Billion-Dollar Orphans: Prescription for Trouble

The Orphan Drug Act is coming under fire from a motley coalition of drug companies, Congress, and AIDS advocates

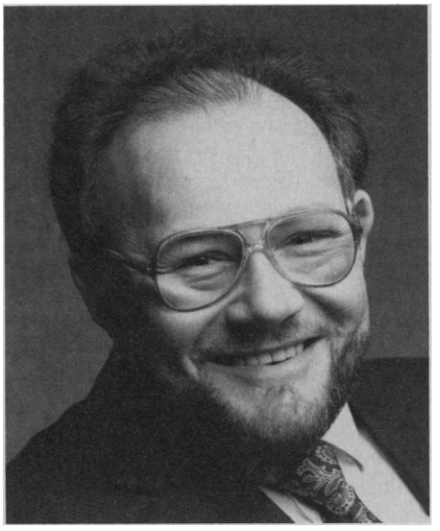
IN SOME SENSE Laura Boren owes her life to the Orphan Drug Act. That act, passed by Congress in 1983, led to the development of PEG-ADA, a drug to treat severe combined immunodeficiency disease (SCID), from which 7-year-old Laura suffers. Without that act, no drug company would have invested unknown millions of dollars to develop a pharmaceutical for a market of less than 40 children worldwide. But because the act permitted the government to offer tax breaks and the exclusive right to sell the drug for 7 years, a small New Jersey biotech firm called Enzon Inc. spent 5 years and $2.5 million to develop PEG-ADA. In April, the Food and Drug Administration approved Enzon's drug. As a result, Laura and 13 other children who suffer from SCID were able to end years of almost complete isolation, which had been the only way to handle their disease because they did not respond well to bone marrow transplants; indeed, few children with SCID have lived beyond the age of two.

PEG-ADA isn't the only success story under the Orphan Drug Act. Under its provisions, 333 new drugs have been developed for rare disorders that afflict no more than 200,000 people. Forty-five have received FDA approval, including three for use in treating AIDS patients: AZT, erythropoietin, and aerosol pentamidine. This is a remarkable increase over the 1970s, a decade when only 40 drugs were developed for uncommon diseases. "This has been an exceptionally successful act," says Marlene Haffner, director of the office of Orphan Products Development at the FDA. "It is hard to find something this perfect."

It's clear the act has been a success, but a vocal group of critics say it's far from perfect. An unlikely coalition of AIDS activists, biotechnology firms, and politicians are seeking changes in the act as it comes up for reauthorization this spring, because they think a handful of companies are using loopholes in the statute to make millions of dollars at their expense. "A handful of companies scam this statute," Congressman Ron Wyden (D–OR) charged at a congressional hearing earlier this year.

He was among politicians who complained after they were told taxpayers would pay $100 million for just one orphan drug this year—erythropoietin (EPO). The federal government picks up the tab for kidney dialysis patients who can't afford to pay $8000 a year to treat their anemia with EPO, while the drug's manufacturer—Amgen Inc.—made at least $100 million on the product last year.

AIDS patients think they would get better, cheaper drugs if more than one firm were allowed to market pharmaceuticals for complications of their disease—considered a "rare disorder" because until recently fewer than 200,000 people had the full-blown syndrome (although far more than that are already infected with HIV).



Success story. *Abraham Abuchowski of Enzo, which makes PEG-ADA under the Orphan Drug Act.*

For completely different reasons, some biotech companies don't like the act because they aren't profiting from it. They say the 7-year exclusivity clause is too much of a good thing, because, in a few cases, firms are using it to edge out competition for drugs they would have developed anyway, without the act. Two leading biotech firms feel so strongly about being allowed to compete for those markets that they recently pulled out of their trade organization, which supports the act.

What has the critics steamed up is that three orphan drugs in particular have made their developers hundreds of millions of dollars. Two versions of human growth hormone (hGH), for example, share a market of more than $150 million per year, split by Genentech, Inc., and Eli Lilly & Co. The market for Amgen's EPO is worth more than $100 million a year. Aerosol pentamidine, made by Lyphomed, Inc., has yearly sales estimated at $60 million.

Add up those revenues over 7 years of exclusivity, and it isn't hard to figure that some of these orphans are billion-dollar babies. With revenues like that, politicians and competing biotech companies argue that no special incentives are needed to entice companies to adopt the drugs and invest in their future. "Clearly a billion-dollar drug is no orphan," says Thomas Wiggins, president of Serono Laboratories, a biotech firm in Norwell, Massachusetts, that would like a piece of the market for hGH. "Is it in the public interest to provide a monopoly and tax benefits for billion-dollar drugs?"

Wiggins and officials of other biotech companies that would like to share the wealth argue that both they and consumers would benefit if more than one firm could market an orphan drug. They have the support of AIDS activists who would like to see one company in particular—Lyphomed—share the market for aerosol pentamidine, which is used to treat pneumonia caused by *Pneumocystis carinii*. One of Lyphomed's competitors, Fisons Corp., has tested an injectable form of the drug that AIDS patients could use at home, instead of having to visit a clinic to have Lyphomed's product sprayed into their lungs.

Yet the Orphan Drug Act bans Fisons from the market. Even though the company invested millions of dollars in developing its product and testing it in clinical trials, Fisons lost out to Lyphomed, which won Orphan Drug status first. AIDS activists think that's wrong. "We are not out to gut this act, but I think it's a perversion of its original intent when the act prohibits something that would be an advantage to consumers," says Jean McGuire, executive director of the AIDS Action Council.

Furthermore, although each company does give away some free drugs to those who cannot pay, for those who can pay, certain orphan drugs are extremely expensive: Genentech and Eli Lilly each patient charge between $10,000 and $30,000 a year for hGH and Enzon charges $60,000 a year for PEG-ADA. AIDS patients pay $1,300 a year for aerosol pentamidine and $8,000 a year for EPO. "Who gets hurt by this? We all get hurt," claims McGuire. "In the case of AIDS, the government is becoming more and more the primary payer of services, so ultimately, it's the taxpayers who get hurt."

The companies defend the high prices, saying it takes them years to recoup what they spent on research and development—particularly where the costs are spread out among a small number of patients. And it's the rare orphan drug that makes its manufacturer a profit or is targeted at a disease that afflicts more than 50,000 patients. Enzon president Abraham Abuchowski says he'll never recover his investment in PEG-ADA.

Some say it never was the intent of the Orphan Drug Act to offer exclusive markets to drugs that would prove tremendously profitable and be developed anyway. "You're talking about companies making hundreds of millions of dollars a year," says Robert Fildes, president of Cetus Corp., which sells several less profitable orphan drugs. "No matter which way you cut it, they're making a very handsome profit, and they're deliberately abusing the legislation to keep out fair competition." Such drugs, he says, should no longer be designated orphans.

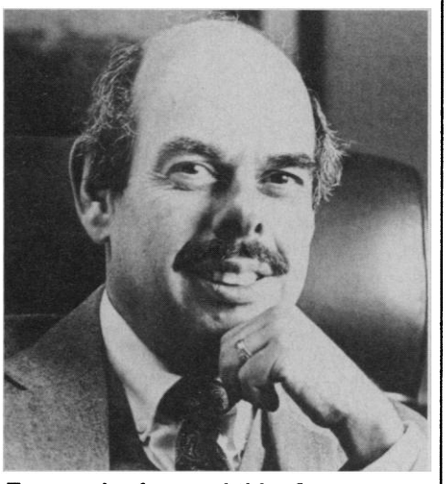
The winners call this sour grapes. "Much of the debate is driven by people who have finished second or third in the research, and now they're trying to do through lobbyists what they weren't able to accomplish in the research lab," according to David Beier, vice president of government affairs for Genentech.

These problems have now begun to engage the attention of some members of Congress, including Congressman Henry Waxman (D–CA) who introduced a bill on 26 April to alter key provisions of the act. His "fine-tuning" changes the 7-year exclusivity clause to allow more than one company to market an orphan drug, if the second company can prove that it really was neck and neck with the first in research, development, and testing.

Waxman's bill also revokes a drug's status as an orphan if the number of patients exceeds 200,000—a decision likely to affect drugs for AIDS, where the caseload will probably pass that threshold this year. The purpose of the legislation is to retain the incentives for most orphan drugs, but to provide more competition in the case of "extremely profitable" drugs—especially those that might have been developed without the incentives of the act.

But even with those safeguards, the proposed changes worry Abbey Meyers, executive director of the National Organization for Rare Disorders. She says she still has to beg sponsors to adopt orphan drugs for many rare diseases, particularly genetic disorders. Although five companies want to market the tremendously profitable hGH, she must struggle to find sponsors for narcolepsy and multiple sclerosis drugs, even though those disorders affect almost 200,000 patients each.

"I can't emphasize strongly enough that we are absolutely opposed to any form of shared exclusivity because it would cut the heart out of the Orphan Drug Act," says Meyers. "We are unwilling to sacrifice the fate of 20 million Americans with orphan diseases because AIDS patients want less expensive drugs."



Too much of a good thing? *Henry Waxman (D–CA) thinks some drug companies profit too much under the Orphan Drug Act.*

David Barr, however, says the cost of drugs can be an issue of life and death to AIDS patients who can't afford them. He pays $4000 a year for AZT, which is just one of three drugs he's taking. "I think there's a middle ground between providing incentives to a company to do research and getting fair pricing for a drug," says Barr, a staff attorney with LAMBDA Legal Defense and Education Fund in New York.

Some AIDS activists, including McGuire, suggest that drugs used for treating AIDS be removed from orphan drug status. But that won't bring down prices for drugs that are used in healing other illnesses. And indeed, there's no guarantee that competition will actually drive down the price of any particular orphan drug: when Eli Lilly started to compete with Genentech, the price for hGH didn't go down.

There's little to gain and much to lose, in fact, by tampering with the act, says the Industrial Biotechnology Association, most of whose 107 member companies support the act. The act's incentives are critical for the development of most orphan drugs, says Lisa Raines of the IBA, which opposes Waxman's change to the exclusivity provision. Not only have they stimulated the development of new drugs, but they've also prompted companies to take a new look at old ones whose original patents have expired, such as AZT. "Our view at the IBA is that the orphan drug law has been successful, and that it's an important incentive to developing products that aren't eligible for patents," Rains said. "We're worried that tinkering with the exclusivity provisions will probably result in a reduction of the number of new products being developed."

But the debate has evoked sufficient heat that two of the IBA's members—Cetus Corp. and Genetics Institute of Cambridge, Massachusetts—resigned in March because the trade group opposed changes. "It's been a contentious issue for some time," says Rains. "What has brought it to a head is, in some cases, particular companies are feeling the pressure of not having their product approved."

This debate comes at a time when the biotech companies already are worried about losing their market monopoly to competitors in a more subtle way. Amgen has gone to court to prevent its competitor, Genetics Institute, from trying to convince the FDA that they've made a "new" orphan drug by making minor structural changes to the molecules by adding sugar groups to a protein chain—a process known as glycosylation that may change the form but not the function of a glycoprotein, according to Amgen. In February 21 university researchers sent a petition to the FDA, urging it to form a panel to provide advice on new standards for determining whether two drugs are the same.

The combined effect of Waxman's proposed regulations and the glycosylation problem could be enough to dissuade some companies from developing orphan drugs—particularly firms that have yet to market a profitable product and are still operating in the red as they work on research and development for a drug. For Abuchowski at Enzon, the task of developing PEG-ADA would have been far more daunting without the incentives of the Orphan Drug Act, which gave him seed money and research grants to keep the project going. "Why develop a drug for a dozen patients," he asks. "That's doesn't make economic sense. There are lots of other diseases."

The debate is likely to continue as Congress considers Waxman's changes. And judging from the high stakes, there will be no miracle cure that makes both sides happy. Says the FDA's Haffner: "It may be time to fine tune the act, but my main concern is how to change it without destroying it. I don't have a magic wand to do that. Many good heads have thought about this, but no one's woken up in the middle of the night with a Eureka." ■ **ANN GIBBONS**