



# What's behind the whopping price tags on the newest generation of drugs

The story behind the production of Enbrel, Amgen's popular rheumatoid- arthritis drug, provides insights as to why bioengineered drugs are so expensive.

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**BOTHELL** — They are the sturdy, docile workhorses of the biotech revolution: Chinese hamster ovary cells, microscopic living factories that churn out proteins that eventually become drugs such as Enbrel, Amgen's blockbuster treatment for rheumatoid arthritis. These cells start their journey in small flasks, swirling in a nutrient broth that looks like orange Kool-Aid. For weeks, the genetically modified "CHO" cells will be gently encouraged to reproduce — and they do, doubling in number every day. The delicate newborn cells will be pampered with just the right food, just the right temperature and just the right amount of oxygen, and protected from invading microorganisms. CHO cells that produce Enbrel spent years at Amgen's Bothell plant, where scientists learned how to keep them healthy and reproducing. Now, their cellular offspring are hard at work in a two-story, 20,000-liter stainless-steel tank in Rhode Island, cranking out a protein that will be sold as Enbrel, treatment for a disease that is twisting and crippling the joints of 2.1 million Americans.

**The long journey — complicated, delicate and hard to re-create — is one reason why Enbrel, and other new-generation bioengineered drugs, are so expensive.** Enbrel costs about \$1,500 a month. Since the drug was approved for use in 1998, other new-generation, bioengineered drugs for rheumatoid arthritis, multiple sclerosis, cancer and other diseases have come to market, all made possible by the same breakthroughs in molecular biology. For many patients, these specialty drugs have proved near-miraculous. **Most insured patients still pay only a fraction of their cost. But an increasing number, often those with chronic, long-term diseases, are finding they must pay more — 20 to 50 percent of the cost, in some cases.**

The story of Enbrel, one of the first big biotech drugs, provides a look at forces that may transform the pharmaceutical industry — and health insurance, as well.

## The history

Rheumatoid arthritis is a nasty disease. Unchecked, the inflammation, destructive changes to joints and dissolution of bone it causes — along with the pain — can lead to

disability, lost work time and the need for orthopedic interventions. In the mid-1980s, injections of gold salts and methotrexate pills, along with anti-inflammatory medicines such as aspirin, ibuprofen and steroids, were all doctors had to offer. For most patients, gold wasn't very helpful, and not much was known about its long-term use. Methotrexate, initially approved for cancer, got better results, but there could be "significant liver toxicities" and other side effects, noted Dr. Philip Mease, a Seattle rheumatologist. And neither completely stopped the underlying disease from progressively damaging joints. "I can't even believe what we thought was pretty good at the time," Mease said. The goal then, he said, was simply to "take the edge off" the pain and destructive changes.

The "quiet revolution in the field of molecular biology and molecular immunology" changed all that, said Mease, director of rheumatology research for Swedish Medical Center. Scientists gained a much better understanding of the basic mechanisms underlying arthritis — why immune cells start attacking the body they are intended to protect. Enbrel, developed by Immunex in Bothell, was approved in 1998. Amgen, based in Thousand Oaks, Calif., bought Immunex four years later. Production of Enbrel takes place at labs in Bothell, Interbay and Rhode Island. Early on, Mease was surprised by Enbrel's effect in patients with rheumatoid arthritis and psoriatic arthritis.

"We were able to dramatically help patients," he said. Best of all, X-rays of joints showed that in many cases, the drug was significantly inhibiting — or even stopping — the disease's progressive damage. "People were saying, 'You've given me back my life.' 'I can get back to work.' It was quite impressive."

### **"A tough situation"**

In Greenwich, R.I., Amgen has invested more than \$1.5 billion in a campus that includes Enbrel's "mammalian protein" manufacturing facility, one of the largest in the world. There, the protein spit out by CHO cells in the huge tank undergoes a final series of purifications and filtrations, delicate processes conducted under scrupulously sterile conditions. All along the way, tests confirm quality and purity — or the batch is scrapped. If all goes well, what's left from that huge tank — a fraction of its original volume — will be sold as Enbrel. **The payoff for Amgen has been enormous. Last year, Amgen's Enbrel sales in North America totaled \$3.2 billion.**

Over the past decade, other biotech drugs have come along, working slightly differently but using similar principles. Because they suppress the immune system, though, these drugs all have safety issues; in some people, they can cause infection to occur or another autoimmune disease to "pop out," Mease said. Even so, for many of his patients, they work very well — controlling symptoms and the disease's progressive joint destruction. Today, Mease estimates, up to 50 percent of rheumatoid-arthritis patients in medically sophisticated Seattle use one of the new-generation biotech injectable drugs, including Enbrel, Humira, Remicade, Orencia and Rituxan.

**For some patients, though, price has been a barrier.** "We have people where we literally can't find a way for an insurance company or a government source to help them,"

Mease says. "That is a tough situation. We try to do the best we can with older drugs to make do, and they live with them. That's the way it's done." Mease, who was involved in early research on Enbrel — and who is still involved in research and consultation for companies developing new drugs, including Amgen — says such drugs are costly to develop.

From a patient's point of view, **\$18,000 a year, no matter how justified, can make the drug unaffordable.** For patients who have health insurance, Enbrel, a self-injectable, is typically covered under a commercial plan's pharmacy benefit or a Medicare prescription-drug plan. Most **Medicare plans now require patients to pay from 25 to 33 percent coinsurance for specialty drugs or those costing at least \$600 a month**, according to the Kaiser Family Foundation, a nonprofit that works on health-care issues. And an increasing number of private plans are following suit, requiring percentage coinsurance instead of flat co-pays.

### **Cut costs? Can't be done**

At this point, **each bioengineered drug is unique, with no less-expensive generic version, often called a "biosimilar."** Generics for traditional pills have pushed costs down because they don't have to undergo the long development and trials required for approval of the original drug. But bioengineered drugs, unlike pills, **don't have a chemical "recipe" that can be easily re-created**, notes Amgen's Stephen Hill, executive director of clinical manufacturing. Like Enbrel, they're developed and manufactured through complex processes that begin with genetically modified cells from mammals, such as the CHO cells, yeasts or bacteria. Up to now, the **Food and Drug Administration hasn't allowed biosimilars of these drugs.**

Hill says a company trying to produce a biosimilar version of Enbrel would have to re-create the entire development process. Just one tiny change to the molecule, Hill said, could change its potency or safety. Dr. Jim Thomas, vice president of Amgen's process and product development, said scientists have been working for 17 years to improve the production of Enbrel. But when Amgen tried to make it in a more cost-effective way, the end product was slightly different, and Amgen scrapped the project. "It wasn't Enbrel," he said.

Any attempt to re-create it by another company must be rigorously tested, he said. "If you can't make it identical, then you don't know what the safety of that molecule is without doing clinical studies," Thomas said. And that would increase the price. Mease believes **costs may drop as scientists find cheaper ways to produce new drugs. But they could grow again if they learn how to genetically tailor drugs for each patient**, which he predicts will happen.

**"You can't suppress the smartness of some of these molecular biologists," Mease said. Innovation, he knows, is bringing new pressures from politicians, employers and insurers. "Everybody is sensitive about this cost issue."**

