THE YEAR IN NEW DRUGS

FDA's drug approvals in 2014 were remarkable for both their QUANTITY AND QUALITY

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FOR THE PHARMACEUTICAL industry, 2014 was one for the record books: sky-high merger and acquisition activity, unprecedented levels of financing, and, last but not least, a peak in new drug approvals. The Food & Drug Administration's green light for 41 new molecular entities—the biggest crop in nearly two decades—signaled a return to innovation for an industry that just five years ago seemed stagnant.

As important as the quantity of new products was their quality. In years past, a surge in drug approvals often meant a glut of me-too products and molecules that, after many regulatory setbacks, finally squeaked their way onto the market.

The 2014 class, in contrast, featured numerous examples of scientific breakthrough. An improved regulatory environment allowed some of them to reach patients at breakneck speed, albeit often at hefty price tags. And although the quantity of new drugs might not keep up in 2015, the hope is that the quality will persist.

"A large part of the industry has re-embraced breakthrough science, and it shows—both in the breakthrough approvals and the pipeline," says Bernard Munos, founder of the InnoThink Center for Research in Biomedical Innovation and a former R&D adviser to Eli Lilly & Co. "I am optimistic that the bolder companies will continue to deliver exciting innovation."

Among the 41 new molecular entities approved, 17 offer a novel way of treating a disease, in many cases through a new mechanism of action. Whereas small molecules dominated in 2013, accounting for all but three of the 27 drugs approved, a quarter of 2014's new products were antibodies, peptides, and enzymes.

Many of the large molecules were for cancer, an area where eight new drugs were approved. Meanwhile, the number of new rare disease treatments surged in 2014. Overall, 17 drugs approved last year carried "orphan" status, meaning they treat a disease that affects fewer than 200,000 people. Just nine drugs had the orphan stamp in 2013.

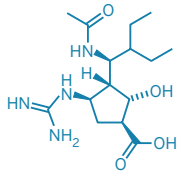
REGULATORY RUSH

The record-setting year for new drug approvals would not have been possible without speedier regulatory reviews. Thanks to new legislation, FDA has more tools at its disposal to expedite the review of New Drug Applications, and it is clearly committed to using them.

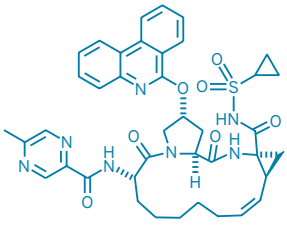
"The FDA pendulum moves back and forth," says Stephen Bloch, general partner at the venture capital firm Canaan Partners. Following a high-profile safety issue with an approved drug, FDA tends to swing

FRUITFUL YEAR FDA approved 41 new drugs in 2014, an 18-year high and up from 27 in 2013.

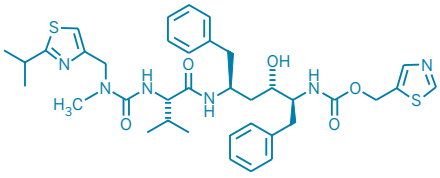
DRUG NAME	ACTIVE INGREDIENT	MARKETER	MODE OF ACTION	INDICATION
Opdivo	Nivolumab	Bristol-Myers Squibb	PD-1 inhibitor ▮	Melanoma
1 Rapivab	Peramivir	BioCryst Pharmaceuticals	Neuraminidase inhibitor	Influenza
Zerbaxa	Ceftolozane/ tazobactam	Cubist Pharmaceuticals	Cephalosporin/beta-lactamase inhibitor	Intra-abdominal and urinary tract infections
2 Viekira Pak	Ombitasvir, paritaprevir, and ritonavir tablets copackaged with dasabuvir tablets	AbbVie	NS5A, NS3/4A, NS5B polymerase inhibitor ♦	Hepatitis C virus
3 Lynparza	Olaparib	AstraZeneca	PARP inhibitor ♦	Ovarian cancer
Xtoro	Finafloxacin otic suspension	Alcon Laboratories	Topoisomerase and DNA gyrase inhibition	Swimmer's ear
Blincyto	Blinatumomab	Amgen	CD19 and CD3 targeted ▮●♦	A rare form of acute lymphoblastic leukemia
4 Esbriet	Pirfenidone	InterMune/Roche	Unknown ▮●♦	Idiopathic pulmonary fibrosis
Ofev	Nintedanib	Boehringer Ingelheim	VEGF, FGFR, and PDGFR inhibitor ▮●♦	Idiopathic pulmonary fibrosis
Lumason	Sulfur hexafluoride lipid microsphere	Bracco Diagnostics	Contrast imaging agent	Certain ultrasound patients
Akynzeo	Netupitant/ palonosetron	Eisai	NK_1 substance P receptor antagonist/5-HT_3 receptor antagonist	Nausea in chemotherapy patients
5 Harvoni	Ledipasvir/ sofosbuvir	Gilead Sciences	NS5A inhibitor/ polymerase inhibitor ●♦	Hepatitis C virus
Trulicity	Dulaglutide	Eli Lilly & Co.	GLP-1 receptor agonist	Type 2 diabetes
Movantik	Naloxegol	AstraZeneca	Peripherally selective opioid antagonist	Opioid-induced constipation
Keytruda	Pembrolizumab	Merck & Co.	PD-1 inhibitor ▮♦	Melanoma
Cerdelga	Eliglustat	Genzyme/Sanofi	Glucosylceramide synthase inhibitor	Type 1 Gaucher's disease
Plegridy	Peginterferon beta-1a	Biogen Idec	Unknown ▮♦	Relapsing multiple sclerosis
6 Belsomra	Suvorexant	Merck & Co.	Orexin receptor antagonist	Insomnia
8 Orbactiv	Oritavancin	The Medicines Co.	Cell membrane disrupter	Skin infections
Jardiance	Empagliflozin	Boehringer Ingelheim	SGLT2 inhibitor	Type 2 diabetes
Striverdi Respimat	Olodaterol	Boehringer Ingelheim	LABA agonist	Chronic obstructive pulmonary disease



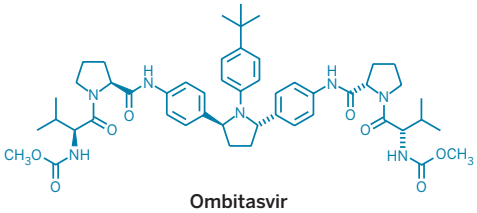
1 Rapivab (peramivir)



Paritaprevir

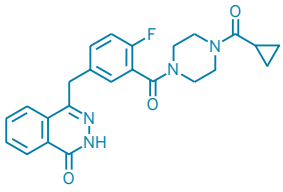


Ritonavir

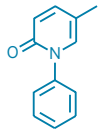


Ombitasvir

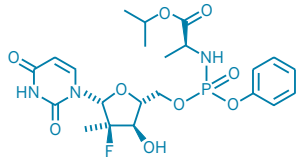
2 Viekira Pak



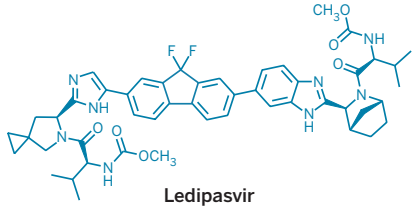
3 Lynparza (olaparib)



4 Esbriet (pirfenidone)



Sofosbuvir



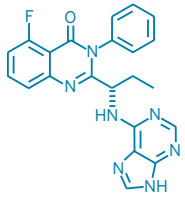
Ledipasvir

5 Harvoni

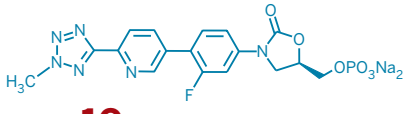
KEY: Small molecule | Bispecific anitbody | Peptide | Antibody | Glycopeptide | Phospholipid | Enzyme
Orphan drug | FDA breakthrough status | Novel mode of action

DRUG NAME	ACTIVE INGREDIENT	MARKETER	MODE OF ACTION	INDICATION
9 Zydelig	Idelalisib	Gilead Sciences	PI3K delta inhibitor	Three types of blood cancers
Kerydin	Tavaborole	Anacor Pharmaceuticals	tRNA synthetase inhibition	Toenail fungus
Beleodaq	Belinostat	Spectrum Pharmaceuticals	pan-HDAC inhibitor	Peripheral T-cell lymphoma
10 Sivextro (tablet)	Tedizolid	Cubist Pharmaceuticals	Bacterial protein synthesis inhibitor	Skin infections
Jublia	Efinaconazole	Valeant Pharmaceuticals	14α-Demethylase inhibitor	Toenail fungus
Dalvance	Dalbavancin	Durata Therapeutics	Cell wall synthesis inhibition	Skin infections
Entyvio	Vedolizumab	Takeda	Integrin receptor antagonist	Ulcerative colitis and Crohn's disease
11 Zontivity	Vorapaxar	Merck & Co.	PAR-1 antagonist ♦	To reduce the risk of heart attacks and stroke
12 Zykadia	Ceritinib	Novartis	ALK inhibitor ▮ ●	Late-stage non-small-cell lung cancer
Sylvant	Siltuximab	Johnson & Johnson	IL-6 inhibitor ▮ ♦	Multicentric Castleman's disease
Cyramza	Ramucirumab	Eli Lilly & Co.	VEGFR2 inhibitor ▮	Advanced stomach cancer
Tanzeum	Albiglutide	GlaxoSmithKline	GLP-1 receptor agonist	Type 2 diabetes
Otezla	Apremilast	Celgene	PDE4 inhibitor ♦	Psoriatic arthritis
Impavido	Miltefosine	Paladin Labs	Unknown ▮ ♦	Leishmaniasis
Neuraceq	Florbetaben F18 injection	Piramal Imaging	Radioactive diagnostic	PET imaging of the brain
Myalept	Metreleptin for injection	AstraZeneca	Leptin receptor activation ▮ ♦	Complications of leptin deficiency
13 Northera	Droxidopa	Chelsea Therapeutics	Prodrug of norepinephrine and epinephrine ▮ ♦	Neurogenic orthostatic hypotension
Vimizim	Elosulfase alfa	BioMarin Pharmaceutical	Enzyme replacement therapy ▮ ♦	Mucopolysaccharidosis type IVA
Hetlioz	Tasimelteon	Vanda Pharmaceuticals	Melatonin receptor agonist ▮	Sleep-wake disorder in the blind
7 Farxiga	Dapagliflozin	Bristol-Myers Squibb/ AstraZeneca	SGLT2 inhibitor	Type 2 diabetes

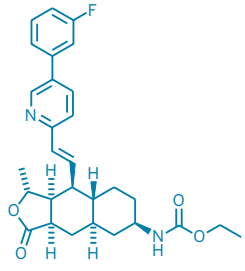
NOTE: Drugs are listed in order of most recent to least recent approvals.
SOURCE: FDA



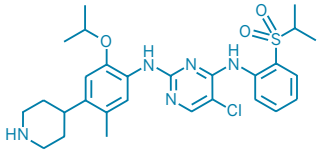
9 Zydelig (idelalisib)



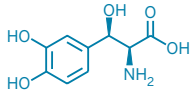
10 Sivextro (tedizolid)



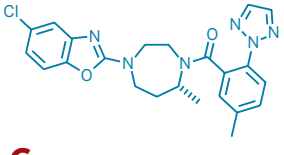
11 Zontivity (vorapaxar)



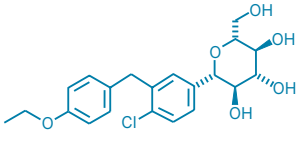
12 Zykadia (ceritinib)



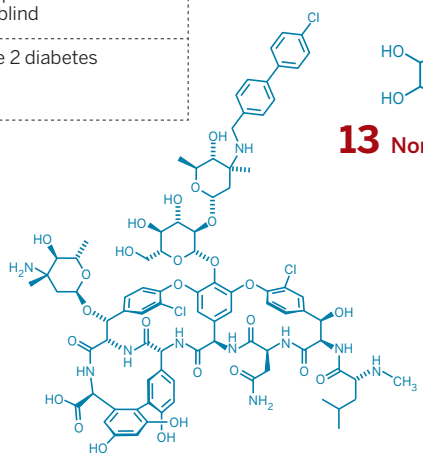
13 Northera (droxidopa)



6 Belsomra (suvorexant)



7 Farxiga (dapagliflozin)



8 Orbactiv (oritavancin)

to conservative decision-making, he observes, giving the example of the period after Merck & Co.'s pain medicine Vioxx was pulled from the market in 2004.

Now, Bloch says, consumers are "pushing FDA to be more focused on trying to get therapies to help people, and in certain areas like infectious diseases or rare diseases, there's a real effort by FDA to get things out there quickly."

Breakthrough therapy designation has played a major role in that effort. Introduced in 2012 as part of the FDA Safety & Innovation Act, the designation is granted to molecules that address serious diseases and have shown early signs of working better than existing therapies. FDA takes an "all hands on deck" approach to drugs with the breakthrough imprimatur, working closely with firms on the fastest route to proving efficacy.

Although three drugs approved in 2013 had breakthrough status, they were already far along in development when the program was in full swing. Last year was arguably the first time the industry got to see the effect of breakthrough status on speeding drugs to market.

NEW DRUG APPROVALS IN 2014 BY THE NUMBERS

Breakthrough therapies approved: 9

Antibiotics approved: 4

New molecular entities approved: 41

Cancer drugs approved: 8

Drugs with a novel mechanism of action: 17

One-year supply of BioMarin's Vimizim: $380,000

Compounds that were in-licensed or acquired: ~65%

Drugs that are for rare diseases: ~40%

SOURCES: FDA, companies

The result was impressive. "There is no question that the breakthrough therapy designation delivered nine approvals that would otherwise still be in the pipeline," Munos says.

Indeed, several drugs approved last year sped through development at a never-before-seen pace. Merck's cancer immunotherapy Keytruda, the first PD-1 inhibitor to reach the market, was approved to treat melanoma just three-and-a-half years after the first patient was dosed in a clinical study. Similarly, Novartis's lung cancer drug Zykadia went from its first clinical trials to approval in a little more than three years. Both drugs had breakthrough status.

Companies on the fast track are also taking a new approach to how drugs are developed. For example, Keytruda's Phase I clinical trial—the stage where researchers historically just tried to gauge the safety and proper dosage for a product using a small number of patients—had a whopping 1,300 patients with a wide variety of tumor types. Merck's goal was to capture signals of efficacy early and swiftly move into the next stage of development.

PRIMPING PORTFOLIOS

The approval of Keytruda helped end a dry spell for new drugs at Merck, which was one of several big pharma firms to finally push new products onto the market last year. In addition to Keytruda, Merck gained approval for the blood thinner Zontivity and the sleep aid Belsomra, and its just-completed acquisition of Cubist Pharmaceuticals gives it two of the four antibiotics approved in 2014.

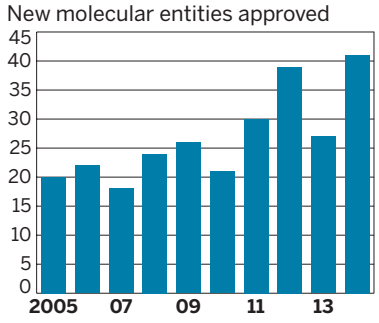
AstraZeneca and Lilly also ended their drug droughts. The need for a portfolio refresh was most acute at Lilly, which aside from an Alzheimer's disease diagnostic in 2012 had not managed an FDA win since 2009.

The Indianapolis-based drugmaker scored approval for a cancer treatment and two diabetes drugs, one of which came through a development pact forged in 2011 with Boehringer Ingelheim. And after three dry years, AstraZeneca had the most new drug approvals in 2014, racking up four new products.

However, AstraZeneca's productivity burst cannot be traced to its own research labs; all four of its new drugs came from acquisitions. And AstraZeneca is far from alone in looking outside its own walls for innovation.

A C&EN analysis found that roughly 65% of the new drugs approved were licensed from another firm or came into a company's

TRACK RECORD The 10-year new drug approval trend is choppy but generally up.



SOURCE: FDA

fold through an acquisition. For example, most of the cancer medicines originated at a biotech firm that was bought by a big pharma company, and all four of the new antibiotics passed through multiple owners before finally getting FDA's green light.

An outlier was Boehringer, which had its name attached to three new drugs borne from its own research. Lilly invented one of the drugs on its own roster as well as the antibiotic Orbactiv, which it out-licensed in 2001.

As they look outside for innovation, companies are showing a special interest in drug candidates in the late stages of development. In fact, four firms accounting for five of the 41 new drugs were acquired by bigger companies during the regulatory review phase or soon after FDA approval.

Lundbeck paid $658 million for Chelsea Therapeutics not long after the approval of Northera, Chelsea's treatment for a side effect of Parkinson's disease, and Actavis shelled out $675 million for Durata Therapeutics a few months after it got FDA's green light for the antibiotic Dalvance. Roche paid $8.3 billion for InterMune after the smaller firm filed a New Drug Application for the idiopathic pulmonary fibrosis drug Esbriet, and Merck's $8.4 billion bid for Cubist came just before the biotech won its second FDA nod of the year.

MORE BLOCKBUSTERS AHEAD

Regulatory filings to date suggest that this year could bring a similarly strong crop of drugs, again offering quantity and quality. Attention is shifting to the cardiovascular arena, where several drugs with the poten-

"The breakthrough therapy designation delivered nine approvals that would otherwise still be in the pipeline."

tial for multi-billion-dollar sales are expected to be approved this year. The most buzz is around a new class of powerful cholesterol-lowering treatments that block PCSK9, a protein that keeps the liver from removing "bad" LDL cholesterol.

Amgen was the first to file for approval of a PCSK9 inhibitor, with FDA setting Aug. 27 as a deadline for review. Sanofi and its development partner, Regeneron Pharmaceuticals, submitted an application late last year and expect their drug to be on the market in the second half of 2015. Consultancy Datamonitor expects both drugs to rack up $5 billion in annual sales by 2023.

Another highly anticipated cardiovascular therapy is Novartis's heart failure treatment LCZ696, which combines the active ingredient in the firm's heart drug Diovan with the novel neprilysin inhibitor sacubitril. The combo made headlines last fall when a Phase III study showed it reduced by 20% the number of cardiovascular deaths compared with the ACE inhibitor Vasotec. Novartis anticipates FDA approval in the second half of the year; Datamonitor forecasts the drug to reach $6 billion in annual sales by 2023.

Beyond cardiovascular treatments, industry watchers anticipate several other innovative drugs this year. Novartis has already gained approval for Cosentyx, a psoriasis treatment that stock analysts expect to reach blockbuster status by 2019. Cosentyx is the first antibody approved to block IL-17A, a cytokine implicated in inflammation. Lilly and Amgen are both working on their own IL-17A inhibitors.

Pfizer expects to win approval for palbociclib, a CDK 4/6 inhibitor for the treatment of breast cancer, in April. Leerink stock analyst Seamus Fernandez predicts that the drug will bring in $4 billion in annual sales by 2020.

And analysts expect Vertex Pharmaceuticals to win FDA's nod in the first half of the year for a pill that pairs its cystic fibrosis treatment Kalydeco with the novel molecule lumacaftor to aid roughly 30% of cystic fibrosis patients. On its own, Kalydeco, which Vertex pegged at about $460 million in sales last year, can treat just 5% of patients.

As the next wave of potential blockbusters approaches, battle lines are already being drawn over their cost. Last year's drugs included many with eye-popping price tags, and a particular furor has risen over the cost of new treatments for hepatitis C. This year more than ever, as companies hail the approval of each new drug—no matter how innovative—they will also need to prove it is worth paying for. ■