Genentech Sues FDA On Growth Hormone

Company fights FDA approval of second-generation Eli Lilly product; Congress may alter Orphan Drug Act

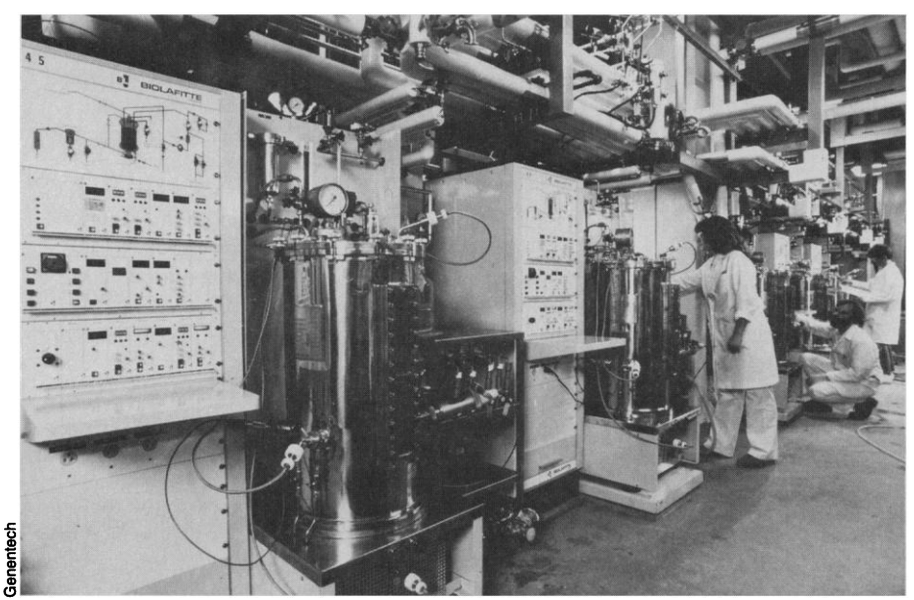
In the spring of 1985 children suffering from growth hormone deficiency faced a crisis. The Food and Drug Administration (FDA) cut off distribution of human growth hormone derived from the pituitary glands of cadavers. The action was spurred by the possibility that the extracted growth hormone was contaminated with a virus that causes Creutzfeldt-Jakob disease, a rare brain infection (*Science*, 7 June 1985, p. 1176). Genetically engineered growth hormone was being developed by three or four companies, but it was uncertain then when this purer drug would become available.

A resolution of the medical crisis came in October of the same year when FDA approved the marketing of Protropin, a recombinant DNA growth hormone developed by Genentech, the largest and most prominent of the so-called "biotechnology" companies. For the affected children, FDA's action was a godsend, and the decision gave Genentech its first big money-maker. Sales totaled approximately $41 million in 1986 and analysts estimated that revenues from the drug would reach $60 million in 1987.

But he who giveth can taketh away—and in a sense FDA has done just that. On Sunday, 8 March, FDA Commissioner Frank E. Young approved Eli Lilly, Inc.'s Humatrope, a human growth hormone product with 191 amino acid residues. Humatrope may be superior to Protropin, which has one extra amino acid—a methionyl, that produces antibody responses in approximately 30% of the drug's users. Genentech officials say that this antibody reaction has been reduced to about 8% of users following changes in the manufacturing process, but the company's literature does not yet reflect this.

Researchers have expressed surprise at the high occurrence of antibody responses to Protropin. Clinical studies,* however, have shown no apparent side effects from the drug and growth rates in children were similar to those in patients receiving pituitary-derived natural growth hormone. Gilbert P. August of the Children's Hospital of Washington, D.C., says it is not clear that Humatrope is superior to Protropin from a clinical standpoint.

*"Clinical studies with recombinant-DNA-derived methionyl human growth hormone in growth hormone deficient children," *The Lancet*, 29 March 1986, p. 697.



Genentech

Protropin production. *Technicians at Genentech monitor the performance of a series of fermenters used for production of its human growth hormone, Protropin.*

Still, when Lilly's product hits the market in the next few weeks, the literature accompanying its drug is expected to state that approximately 2% of users will develop an antibody reaction. Because the long-term effects of these raised antibody levels are not yet understood, patients may choose to switch to the Lilly drug. "Which product would you give to your kid?" is a question physicians are sure to be asked by parents, says Kathleen Behrens, an analyst with Robertson, Coleman, and Stevens of San Francisco.

FDA's approval of Humatrope could deal Genentech a double blow. Not only will some patients shift away from Protropin but Genentech could be blocked from marketing a 191–amino acid hormone of its own. Serono Laboratories, Inc., of Randolph, Massachusetts, which has a similar drug under development, could also be affected. The problem lies in the Orphan Drug Act. Protropin was approved as an orphan drug, which in theory should give it 7 years without competition. But FDA approved the Lilly drug on the grounds that it is a different product because it contains one fewer amino acids than Protropin. However, Humatrope was also given orphan drug status, which could keep other 191–amino acid hormones off the market for 7 years.

Genentech has filed a lawsuit against FDA claiming that its constitutional property rights have been violated and that the agency has not complied with the Administrative Procedures Act. The company says it should have had time to respond to the Lilly decision before it became final. An issue that underlies the litigation is whether a tiny change in the chemical structure of Genentech's drug results in the formation of a "new drug," one that is substantially different from a drug already marketed—in this case Genentech's Protropin. Lilly's Humatrope should not be sold during Protropin's exclusive 7-year marketing period, Genentech officials argue, because the clinical differences in the performance of a 191– versus a 192–amino acid growth hormone are insignificant.

On 6 March, however, John M. Taylor, associate commissioner for regulatory affairs, ruled that "by themselves, chemical differences between natural sequence hGH [human growth hormone] and methionyl-containing hGH mean that the two drugs are 'different' within the meaning of the Orphan Drug Act. Combined with . . . the decreased antigenicity of natural sequence hGH, this means that there are no sound public policy grounds supporting" Genentech's position.

Genentech's chances for prevailing in court may become evident on 26 March when the U.S. District Court for the Dis-

trict of Columbia hears oral arguments on the company's request for a preliminary injunction against FDA and Lilly. The court already has rejected the company's request for a temporary restraining order. One telling indicator of Genentech's legal standing may be a 27 February letter from Robert A. Swanson, the company's chief executive officer, to FDA's Young. Swanson offered to waive any right to exclusivity if other manufacturers with human growth hormone applications before the agency would waive their rights, too. This would have assured Genentech a market for its improved version of Protropin.

Equally uncertain is how Sorono will fare. Its 191–amino acid growth hormone, Saizen, is derived from a recombinant mammalian cell technique, instead of the *Escherichia coli* bacterial processes that Genentech and Lilly rely on. Bruce F. Mackler, counsel to Sorono, argues that differences in the manufacturing process make it a distinct new product that should not be excluded from the market regardless of the outcome of *Genentech* v. *FDA*.

No matter how the court rules, Congress is likely to take up Genentech's complaints about FDA lacking a clear, predictable process for classifying drugs under the Orphan Drug Act. After more than 4 years, FDA has yet to even publish a proposed rule for implementing the act. "We are concerned that FDA has not published regulations," says Henry Waxman (D–CA), chairman of the House Commerce Committee's subcommittee on health and environment. FDA officials say the Office of Management and Budget is partly to blame for the delay.

When Congress enacted the law in 1983 it sought to encourage companies to produce medicines for rare diseases where patent protection was lacking, production costs were high and demand limited, or where profits were slim. FDA officials say the loosely written legislation has attracted a lot of interest because drugs designated as orphans can obtain tax credits during the research phase, and because of the exclusive marketing provision for products that win FDA approval.

Aides to Waxman say that Congress did not anticipate that there would be several companies racing to develop virtually the same drugs. It provided FDA with no direction on how to differentiate between products such as Protropin and Humatrope. But with the Orphan Drug Act slated for reauthorization in 1988, members of Congress such as Waxman and Senator Orrin G. Hatch (R–UT) are expected to try to reform the act, especially as it applies to situations where competition exists. ■

MARK CRAWFORD

The Vatican Weighs In

The recent Vatican "instruction" condemning in vitro fertilization and other artificial reproductive technologies is unlikely to have any significant impact on research or clinical practice, at least in the United States. Rather, it explicitly codifies what the Catholic church has said all along: that the only right way to have a baby is through normal sexual intercourse within the context of marriage.

In a wide-ranging manifesto, the church spells out its opposition to artificial insemination, surrogate motherhood, prenatal diagnosis for other than therapeutic ends, research on embryos, genetic manipulation to determine infant characteristics, and futuristic techniques such as human cloning.

Catholic hospitals would seem to be the most likely parties affected by the Vatican pronouncement, although many already have a policy of discouraging surrogate mothers as patients. Father Kevin O'Rourke of the St. Louis University Center for Medical Ethics says Catholic hospitals already abide by church doctrine. The Catholic Health Association says it does not know how many of its 623 hospital members may have fertility programs that impinge on the doctrine and is now sending copies of the instruction out with requests for responses.

With regard to basic research, the papal document might be construed as having a bearing on gene therapy. But genetics researcher French Anderson of the National Heart, Lung, and Blood Institute points out that the Vatican has taken care to separate the issue of therapeutic intervention from fertility manipulation and that it has already taken a stand in support of research on gene therapy.

The document is only the latest in a series of proclamations issued in recent years by governments and professional and religious groups. LeRoy Walters, director of the Center for Bioethics at Georgetown University, says he has been able to locate 50 such statements—the most recent being a September 1986 statement from the American Fertility Society—issued from Western nations and Japan over the past 8 years. The vast majority approves of the new technologies with appropriate safeguards. Some, such as the Japanese Society of Obstetricians and Gynecologists, endorse in vitro fertilization only within the marriage context. Most of the statements, such as the 1984 report from Britain's Warnock Committee, favor permitting research on embryos up to 14 days old. West Germany's Benda commission, which reported in 1985, favored a 2- to 3-day cutoff point.

Among the most extensive reports, the greatest reservations are expressed with regard to surrogate motherhood, which is, as Walters points out, "an old technology with a new social arrangement." Seven of the nine biggest reports oppose commercial surrogate motherhood; the American Fertility Society believes it should be treated as a clinical experiment supervised by an ethics committee.

Most of the reports have been pretty much in line with the results of the few public opinion polls relating to fertility technology. Walters says seven U.S. polls have revealed that 60 to 74% of the public support in vitro fertilization in the context of marriage. Among Catholics, a 1978 Gallup poll found 56% favored the procedure. The figure was somewhat higher in a 1982 Australian poll. The support seems to be less in non-English-speaking countries, with 50% of West Germans supporting in vitro fertilization in 1978 and 18% of Japanese in a 1982 poll (in which 47% of the respondents said "babies should be given by heaven"). People are considerably more negative about surrogate motherhood, with fewer than one-third endorsing such arrangements in several polls.

It is not clear to what extent the latest document, 2 years in preparation, relied on advice from the scientific community. The Vatican supports a Pontifical Academy of Sciences, but this body is not used as a routine source of advice. Molecular biologist Beatrice Mintz of the Fox Chase Cancer Center in Philadelphia, who became a member of the pontifical academy last fall, says that to her knowledge the academy was not consulted as a body and she does not know of any individual members who have been consulted.

The United States now has no central body to provide guidance on these questions. The President's commission on bioethics was dissolved in March 1983. The National Institutes of Health is prohibited by law from doing any research on embryos in absence of a review by a nonexistent ethics advisory board. ■

CONSTANCE HOLDEN