, Gilead steered into a headwind of market reaction against high-priced drugs.

THE UPSIDE

The good and bad news about Sovaldi played out in a 2014 of mostly good news for drugmakers by conventional measures. The year saw the introduction of breakthrough drugs in oncology and hepatitis C. Overall global sales for the year ending in June reached $901 billion, a rise of 5.5% over 2013, according to the market research firm IMS Institue for Healthcare Informatics.

The increase is driven primarily by business in the U.S., where sales are expected to achieve 12% growth this year to about $375 billion, IMS says, markedly better than the 3 to 5% growth the firm predicted a year ago. Despite the healthy numbers, sales among the top 10 companies tracked by IMS remained flat this year.

With much of the macro restructuring—facility closures and staff reductions—completed more than a year ago, the major drug companies turned to portfolio rationalization this year with a run of deals in which players exited therapeutic areas of less strength and bulwarked their specializations.

Two top 10 pharma companies failed to pull off major planned acquisitions in 2014. Midsized firms, however, were extremely active in mergers and acquisitions (M&A) and accounted for a record level of activity. Big layoffs were also more prevalent this year among midsized firms than among the major drug companies.

"The most significant thing in 2014 is that global growth is going to be at the highest point it's been at for over a decade," says Michael Kleinrock, research director at IMS's health care informatics group. "Most if not all the uptick in global drug sales is coming from the U.S."

Kleinrock notes that the sales impact of patent expirations dropped from $30 billion across the industry in 2012 to $19 billion in 2013. He expects the impact figure to fall below $10 billion in 2014. At the same time, drugs that reached the market in 2013 are poised to have an even more dramatic effect on sales this year, he says.

THE YEAR IN PHARMACEUTICALS

MICHAEL MCCOY/C&EN

Merck's site in Kenilworth, N.J.

Merck and Lilly announce R&D cuts
Merck & Co. details plans to dial back in-house research and establish regional innovation hubs; Lilly says it will cut R&D spending by $1 billion.

FDA bans Indian drug plant
In the latest crackdown on India, U.S. regulators halt imports from a Sun Pharmaceutical plant, citing noncompliance with quality standards.

December 2013 — January 2014 — February 2014 — March 2014 — April 2014 — May 2014

Sovaldi approved
Gilead Sciences' hepatitis C drug is a faster, more palatable cure for the liver-destroying disease, heralding an upcoming year of significant new drug approvals.

Actavis buys Forest Labs
Generics firm pays $25 billion in cash and stock to acquire the rejuvenated specialty pharmaceuticals maker.

Pharma firms swap assets
Novartis, GSK, and Lilly trade businesses to create more focused companies.

Pfizer rebuffed
Attempt to acquire AstraZeneca is undone by U.S. regulators' and U.K. workers' concerns.

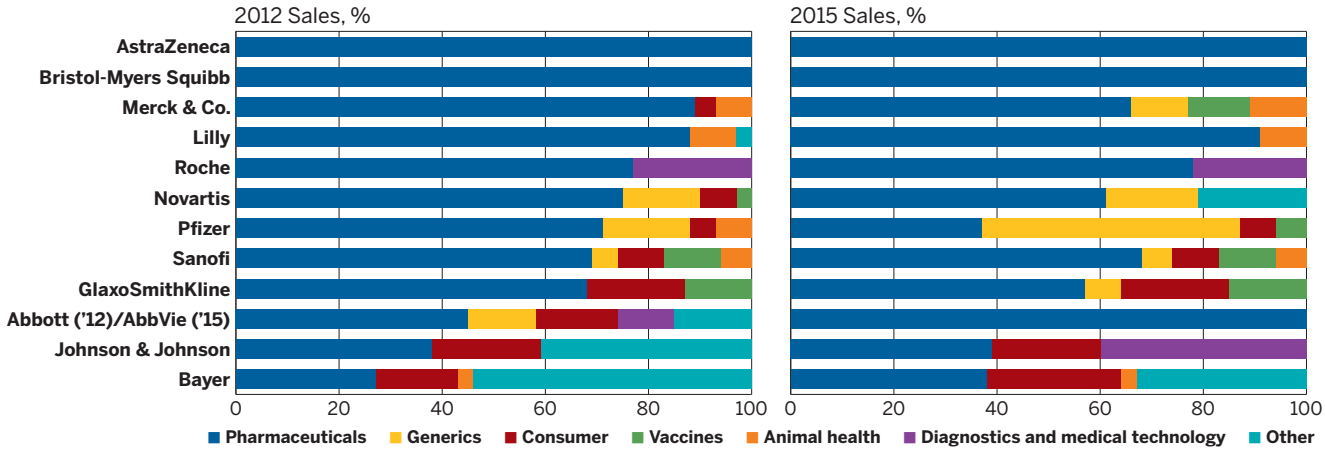
AstraZeneca shutters India R&D site
Dropping work in neglected tropical diseases, tuberculosis, and malaria, AstraZeneca announces closure of Avishkar R&D site in Bangalore.

ASTRAZENECA

AstraZeneca's London headquarters.

Pfizer pursues AstraZeneca
Pfizer, known for huge acquisitions, announces a bid to buy the U.K. drug major.

PORTFOLIO SHUFFLE Through swaps and divestitures, companies are rationalizing portfolios to focus on fewer businesses.



NOTE: Figures for 2015 are based on pro forma sales estimates, including deals announced in 2014.
SOURCE: Ernst & Young

"It's looking like one of the best launch cohorts in aggregate in the past decade," Kleinrock says. Prices continue to increase for branded and generic drugs, he says.

Then there is Sovaldi. "This one incredibly successful medicine, a cure for hepatitis C, directly impacts the patient population, curing most of them," he says. "That one drug drives the market 2 to 2.5% in terms of growth." In part due to Sovaldi, Kleinrock characterizes growth this year as an unexpected spike. He expects it to drop to between 5 and 8% annually through 2018.

Glen Giovannetti, life sciences sector leader at Ernst & Young, notes that Sovaldi is at the head of a line of significant new drugs introduced over the past year. Big debuts include Gilead's Zydelig, a leukemia and lymphoma treatment; Merck & Co.'s Keytruda, a cancer immunotherapy; and Novartis's Zykadia, a lung cancer drug. Add to that Gilead's Harvoni, a combination pill used with Sovaldi for hepatitis C.

Overall, the Food & Drug Administration lists 34 approvals of new chemical entities this year as of mid-October. All of last year saw the approval of 27 new drugs. By the end of 2014 the number could be back to the level of 2012, which boasted 39 new entries. Giovannetti says the strength and number of new entrants reflect R&D efficiency improvements of recent years.

"I don't know if we are through the woods, but it looks like a lot of the restructuring efforts and strategies put in place around R&D are starting to bear fruit," he says.

And a new round of restructuring is under way, Giovannetti adds, as companies

June 2014

Merck acquires Idenix
Drug firm bolsters its hepatitis C portfolio in $3.8 billion deal.

AbbVie moves on Shire
U.S. firm seeks a tax inversion in deal to acquire Ireland's Shire.

July 2014

Amgen launches first round of job cuts
The biotech major reveals that 2,900 jobs will be eliminated next year, with R&D sites closing in Seattle and Bothell, Wash.

Novartis goes for Google lens
New technology moves into mainstream drug research.

NOVARTIS

A prototype smart lens.

Gilead scrutinized on Sovaldi
Congressional committee launches probe into the $84,000-per-course-of-treatment price of Gilead's Sovaldi.

August 2014

September 2014

Exelixis joins in headcount reductions
Bad news from the clinic is followed by a 70% workforce reduction.

October 2014

AbbVie's bid for Shire is scuttled
New U.S. tax regulations thwart the $54 billion merger.

November 2014

Amgen ups cuts
Job cuts through 2015 will run to between 3,500 to 4,000.

Bristol-Myers Squibb to build in Ireland
The $900 million biologics manufacturing project follows a similar investment in Devens, Mass.

BMS

BMS biologics manufacturing plant in Devens, Mass.

TOP 10 PRODUCTS

Solid growth conitnued for industry's biggest-selling brands

BRAND NAME	COMPOUND	MARKETER	INDICATION	SALES[a] ($ BILLIONS)	12-MONTH CHANGE IN SALES
Humira	Adalimumab	AbbVie	Rheumatoid arthritis	$10.8	20.40%
Lantus	Insulin glargine	Sanofi	Type 2 diabetes	9.1	31.8
Seretide	Fluticasone & salmeterol	GlaxoSmithKline	Asthma	8.9	0.6
Abilify	Aripiprazole	Bristol-Myers Squibb & Otsuka	Schizophrenia	8.6	19.0
Enbrel	Etanercept	Amgen & Pfizer	Rheumatoid arthritis	8.4	10.3
Crestor	Rosuvastatin	AstraZeneca	Hypercholesterolemia	8.3	5.1
Nexium	Esomeprazole	AstraZeneca	Acid reflux disease symptoms	7.9	8.2
Remicade	Infliximab	Janssen Biotech	Crohn's disease & rheumatoid arthritis	7.8	8.8
MabThera	Rituximab	Roche	Non-Hodgkin's lymphoma	5.9	3.4
Avastin	Bevacizumab	Genentech, Chugai, & Roche	Metastatic colorectal cancer	5.5	6.1
TOTAL				$81.2	6.7%

a For the 12 months ending on June 30, 2014. **SOURCE:** IMS Institute for Healthcare Informatics

surgically divest and acquire businesses and research programs to capitalize on strengths.

"This goes back a couple of years, with Abbott and AbbVie splitting and Pfizer spinning off animal health," Giovannetti says. "But that whole trend exploded this year." Nearly every major drug company acted in an industry that continues to move as a herd, he says. "Once someone has taken action like this, and the market reacts positively, which it certainly did with Pfizer, you get pressure going up to the boardroom for every company to think about doing the same."

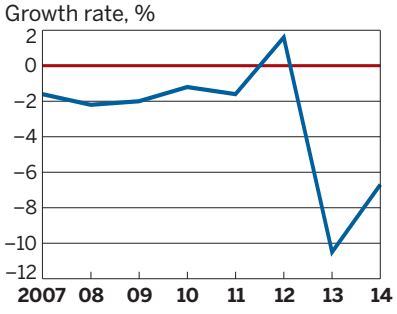
He points to a lively swap meet that occurred in April when Novartis sold its vaccines business to GlaxoSmithKline for $7.1 billion and purchased the U.K. firm's oncology products for $16 billion. The two companies also formed a joint venture comprising their consumer health businesses. Meanwhile, Novartis struck a deal to sell its animal health business to Eli Lilly & Co. for $5.4 billion. And Merck sold its consumer products business to Bayer.

As decks were shuffled across the industry, Bayer announced plans for an initial public offering of stock in its materials science business to increase focus on pharmaceuticals. Johnson & Johnson, meanwhile, sold its diagnostics business.

HANGOVER

For all its portents of evolution, however, 2014 started with more of the same as Merck and Lilly announced R&D cutbacks in the first weeks of January. At Merck, Roger M. Perlmutter, who had recently left Amgen to take the R&D reins, revealed that the company will lessen its focus on in-house research and place a heavier emphasis on accessing discoveries made outside its own labs. Following the lead of Pfizer, Merck set out to establish innovation hubs, listing Boston, the San Francisco Bay Area, London, and Shanghai as target sites.

R&D BOUNCE Pipelines, out of free fall, still headed down.



NOTE: Number of active products in drug company pipelines counted in June of each year. There were 4,852 products as of June 2014.
SOURCE: IMS Institute for Healthcare Informatics

Lilly reported that it will cut its R&D budget by $1 billion in 2014. The firm had been a holdout among large drug companies on R&D staff cutbacks, but a forecasted drop in 2014 revenue, late-stage clinical failures, and the imminent loss of patent protection for its antidepressant Cymbalta and its osteoporosis drug Evista caught Lilly up with its cohort.

The year also ended with cuts as GlaxoSmithKline said it will downsize its Research Triangle Park, N.C., research facility.

The ax fell in biotech as well. In August, Amgen announced the first tranche of job cuts in a restructuring program that by November targeted an overall headcount reduction of 3,500 to 4,000. In an attempt to cut costs and focus on the launch of new drugs, the firm said it would close its R&D facilities in Seattle and Bothell, Wash., and scale back on total facilities by 23%.

Meanwhile Exelixis, once a biotech powerhouse with 300 research-related employees, said it would cut 70% of its workforce following disappointing results in a Phase III trial of cabozantinib, its thyroid cancer drug, for the treatment of metastatic castration-resistant prostate cancer.

While drugmakers cut resources in-house, they advanced their R&D causes through a variety of partnerships. Among the research consortia announced in 2014, the Accelerating Medicines Partnership teams 10 leading pharma and biotech companies—including Pfizer, GlaxoSmithKline, Lilly, and Biogen Idec—with the National Institutes of Health and a dozen nonprofit and patient advocacy groups. The group has staked out Alzheimer's

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disease, type 2 diabetes, and autoimmune diseases for joint discovery research.

The push for industry-academic partnerships found Bristol-Myers Squibb in business with Boston-based Allied Minds, a group that brokers research and preclinical drug development alliances among its 33 university associates and drug and biotech firms. The pair created Allied-Bristol Life Sciences, which will work with universities on forming drug discovery companies that BMS will have an option to acquire.

Pooled research efforts with an eye on fostering entrepreneurial drug companies came into focus this year in New York City, which neared full stride as a research hub on par with Boston and San Francisco. In June, the venture capital firm Accelerator Corp. announced a $51 million investment to foster small, scientist-run companies at the Alexandria Center for Life Science, a new complex nestled between research hospitals on the city's East River. The center already houses Pfizer, Roche, and Lilly R&D labs, as well as several start-up firms.

MERGERS

Two attempts by large U.S. drug companies to make major acquisitions in Europe were unsuccessful. Pfizer's bid for AstraZeneca and AbbVie's pass at Shire focused attention on tax "inversion," the practice of moving a company's tax liabilities from the U.S. to a country with a lower rate, the U.K. in these cases. Whereas AbbVie specifically cited new tax rules issued by the U.S. Treasury Department for ending its $54 billion deal for Shire, Pfizer's pursuit of AstraZeneca ran into several problems.

Pfizer Chief Executive Officer Ian C. Read's rationale for the merger was the creation of an "innovation core" strengthened by the two companies' combined research efforts and portfolios, specifically in oncology, inflammation, and cardiovascular health. He also pointed to operational and financial synergies that would benefit a combined company.

Read dismissed concerns that Pfizer sought merely to reduce its tax burden. "I don't believe it should be any concern to the U.S. government that we're becoming

TOP 10 COMPANIES

Sales decline as patents expire

	SALES[a] ($ BILLIONS)	12-MONTH CHANGE IN SALES
Novartis	$50.5	4.0%
Pfizer	43.4	3.0
Sanofi	37.5	6.2
Merck & Co.	35.4	0.2
Roche	35.0	4.1
Johnson & Johnson	32.7	18.3
AstraZeneca	32.3	5.3
GlaxoSmithKline	30.9	1.2
Teva	24.9	3.8
Eli Lilly & Co.	21.2	-2.0
TOTAL	$343.8	0.1%
GLOBAL MARKET	$901.3	5.5%

a For the 12 months ending on June 30, 2014.
SOURCE: IMS Institute for Healthcare Informatics

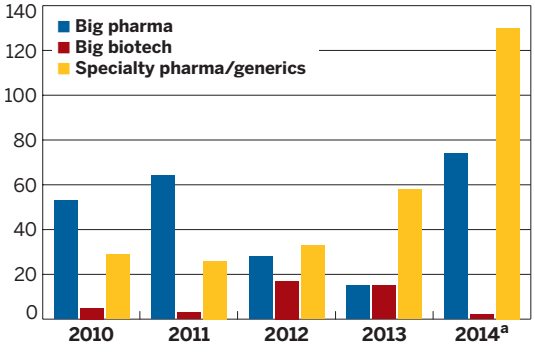
a stronger company and more competitive on a global scale," he said.

AstraZeneca rebuffed Pfizer's overture for months, claiming that it undervalued the company and presented significant risks to shareholders and employees. The deal also met political resistance in the U.K., where memories of Pfizer's 2011 shutdown of its Sandwich R&D center following a merger with Wyeth prompted concerns about a new round of U.K. job cuts. In May, AstraZeneca rejected Pfizer's final offer of $119 billion.

Ernst & Young's Giovannetti says the fate of the two deals does not necessarily portend the end of huge acquisitions in the sector. "Never say never on the megadeal," he says. "Pfizer has a long history of them and clearly didn't shy away from AstraZeneca." He adds, however, that the industry is generally growing weary of the consequences of merging major players.

"The bigger lesson from these deals is that they impact R&D productivity," Giovannetti says, Read's vision of an innovation powerhouse in a combined Pfizer and AstraZeneca to the contrary. "When R&D appears to be back in a more positive position, do we want to take on another deal and throw it into disarray?" Big pharma megadeals could arise in 2015 and beyond, he says, "but it won't be a trend."

MERGERS & ACQUISITIONS Specialty and generic pharma deals surged in record year.



a Data through Nov. 17, 2014.
SOURCE: Ernst & Young

On the other hand, 2014 saw several acquisitions of smaller firms by top 10 drug companies as well as some high-priced deals by the midsized and generic drug makers that led in this year's big rise in M&A activity. Some deals had a transformative effect.

In February, generic drug specialist Actavis announced it would spend $25 billion to buy Forest Laboratories, a recently revamped specialty drug firm. Then last month Actavis announced one of the biggest deals of the year for any industry: the $66 billion purchase of Allergan, best known as the maker of ophthalmic pharmaceuticals and the cosmetic enhancer Botox. In doing so, Actavis rescued Allergan from the clutches of Valeant Pharmaceuticals, which had teamed up with the activist investment firm Pershing Square Capital Management in a hostile takeover attempt.

"Mobile technologies will have a big impact over time in helping people manage their disease effectively."

Merck's $3.85 billion purchase of Idenix Pharmaceuticals typified the deals many larger companies are focused on and supports the firm's strategy of accessing outside innovation. With the acquisition, Merck gained IDX21437, a nucleotide polymerase inhibitor in Phase II trials as a treatment for hepatitis C. Roche moved to bolster its oncology program with the $725 million acquisition of Seragon Pharmaceuticals, a privately held oncology drug developer.

ACCESSING EXPERTISE

Licensing also advanced as a strategy for accessing emerging technology in 2014, exemplified by Novartis's $14 million deal for rights to Oxford BioMedica's viral vector technology to support its T-cell immunotherapy program.

And typifying deals in which drug companies seek to access better phenotypic data from patients via emerging digital technology, Novartis's Alcon eye care division licensed a "smart lens" from Google. Novartis plans to use the technology, which embeds contact lenses with noninvasive sensors, microchips, and other electronics, to measure glucose levels in the eye fluid of patients with diabetes.

Ernst & Young's Giovannetti expects digital technology to play an increasing role in health care as the emphasis shifts from treating symptoms to preventing and managing chronic disease. "There will be a huge change," he says. "Mobile technologies will have a big impact over time in helping people manage their disease effectively."

The push for more and better data on patients will only increase in the development of targeted therapies for rare diseases, according to industry watchers. Heightened requirements from FDA and health care payers for data on the benefits of new drugs compared with those already on the market will also force a closer look at individual patients. But as seen in Sovaldi's postmarket saga, the focus on the patient is morphing into the problem of getting breakthrough drugs to patients who can't afford them.

"The cost-pressure dynamic is really staying front and center," IMS's Kleinrock says. "It's all a bit of a mess at the moment, and the key issue for the next few years will be achieving clarity on pricing. There will be a lot of confusion and statements from different players in the system about how they are working in the best interest of society or the patient or whomever. But we may not come to the best outcome for everybody." ■