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Drug Makers Refill Parched Pipelines

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The pharmaceutical industry, after years of research flops that led some to write its obituary, shows signs it is coming back to life.

Credit a revamped research approach by the industry, which, after years of focusing on me-too drugs for ills that were already well treated, is pouring firepower into diseases that aren't.



Associated Press

FDA drug division head Janet Woodcock said, 'We're seeing a lot of innovation, much more than in recent memory.'

Companies have won marketing approval so far this year for 20 innovative medicines that work differently or better than existing drugs, or tackle ailments lacking good treatments, according to the Food and Drug Administration. "New molecular entities," the FDA calls them. There were just 21 such approvals all last year.

Recently approved are the first therapy shown to extend life for people with advanced melanoma, the deadly skin cancer; the first new treatment for lupus in over 50 years; and two drugs for hepatitis C that are far more effective than current care.

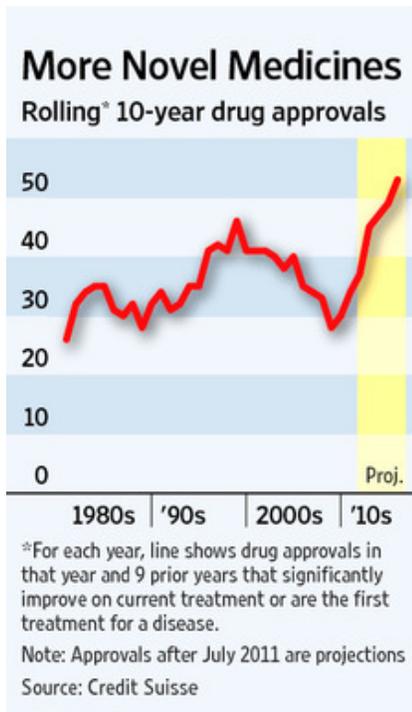
"We're seeing a lot of innovation, much more than in recent memory," said Janet Woodcock, director of the FDA's drug division, calling today's laboratory output a "turning point" in drug development.

She added: "If you're a patient with a terrible disease, a serious cancer or something like that, I think you ought to take heart from what we are seeing."

That would include Sharon Belvin, who was diagnosed at age 22 with melanoma that had spread, but who, in a 2005 clinical trial, received the melanoma drug that has just been approved. Ms. Belvin is now a 29-year-old mother of two with no sign of the disease.

"It is not just the risky, nimble biotechs that are developing these novel agents," said Ms. Belvin's doctor, Jedd Wolchok of Memorial Sloan-Kettering Cancer Center in New York. "It is the large pharma companies that are making substantial commitments to a field that was considered very speculative until recently."

Results can't come soon enough for these companies. They are losing patent protection on a host of big sellers, including the biggest of all, Pfizer Inc.'s cholesterol drug Lipitor, which goes off-patent in November. Companies are looking at a cumulative loss of more than \$100 billion in revenue through 2015, by some estimates, as these drugs face competition from low-priced generics.



The new medicines can't avert a tumble from this steep "patent cliff" but should cushion it. While they don't promise annual sales anywhere near Lipitor's \$11 billion, they belie a common supposition that the drug-industry pipeline is skimpy. More than 20 innovative drugs with the potential for annual sales of \$1 billion or more each have strong odds of winning FDA approval over the next three years, according to a Credit Suisse analyst, Catherine Arnold.

Some could stumble. In January, Merck & Co. scaled back studies of a highly anticipated heart drug after some patients it was being tested on suffered strokes. Merck says it is still pursuing the drug.

In addition, new drugs today arrive in a more cost-conscious marketplace. With generic drugs available for a growing list of conditions, from high blood pressure to high cholesterol, U.S. health plans and foreign governments' health systems are demanding evidence that new medicines are better before agreeing to pay for them.

Filling the Prescription

Novel drugs recently approved and in the pipeline

Drug	Target	Timing	Maker	Estimated peak yearly sales
Bimelysta	Lipids	2011*	GlaxoSmithKline, Human Genome Sciences	\$1.2 billion
Vemurafenib	Metastatic melanoma	2011*	Bristol-Myers Squibb	\$2.8
Vicrelin	Hepatitis C	2011*	Merck	\$1.7
Kareltis	Blood clots	2011*	Bayer, Johnson & Johnson	\$4.7
crizotinib	Lung cancer	2011*	Pfizer	\$2.0
vemurafenib	Metastatic melanoma	2011*	Roche, Daiichi Sankyo	\$1.0
tofacitinib	Rheumatoid arthritis	2012**	Pfizer	\$2.2
faricimab	Chronic kidney disease	2013**	Abbott, Roche	\$1.1
dakizipib	Cardiovascular risk	2014**	Roche	\$4.0
maritacrine	Hepatitis C	2014**	Roche, Pharmasset	\$1.7
anti-IL17 antibody	Rheumatoid arthritis, psoriasis	2015**	Eli Lilly	\$1.2
darapladib	Alzheimer's disease	2016**	GlaxoSmithKline	\$3.8

Note: Novel drugs are those that work differently from existing drugs or are aimed at poorly treated diseases. *Approved / Submitted to FDA for review **In final clinical trials / In early-stage trials. Source: Credit Suisse; the companies.

That is one reason for drug companies' increased focus on innovation. Gone are the days when they could make a few changes in a stomach-acid or depression drug that was facing patent expiration—tweaking it enough to get a new patent—and reap many more years of brand-name-drug sales.

But if they can offer the only effective treatment for a serious disease, it is all but certain health plans will cover the drug, even if the company sets a skyhigh price.

Because developing drugs takes many years, changes in how companies approach the process take a long time to show effects. Today's new-drug output appears to mark the beginnings of a payoff from a research reorientation the industry began undertaking several years ago, after a string of flops.

The low point came in 2006 with the failure of a heart drug Pfizer saw as a successor to Lipitor. A compound called torcetrapib raised so-called good cholesterol, and Pfizer championed it—right up to the moment that a board monitoring the testing learned it was increasing patients' risk of dying. Sixteen years of research and nearly \$800 million went down the drain.

By then, observers both inside and outside the industry were finding fault with what was sometimes described as companies' industrialized approach to drug discovery. They had built huge laboratories covering all aspects of drug development. Management tightly controlled research programs, reviewing projects for their commercial potential and requiring researchers to provide regular updates.

Scientists also had to keep their work secret, exploring new medicines without insight from outsiders. But companies can't keep a tight leash on their researchers if they expect to capitalize on the deepening understanding of how diseases happen, contends the chief executive of Sanofi SA, Christopher Viehbacher.

Cost was also an issue. Prescription-drug companies spent \$45.8 billion on research and development, or 17% of their revenue, in 2006, according to Bernstein Research. "The mass-production approach is not going to help you to be productive in a financially sound manner," says Mikael Dolsten, who heads Pfizer's research and development. Some investors and consultants began to question why the industry was investing in drug research at all, rather than just identifying promising work by small firms hatched from university labs, and then teaming up with them.

The new melanoma drug emerged from a more collaborative approach.

Bristol-Myers Squibb Co. capped its research budget a few years ago to "create a culture" that encouraged collaboration with outsiders, says R&D chief Elliott Sigal, both to save money and to capture new scientific approaches.

Among these approaches was enlisting the body's immune system to fight cancer, instead of just assaulting it with toxic medicines as in chemotherapy.

Hopes of spurring immune-system attacks on cancer had frustrated researchers. But in the 1990s, a scientist then at the University of California, Berkeley, made a discovery: A certain molecule was serving as a kind of traffic cop, telling the immune system's attack cells when they should launch an assault and when they should hold off.

The scientist, James Allison, couldn't interest big pharmaceutical companies in exploring this. At that time, they saw themselves as competing against academic scientists.

Only small biotechs were interested. Eventually, Dr. Allison joined with one called Medarex Inc. in Princeton, N.J., to see if they could release the molecular brakes on the immune system and let it attack a tumor.

Their work caught the attention of Bristol-Myers. In 2004, Bristol-Myers formed a partnership with Medarex. The big company agreed to pay the little one \$50 million up front and as much as \$205 million if certain regulatory goals were met.

Expensive as that sounds, it was a relative bargain in the world of drug development, where a pharmaceutical company can spend up to \$1 billion developing a drug in-house from start to finish.

And not having the Medarex labs and researchers on its books meant Bristol-Myers could walk away if the approach didn't appear to be working.

But it did. When Ms. Belvin's melanoma was first diagnosed in mid-2004, tumors that had spread to the young woman's lungs "lit up like a Christmas tree" on a CT scan, she recalls today. Dr. Wolchok prescribed several months of chemo, to limited effect. Then two courses of another existing drug, interleukin-2, made the tumors in her lungs worse, and made her skin peel off. "It was hell on earth," she says.

In September 2005, Dr. Wolchok enrolled Ms. Belvin in a trial started by Bristol-Myers and its biotech partner to test the immune-system approach to fighting cancer. Though she might have gotten a placebo, it turned out she did receive the chemical compound the companies were testing, called ipilimumab.

Within four months, scans showed her tumors melting away. After several more months, there was no sign of them.

"It's because the doctors and the people who worked on it had the foresight to think out of the box," Ms. Belvin says.

The benefit to many others in the trial was far less, just a median four-month increase in survival. This March, that proved enough to win FDA approval of the drug for Bristol-Myers, which by that time had purchased full control of Medarex, for \$2.1 billion.

Bristol-Myers now counts on such collaborations to gain access to "a bigger universe of innovation, and also balance

the tremendous failure rates you see in the industry," says its Dr. Sigal. The pharmaceutical industry as a whole has spent more than \$130 billion acquiring small biotechs since 2006.

Bristol-Myers named the melanoma drug Yervoy and plans to charge \$120,000 for a course of treatment. Steep as that is, insurers are expected to cover the drug, given the lack of alternatives. Analysts predict annual sales will eventually top \$1.2 billion.

It could soon get some company. Already under review at the FDA is another melanoma drug—based on yet another new therapeutic approach. This one comes from units of Roche Holding AG and Japan's Daiichi Sankyo Co.

Says Pfizer's Mr. Dolsten: "We're coming back to a period where companies are starting to grow and have a reasonable flow in their pipelines again."

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