A BOUNTIFUL YEAR

NEW DRUG APPROVALS soared in 2012, with treatments for cancer and rare diseases leading the pack

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THE PHARMACEUTICAL industry might still be dusting itself off after its recent fall from the patent cliff—a difficult period of losing exclusive markets for big-selling drugs—but companies have a reason to stop and celebrate. Last year, the Food & Drug Administration approved 39 new products, a 16-year high.

In recent years, companies have faced withering criticism from shareholders and industry watchers about their research prowess as they struggle to replace the blockbuster drugs losing patent protection. The temptation now is to draw conclusions about what the flood of new drugs could mean about the health of the industry.

Although the data are impressive, it may be too soon to judge the R&D enterprise. But a clearer case can be made for what this bountiful crop means about the health of companies' relationship with FDA. After several lean years, 2012 marked the second year in a row of a substantial increase in the number of new drug approvals. Industry watchers see a willingness by FDA to be more efficient with its reviews and build better relationships with companies developing truly novel drugs.

More firms are "moving away from the disastrous low-risk culture that had depressed innovation and are being rewarded by drug approvals," says Bernard H. Munos, a former corporate strategist with Eli Lilly & Co. and founder of the InnoThink Center for Research in Biomedical Innovation. "Altogether, we are making progress. Better leadership across much of the industry is producing better drugs that more-innovation-friendly regulators help bring to patients sooner."

The crop of new drugs features several firsts: a breakthrough therapy for cystic fibrosis (Kalydeco), a treatment for drug-resistant tuberculosis (Sirturo), a drug made in carrot cells (Elelyso), and 18 products with novel mechanisms of action. The collection skews heavily toward oncology drugs and, in a reflection of the industry's recent interest in rare diseases, includes a number of treatments for so-called orphan diseases. But many of them come at a premium, carrying price tags that are raising red flags for governments, insurers, and patients.

In an encouraging sign for medicinal chemists, small molecules represent the lion's share of the year's graduating class, with 26 products—two-thirds of the overall collection—getting a green light. Despite the industry's enchantment with monoclonal antibodies, only two were approved in 2012: Genentech's Perjeta, for HER2-positive breast cancer, and GlaxoSmithKline's antibody against inhaled anthrax. Most of the biologic drugs to reach the market are peptides or enzyme replacements.

Of the 39 new products, 18 have a big pharma name attached, either through a discovery in its own labs or through a licensing deal. This compares with 19 of the 30 drugs approved in 2011.

LAST YEAR'S BOUNTY was not spread evenly. Notably, neither AstraZeneca nor Lilly brought a new treatment to market. Both companies are experiencing brutal losses to generics alongside significant setbacks to late-stage drug candidates.

Pfizer, on the other hand, has a stake in five of the drugs on the list. They are a broad range of products that the firm hopes will help recoup the billions of dollars in sales that almost instantly disappeared in late 2011 when the patent expired on Lipitor, its cholesterol-lowering drug.

Among Pfizer's new products are two potential blockbusters: the rheumatoid arthritis pill Xeljanz and the blood thinner Eliquis, which it comarkets with Bristol-Myers Squibb. Xeljanz is the first JAK3 inhibitor to cross the finish line in the arthritis arena, and analysts are encouraged that FDA is allowing the drug to be used in a wider population than expected. Pfizer hopes to improve its competitive edge with the price: At $25,000 per year, the drug costs slightly less than current biologic treatments for rheumatoid arthritis such as Enbrel and Humira.

Meanwhile, Eliquis, a Factor Xa inhibitor, enters a crowded field with two similar inhibitors already on the market and several

STICKER SHOCK

New drugs for cancer and rare diseases come with big price tags

DRUG	COST
Gattex[a]	$295,000/year
Kalydeco[a]	$294,000/year
Juxtapid[a]	$200,000–$300,000/year
Elelyso[a]	$150,000/year
Iclusig[a,b]	$115,000/year
Zaltrap[b]	$11,000/month
Cometriq[a,b]	$9,900/month
Kyprolis[b]	$9,550/month
Stivarga[a,b]	$9,350/month
Inlyta[b]	< $8,900/month
Bosulif[a,b]	$8,200/month
Erivedge[b]	$7,500/month
Xtandi[b]	$7,450/month

a Drug for orphan disease. **b** Cancer treatment.
SOURCE: Companies

NEW DRUG APPROVALS IN 2012 BY THE NUMBERS

The last year to see more NDAs: **1996**

Products with a novel mechanism of action: **18**

Drugs added to Pfizer's portfolio: **5**

Oncology therapies: **11**

New blood cancer drugs: **4**

Highest annual cost among all new drugs, Gattex: **$295,000**

New molecular entities approved: **39**

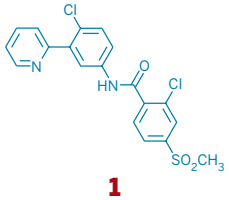
Monoclonal antibodies approved: **2**

SOURCES: FDA, companies

DRUGS APPROVED BY FDA IN 2012

Small molecules dominate the 39 drugs cleared for marketing last year

DRUG NAME	ACTIVE INGREDIENT	MARKETER	MODE OF ACTION	INDICATION
Voraxaze	Glucarpidase	BTG International	Carboxypeptidase that inactivates methotrexate	Methotrexate toxicity because of kidney failure
Picato	Ingenol mebutate	LEO Pharma	Natural product with unknown MOA	Actinic keratosis
Inlyta	Axitinib	Pfizer	VEGF1, VEGF2, and VEGF3 inhibitor	Advanced kidney cancer
1 Erivedge	Vismodegib	Genentech	SMO receptor antagonist ♦	Basal cell carcinoma
2 Kalydeco	Ivacaftor	Vertex Pharmaceuticals	CFTR potentiator ♦	Cystic fibrosis
Zioptan	Tafluprost	Merck & Co.	Prostaglandin analog	Open-angle glaucoma or ocular hypertension
Surfaxin	Lucinactant	Discovery Labs	Nonpyrogenic pulmonary surfactant	Prevention of respiratory distress syndrome
Omontys	Peginesatide	Affymax	Erythropoietin analog	Anemia related to chronic kidney disease
3 Amyvid	Florbetapir F 18	Avid Radiopharmaceuticals	Radioisotope	PET imaging for Alzheimer's disease
Stendra	Avanafil	Vivus	PDE5 inhibitor	Erectile dysfunction
Elelyso	Taliglucerase alfa	Pfizer, Protalix Biotherapeutics	Glucocerebrosidase enzyme replacement	Gaucher disease
Perjeta	Pertuzumab	Genentech	HER2 inhibitor	HER2-positive breast cancer
4 Belviq	Lorcaserin	Arena Pharmaceuticals	Serotonin 2C receptor agonist	Obesity
Myrbetriq	Mirabegron	Astellas Pharma	β_3 adrenergic receptor activator ♦	Overactive bladder
Prepopik	Sodium picosulfate, magnesium oxide, and citric acid	Ferring Pharmaceuticals	Colonic peristalsis stimulator	Colonoscopy preparation
5 Kyprolis	Carfilzomib	Onyx Pharmaceuticals	Proteasome inhibitor	Multiple myeloma
Tudorza Pressair	Aclidinium	Forest Laboratories	Muscarinic antagonist	Chronic obstructive pulmonary disease
Zaltrap	Ziv-aflibercept	Sanofi	VEGF-A, VEGF-B, and PlGF inhibitor ♦	Colorectal cancer
Stribild	Elvitegravir, cobicistat, emtricitabine, tenofovir	Gilead Sciences	Two nucleoside reverse transcriptase inhibitors, an integrase inhibitor, and a liver enzyme metabolism inhibitor	HIV



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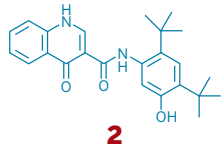

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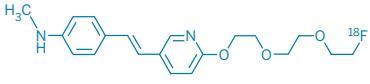

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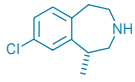

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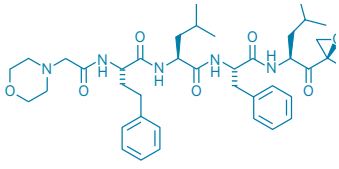

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more in late-stage studies. But Seamus Fernandez, a stock analyst who covers the drug industry for Leerink Swann, notes that Eliquis is effective and has a better safety profile than its competitors. He expects it could reach blockbuster status as quickly as 2014.

THE APPROVALS also marked an important milestone for eight biotech firms—Ariad Pharmaceuticals, Exelixis, Aegerion Pharmaceuticals, NPS Pharmaceuticals, ThromboGenics, Arena Pharmaceuticals, Vivus, and Affymax. Each firm scored its first-ever product approval, a critical achievement that for all was more than a decade in the making.

FDA approval, however, does not mean automatic success. Exelixis, for example, struggled for years to get its multikinase inhibitor Cometriq across the finish line. Over the course of the drug's development, Exelixis won, and then lost, two different big pharma partners. Furthermore, the company sparred with FDA over how to test the drug's efficacy in prostate cancer.

In the end, Exelixis' approval for Cometriq was for medullary thyroid cancer, which affects roughly 2,260 Americans each year. Although Cometriq is being studied as a treatment for other cancers with larger patient populations, including prostate cancer, data that could expand its therapeutic reach won't surface until 2014.

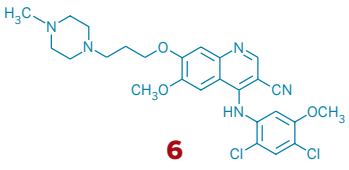
Cometriq is one of many oncology drugs on the list. Nearly a third of the new drugs approved are for cancer, and the set includes four new treatments for blood cancers. "There is lots of evidence that suggests innovation comes in waves. That's pretty much the way science works," InnoThink's Munos says. "It seems that such a wave is now carrying oncology, and many companies are trying to ride it."

In fact, the industry's pursuit of new cancer treatments is likely to continue for the foreseeable future. Some 29% of the compounds in the new-product pipeline—and 40% of the projects in Phase II studies—are for oncology, according to a recent report by Pharmaceutical Research & Manufacturers of America, the drug industry's main trade association.

Between cancer drugs and the handful of products for rare diseases, patients may be experiencing sticker shock. This year's list includes three products with a price tag of more than $200,000 per year, and many others hover around $100,000 per year.

But for some drugs, soaring prices could soon hit a ceiling. Three oncologists from Memorial Sloan-Kettering Cancer Center took a stand in October against the $11,000-per-month price tag on Sanofi's colorectal cancer drug Zaltrap. In a damning op-ed in the *New York Times* that outlined the precipitous climb in the cost of new cancer drugs, the doctors said they refused to give Zaltrap to their patients, noting that it works no better than an existing treatment.

Sanofi backed down, effectively halving the cost of the drug through discounts off the list price.



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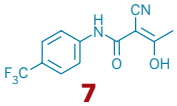

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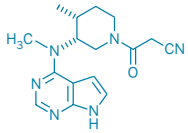

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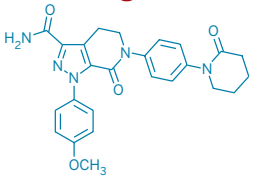

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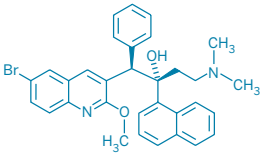

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DRUG NAME	ACTIVE INGREDIENT	MARKETER	MODE OF ACTION	INDICATION
Neutroval	Tbo-filgrastim	Sicor Biotech, Teva Pharmaceutical	Erythropoiesis stimulator	Neutropenia in chronic kidney disease
Linzess	Linaclotide	Ironwood Pharmaceuticals	Guanylate cyclase C agonist ♦	Chronic idiopathic constipation and irritable bowel syndrome
Xtandi	Enzalutamide	Astellas Pharma, Medivation	Androgen receptor inhibitor	Castration-resistant prostate cancer
6 Bosulif	Bosutinib	Pfizer	SRC and ABL inhibitor	Chronic myelogenous leukemia
7 Aubagio	Teriflunomide	Sanofi	Pyrimidine synthesis inhibitor	Multiple sclerosis
Choline C 11 Injection	Choline C 11	Mayo Clinic	Radioisotope	PET imaging agent to detect recurrent prostate cancer
Stivarga	Regorafenib	Bayer HealthCare Pharmaceuticals	Multikinase inhibitor ♦	Colorectal cancer
Jetrea	Ocriplasmin	ThromboGenics	Proteolysis ♦	Symptomatic vitreomacular adhesion
Fycompa	Perampanel	Eisai	AMPA receptor antagonist ♦	Epilepsy
Synribo	Omacetaxine mepesuccinate	Teva Pharmaceutical	Cephalotaxine ester that inhibits protein synthesis ♦	Chronic myelogenous leukemia
8 Xeljanz	Tofacitinib	Pfizer	JAK3 inhibitor ♦	Rheumatoid arthritis
Cometriq	Cabozantinib	Exelixis	cMet and VEGFR2 inhibitor ♦	Medullary thyroid cancer
Iclusig	Ponatinib	Ariad Pharmaceuticals	BCR-ABL inhibitor ♦	Chronic myeloid leukemia and Ph+ acute lymphoblastic leukemia
Raxibacumab	Raxibacumab	Human Genome Sciences, GlaxoSmithKline	Neutralizes toxins made by anthrax ♦	Inhalational anthrax
Signifor	Pasereotide	Novartis	Somatostatin analog ♦	Cushing's disease
Gattex	Teduglutide	NPS Pharmaceuticals	GLP-2 analog ♦	Short bowel syndrome
Juxtapid	Lomitapide	Aegerion Pharmaceuticals	MTP inhibitor ♦	Cholesterol lowering in patients with homozygous familial hypercholesterolemia
9 Eliquis	Apixaban	Pfizer, Bristol-Myers Squibb	Factor Xa inhibitor	Anticoagulant
10 Sirturo	Bedaquiline	Johnson & Johnson	Diarylquinolone that blocks tuberculosis ATP synthase ♦	Multi-drug-resistant tuberculosis
Fulyzaq	Crofelemer	Salix Pharmaceuticals	CFTR and CaCC inhibitor ♦	Diarrhea in patients with HIV/AIDS

NOTE: Drugs are listed in order of approval. **KEY:** Enzyme Small molecule Peptide Antibody Protein Botanical ♦ Novel mode of action
SOURCE: FDA

Given the sky-high prices of recently approved oncology drugs, industry watchers are worried that companies' investment in this area "may not be driven by scientific opportunities but by the fact that oncology is one of the few prescription areas that can carry the extreme prices some companies need to support their failing business model," Munos says. Yet, he doesn't think that strategy will succeed, since a flailing firm lacks the bold thinking and risk-taking culture needed to invent a breakthrough drug.

Pricing controversies aside, industry observers are cheering the burst of new products in 2012. Glen Giovannetti, Ernst & Young's global life sciences sector leader, cautions that using any 12-month period as a benchmark is shortsighted, but he says it is clear that "the decline has reversed itself, which I think is encouraging."

More important, industry's relationship with FDA appears to be improving. "A good dialogue is going on, with senior leadership understanding the industry's issues and making sure good drugs get to patients as soon as they can," Giovannetti says.

INDEED, THE 2012 numbers suggest FDA is trying to make good on its promise to get new drugs to patients faster. When the agency accepts a New Drug Application, it sets a deadline for review and decision making based on the terms of the Prescription Drug User Fee Act. For a normal application, FDA has 10 months to give a thumbs-up or -down; if the agency grants a "priority review" for the drug, that window narrows to six months.

For several years, notably 2008 and 2009, the agency, by its own admission, missed the normal review deadline many times. In its review of approvals for fiscal 2012, FDA noted that it now almost always makes a decision on time or even early. In fact, for some products, including the cystic fibrosis pill Kalydeco and the skin cancer drug Erivedge, approval came several months ahead of schedule.

In another signal of the agency's willingness to do better, 2012 brought the first two drugs to be granted "breakthrough" status, a designation meant to encourage medicines that can substantially improve the lives of people with deadly diseases. Vertex Pharmaceuticals took the honor of having the first two breakthrough drugs, for Kalydeco and VX-809, which is in Phase II trials. Both molecules address the underlying genetic defect of cystic fibrosis, a major advance given that existing drugs treat only the symptoms of the disease.

FDA has yet to clarify what that status entails, but the agency has broadly suggested it means more communication and collaboration with a drug's sponsor to smooth the clinical path and facilitate the review process.

Overall, the improved relationship with regulators and the high approval numbers have industry watchers cautiously optimistic for the coming years. "It's very encouraging," Giovannetti says, "but it's fragile." ■