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THE YEAR IN NEW DRUGS

DRUG APPROVALS were down in 2013, but many that won FDA's nod have strong sales prospects

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AFTER A ROCKETING RISE in new-drug approvals in 2012, the pharmaceutical industry fell back to Earth in 2013. Last year, only 27 new products received Food & Drug Administration approval, down from 39 in the prior year, but on par with approval rates for the past decade.

The good news for industry is that many of the new products have potential to become blockbusters, with peak annual sales of more than $1 billion. Also good news is that FDA has become more efficient than ever at reviewing drug applications by taking advantage of new mechanisms to speed drug approvals.

The bad news for industry is that only half of the big pharma firms gained new drugs. Many of those left empty-handed are the firms that were most desperate to replace revenues lost recently to generic competition. With 2014 unlikely to offer as many top-selling drugs, big pharma will continue its struggle to grow.

As in 2012, cancer treatments formed the largest class of FDA approvals in 2013, accounting for about 30% of all new molecular entities. Only nine of the 27 new drugs offer novel mechanisms of action, compared with 18 of 39 in 2012. Few biologics and no peptides were approved. Indeed, good old-fashioned small molecules made up the lion's share of the approvals.

GlaxoSmithKline led the pack among big pharma firms in 2013, with five approvals, the same number as last year's leader, Pfizer.

Eli Lilly & Co., one of the companies hardest hit by generic competition, had little success in 2013. Except for a poorly received diagnostic for Alzheimer's disease, the company has not seen FDA's green light for a new product since the 2009 approval of the blood thinner Effient.

Lilly's recent streak of late-stage clinical failures continued in 2013: It withdrew two drugs from development—the antidepressant edivoxetine and the lymphoma treatment enzastaurin. And its cancer drug ramucirumab failed in late-stage clinical trials for breast cancer.

For the second year in a row, Merck & Co. and AstraZeneca scored zero for new drugs. In July, FDA asked Merck for more data for its sleep aid suvorexant, even though an advisory committee had recommended its approval in a low-dose form. AstraZeneca, meanwhile, can take consolation in the early-2014 approval of Farxiga, a diabetes treatment previously rejected by the agency.

PHARMACEUTICAL INDUSTRY watchers are also worried about the limited sales potential of products approved in recent years. The hype over the bountiful harvest of drugs in 2012 overshadowed the reality that the group lacked top-selling products needed to replace blockbuster drugs that lost patent protection starting in 2008.

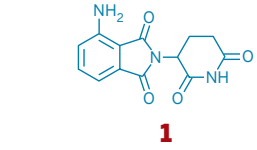
Market prospects improved in 2013. Of the 27 new products, at least seven are expected to enjoy peak sales in excess of $1 billion, according to the health care consultancy Datamonitor.

One new product stood out as having immediate sales potential. In Decem-

The good news for industry is that many of the new products have potential to become blockbusters.

DRUGS APPROVED BY FDA IN 2013 Down from 39 in 2012, many of the 27 new drugs in 2013 have blockbuster potential.

DRUG NAME	ACTIVE INGREDIENT	MARKETER	MODE OF ACTION	INDICATION
Nesina	Alogliptin	Takeda	DPP-4 inhibitor	Type 2 diabetes
Kynamro	Mipomersen sodium	Isis/Genzyme	ApoB-100 synthesis inhibitor ▮♦	Homozygous familial hypercholesterolemia
1 Pomalyst	Pomalidomide	Celgene	Thalidomide derivative; antiangiogenesis agent and immunomodulator ▮	Multiple myeloma
Kadcyla	Ado-trastuzumab emtansine	Genentech	Antibody-drug conjugate pairing a HER2 blocker with a tubulin inhibitor ♦	HER2-positive, metastatic breast cancer
Osphena	Ospemifene	Shionogi	Selective estrogen receptor modulator	Dyspareunia (pain during sexual intercourse)
Lymphoseek	Technetium-99m tilmanocept	Navidea Biopharmaceuticals	Radioactive diagnostic	Lymph node mapping
Dotarem	Gadoterate meglumine	Guerbet	Gadolinium-based contrast agent	MRI of the brain, spine, and associated tissue
2 Tecfidera	Dimethyl fumarate	Biogen Idec	Immunomodulator ♦	Multiple sclerosis
3 Invokana	Canagliflozin	Johnson&Johnson	Sodium-glucose co-transporter 2 (SGLT2) inhibitor ♦	Type 2 diabetes
Breo Ellipta	Fluticasone furoate and vilanterol inhalation powder	GlaxoSmithKline	Corticosteroid and a long-acting β_2-adrenergic agonist	COPD
Xofigo	Radium-223 dichloride	Bayer	α-Particle-emitting radioactive agent ♦	Metastatic castration-resistant prostate cancer
Tafinlar	Dabrafenib	GSK	BRAF inhibitor ▮	Melanoma expressing the BRAF V600E gene mutation
Mekinist	Trametinib	GSK	MEK inhibitor ▮♦	BRAF V600E or V600K gene-mutation-positive tumors
4 Gilotrif	Afatinib	Boehringer Ingelheim	EGFR, HER2, and HER3 inhibitor ▮	Non-small-cell lung cancer featuring EGFR mutations
5 Tivicay	Dolutegravir	ViiV (GSK/Pfizer)	Integrase strand transfer inhibitor	HIV-1 infection
6 Brintellix	Vortioxetine	Takeda/Lundbeck	Serotonin modulator and reuptake inhibitor	Major depressive disorder
Duavee	Conjugated estrogens/ bazedoxifene	Pfizer	Conjugated estrogen and an estrogen agonist/antagonist	Hot flashes associated with menopause
Adempas	Riociguat	Bayer	Soluble guanylate cyclase stimulator ▮♦	Pulmonary hypertension
Opsumit	Macitentan	Actelion Pharmaceuticals	Endothelin receptor blocker ▮	Pulmonary arterial hypertension
Vizamyl	Flutemetamol-18 injection	GE Healthcare	Radioactive diagnostic	Evaluation of Alzheimer's disease and dementia
Gazyva	Obinutuzumab	Genentech	Anti-CD20 antibody ●▮	Chronic lymphocytic leukemia
Aptiom	Eslicarbazepine acetate	Sunovion Pharmaceuticals	Voltage-gated sodium channel inhibitor	Epileptic seizures
7 Imbruvica	Ibrutinib	Pharmacyclics/ J&J	BTK inhibitor ●▮♦	Mantle cell lymphoma
Luzu	Luliconozole	Valeant	Imidazole antifungal	Fungal infections
Olysio	Simeprevir	J&J	Protease inhibitor	Hepatitis C virus
8 Sovaldi	Sofosbuvir	Gilead	Nucleotide analog polymerase inhibitor ●	Hepatitis C virus
Anoro Ellipta	Umeclidinium and vilanterol inhalation powder	GSK	Long-acting muscarinic antagonist plus a long-acting β_2-adrenergic agonist	COPD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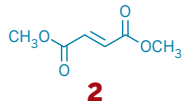
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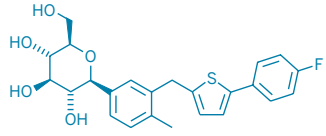
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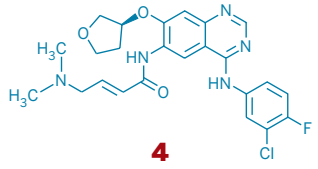
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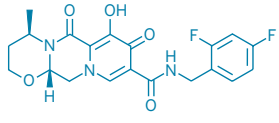
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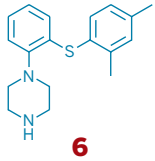
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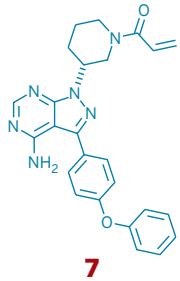
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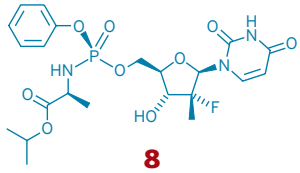
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NOTE: Drugs are listed in order of approval.
KEY: ▢ Small molecule ▢ Oligonucleotide ▢ Antibody-drug conjugate ▢ Antibody ● FDA breakthrough status ▮ Orphan drug ♦ Novel mode of action
SOURCE: FDA

NEW DRUG APPROVALS IN 2013 BY THE NUMBERS

Cost of one day of treatment with Gilead's HCV drug Sovaldi:
$1,000

Drugs added to GlaxoSmithKline's portfolio:
5

New molecular entities approved:
27

Approved in 2012:
39

Requests to FDA for breakthrough therapy designation as of Jan. 3, 2014[a]:
121

Cancer drugs approved:
8

Breakthrough therapies approved:
3

Orphan drugs approved:
9

Portion of new drugs that are small molecules:
85%

a Designation enacted on July 9, 2012. **SOURCES:** FDA, companies

ber, Gilead Sciences gained approval for Sovaldi, a nucleotide analog polymerase inhibitor that treats the hepatitis C virus (HCV). In 2011, Vertex Pharmaceuticals saw strong sales out of the gate when it launched Incivek, an HCV drug intended for use with the pill ribavirin and the injectable drug interferon. But Incivek revenues quickly receded in anticipation of Sovaldi, which will be part of the first all-oral HCV treatment regimen.

Sovaldi costs $1,000 per day, or $84,000 for a complete course of treatment for most HCV patients. Investment firm Cowen & Co. forecasts that sales of Sovaldi will top $3 billion this year, a trajectory that would make its launch the most successful ever for the drug industry.

Another new drug is well on its way to blockbuster status. According to the health care information firm IMS Health, Biogen Idec's oral multiple sclerosis drug Tecfidera has already overtaken the two currently marketed oral MS treatments, Novartis's Gilenya and Sanofi's Aubagio. Approved in late March, Tecfidera brought in roughly $800 million in 2013, analysts say, and should reap more than $2.5 billion this year.

Other potential blockbusters include GlaxoSmithKline's treatment for chronic obstructive pulmonary disease. Called Breo Ellipta, it's a once-daily combination of inhaled corticosteroid and a long-acting β_2 agonist. The prospects for Breo are bright because of Novartis's delays in the development of QMF149, an inhaled drug that has been plagued by problems with the delivery device.

And despite a slow start after its approval in February 2013, Genentech's Kadcyla, an antibody-drug conjugate for HER2-positive breast cancer, will cross $1 billion in sales by 2015, Datamonitor projects. Data are expected to emerge to support the drug's use in the early treatment of breast cancer.

The possibility of healthy sales for many drugs approved in 2013 is tempered by the outlook for the drugs expected to be approved this year. The influx of blockbusters is unlikely to continue, notes Colin White, lead analyst for oncology at Datamonitor.

Among new drugs that could be approved this year is Biogen's Plegridy, a longer-lasting version of the firm's MS treatment Avonex. Plegridy will likely quickly hit the $1 billion-per-year sales mark, Datamonitor says.

A recent addition to possible blockbuster approvals this year is Merck's MK-3475, an anti-PD-1 antibody for the treatment of melanoma. Industry watchers had assumed Bristol-Myers Squibb would be the first to market an anti-PD-1 antibody, but Merck surprised them earlier this month when it began the approval process for MK-3475. Stock analysts believe the immunotherapy could gain approval in the fourth quarter.

MK-3475'S SPEEDY PROGRESS is likely due to the breakthrough therapy designation, or BTD, it received from FDA. Introduced in July 2012 as part of the Food & Drug Administration Safety & Innovation Act, the status is bestowed on drug candidates that treat serious or life-threatening diseases and have the potential to offer meaningful benefits to patients.

When FDA rolled out BTD, it provided little detail about what the status meant beyond the promise that a drug candidate would be given "all hands on deck" treatment, meaning advice and close contact from the agency on everything from clinical trial design to manufacturing of the drug. Last year, the industry started to understand how the program might impact

NOT APPROVED Notable late-stage drug development setbacks in 2013

	DRUG CANDIDATE	INDICATION	STATUS
AstraZeneca	Fostamatinib	Rheumatoid arthritis	Rights returned to Rigel Pharmaceuticals
Biogen Idec	Dexpramipexole	Amyotrophic lateral sclerosis	Withdrawn from development
GlaxoSmithKline	Drisapersen	Duchenne muscular dystrophy	Rights returned to Prosensa
	Vercirnon	Crohn's disease	Rights returned to ChemoCentryx
Eli Lilly & Co.	Edivoxetine	Depression	Withdrawn from development
	Ramucirumab	Breast cancer	Under FDA review for gastric cancer
	Enzastaurin	B cell lymphoma	Withdrawn from development
Merck & Co.	Suvarexant	Sleep aid	FDA requests more data
Pfizer	Inotuzumab ozogamicin	Non-Hodgkin's lymphoma	Studies ongoing in acute lymphoblastic leukemia
Sanofi	Fedratinib	Bone marrow cancer	Withdrawn from development
	Iniparib	Lung cancer	Withdrawn from development
	Otamixaban	Blood thinner	Withdrawn from development
Takeda Pharmaceuticals	Fasiglifam	Diabetes	Withdrawn from development

SOURCE: Companies

a drug's development timeline and prospects for approval.

Analyzing BTD's first 18 months, stock analysts at the investment firm Leerink Swann believe it has high value for drug companies. "We suspect that the dynamics of FDA interactions could be quite different for an agent that the agency itself believes to be a breakthrough, and lack of BTD could be a disadvantage especially in areas such as oncology, where a large number of BTDs have been granted," the analysts say.

The three products approved thus far under the BTD program were considered to be slam dunks, so it's tough to tell whether the breakthrough stamp makes it easier for a drug to gain approval. But Leerink Swann concludes that the evidence so far suggests that BTD does lead to a shorter review time.

By Leerink Swann's count, the review times for two cancer drugs granted BTD status, Genentech's Gazyva and Johnson & Johnson's Imbruvica, were 164 days and 138 days, respectively. These are considerably shorter than FDA's six-month goal for high-priority drugs. Among the cancer drugs approved in 2013 outside the BTD program, only Bayer's Xofigo won FDA's green light in fewer than six months.

"We expect that BTDs will become an increasingly important tool and arena for companies to gain regulatory attention as well as for investors to gauge early FDA impression on a given compound," Leerink Swann notes.

MORE COMPANIES are seeking breakthrough status, but FDA is granting it to fewer applications, the Leerink Swann report notes. The decline appears to be due partly to limits in FDA's resources and partly to refinements in how the agency applies BTD.

In a presentation last month, John Jenkins, director of FDA's Office of New Drugs, said the agency has seen far more requests for BTD than expected. Although the first drug candidates to receive BTD were often in late-stage studies, the program was conceived as a means of expediting the development of early-stage molecules, Jenkins noted.

FDA is also improving the speed of its existing approval pathways. In 2012, the agency reported, it approved every New Drug Application with priority review status. This pathway requires the agency to decide within six months rather than the 10 months allotted under the standard review process. Meanwhile, only half of NDAs filed without priority review status were approved.

The statistics, which Jenkins touted, are helping restore confidence in the agency, industry watchers say. "The sentiment in the investor community toward the FDA is improving," says Bruce Booth, partner at the life sciences venture capital firm Atlas Venture. "There appears to be more outreach, more engagement, and more predictability than five years ago—and these are all things that give investors better 'line of sight' toward achievable regulatory milestones."

With smoother sailing on the regulatory front, pharmaceutical firms will have to start looking within for ways to increase the quantity and marketability of new drugs in coming years. After all, FDA can only approve drugs if industry invents them. ■