

# Celebrating a Milestone: FDA's Approval of First Genetically-Engineered Product

*This article originally appeared in the "History Corner" column of the September-October 2007 issue of Update magazine, the bimonthly publication of the Food and Drug Law Institute.*

***Suzanne White Junod, Ph.D.***  
***FDA Historian***

This year marks the twenty-fifth anniversary of FDA's approval of the world's first recombinant DNA drug product—human insulin (Eli Lilly & Co.'s Humulin). In 1921, Frederick Banting and Charles Best extracted the hormone insulin, which controls blood sugar levels, from the pancreas' of dogs, and in 1922 administered the extract to a 14-year-old boy suffering from type I diabetes mellitus, saving his life and proving insulin's efficacy in treating human diabetes. Following their discovery, virtually all insulin for human use was harvested from slaughterhouse animals, usually porcine or bovine.

In the 25 years since FDA's approval of Humulin, however, r-DNA human insulin has proven indistinguishable from pancreatic human insulin, has been proven both safe and efficacious for millions of patients, and, as a result, has almost completely displaced animal source insulins. FDA regulatory scientists worked with Lilly scientists in solving novel challenges related to the production of human insulin in bacteria and played a key role in insuring the safety and efficacy of the first medical product of gene-splicing technology approved for use in humans.

Recombinant DNA methodology was just one of many remarkable scientific advances made possible as a result of James Watson and Francis Crick's original discovery of the double helix structure of human DNA, announced in 1953.<sup>1</sup> Precise knowledge of genetic structures has moved many scientific fields forward, including criminology and, more recently, pharmacogenetics and toxicogenetics, which are at the heart of discussions anticipating a new era of "personalized medicine."

## **The Birth of Biotechnology**

For Watson and Crick, however, the gene was a concept. Today, the entire human genome sequence has been mapped and individual genes can be manipulated as chemical entities and pieces of DNA.<sup>2</sup> In 1973, California biochemists created the first recombinant DNA organism, forming the scientific basis for modern biotechnology. In 1980, the U.S. Supreme Court ruled in *Diamond v. Chakrabarty* that genetically engineered microorganisms can be patented.<sup>3</sup> Also in 1980, Congress enacted the Bayh-Dole Act allowing universities and government laboratories such as those within NIH to hold patents on federally funded research.<sup>4</sup> This court decision and congressional legislation in the same year created incentives for both industrial and academic institutions to capitalize on the newfound ability of scientists to create new types of DNA molecules in a test tube by rearranging their genetic information.

Scientists working in this burgeoning field in its early years, however, clearly recall the serious nature of early concerns about the use of this new technology to manipulate the very essence of human life. "We have essentially forgotten the anxieties that accompanied these advances especially with respect to the recombinant DNA methodology," wrote James Watson in 1976.<sup>5</sup> There were fears that these manufactured "mutant" genes carried with them uncontrollable capacities to harm human beings. Scientists themselves began to address these fears. In April 1974, molecular biologists imposed a moratorium on continued r-DNA work until an international meeting could be held to discuss whether such experimentation did, in fact, pose any plausible public health danger. According to Watson, "because those of us who signed the moratorium proposal were respected scientists, not known for environmental or political kookism, we were taken seriously."<sup>6</sup> At the meeting held at the Asilomar Conference Center in California in 1975, 150 scientists gathered and ultimately recommended that the National Institutes of Health provide guidelines for recombinant DNA research. Although some scientists, including Watson, felt as if the conference recommendations were ultimately too restrictive, from a broader perspective they served the important purpose of putting to rest many larger societal fears concerning the responsible uses of recombinant DNA methodologies.<sup>7</sup>

Regulatory officials addressed these same societal and medical fears by insisting on a conservative regulatory approval process for the first r-DNA produced medical proteins. Even though the amino acid sequence of Humulin occurs naturally in humans, FDA reviewers chose to consider it, for purposes of approval, as a new molecular entity (NME). Humulin, therefore, was approved under a full NDA by the Division of Metabolic and Endocrine Drugs in the Center for Drug Evaluation and Research (CDER). The agency's formal position with respect to the need for a full NDA for DNA produced products was not published until June 26, 1986 (51 FR 50878), but by that time, most in the Division felt that eventually FDA might relax its full NDA requirement in favor of an abbreviated NDA after it became more clear that the products produced through DNA technology did not confer special risks.<sup>8</sup> The most active reviewers were Dr. Sol Sobel, the Division Director, Yuan-Yuan Chiu, Division Chemist, and John Gueriguian, Division Medical Director. Only CDER was involved in the Humulin approval because hormones such as growth hormone and insulin are treated as drugs under the Food, Drug, and Cosmetic Act while other biologics, fall under the Public Health Service Act, and are regulated by the Center for Biologics Evaluation and Research.<sup>9</sup>

Lilly submitted NDA 18-790 for Biosynthetic Human Insulin (BHI) on May 14, 1982. The company scientists took great precautions with their first r-DNA product, and FDA and Lilly scientists collaborated on many pioneering ideas to ensure the safety and efficacy of human insulin produced by bacterial cells.<sup>10</sup> At the Asilomar conference in 1975, for example, scientists had agreed that a specific bacteria (e-coli strain K12) used in recombinant DNA experiments should be especially tailored genetically so that even if they did escape into the outside world, they would have no chance to colonize the human digestive tract. Eli Lilly's host bacteria used to create r-DNA human insulin was so "fastidious in its nutritional requirements" that they could not have survived outside the laboratory.

Many production issues involving the fermentation process and possible contamination issues were successfully addressed by scientists and regulators working together in Lilly production facilities. A major issue which confronted both FDA and Lilly scientists was the elimination of

various contaminants that might be introduced during the fermentation procedures which could possibly include proteins derived from the host bacterial cells. Other potential contaminants included host DNA and phages which might be extraneously introduced into the fermentation vats. Stringent production methodologies were devised and implemented to eliminate host protein and DNA contaminants, while a monitoring system was employed to detect phage contamination and interrupt contaminated fermentations.

### **Safety Precautions Used**

Very sensitive methodologies were developed and used to detect any potential contaminating materials that could have escaped the rigorous purification procedures. As an added safety precaution and to ensure that even if a bacteria containing recombinant DNA did escape into the environment that it would not result in colonic colonization of animals (including humans) and create unbridled insulin production, two separate fermentation procedures producing the A and B chains of insulin were utilized. The separate peptide chains were then combined to yield the final BHI product.

Some lingering concerns about possible immune reactions in patients given the genetically engineered insulin were also laid to rest during the clinical trials with r-DNA human insulin. Researchers were able to document that although diabetic control diminished slightly during the first month of BHI (r-DNA) therapy, it returned to "Very Good" or "Good" during the two succeeding months. After production problems were solved and the final product was carefully characterized and underwent pre-clinical studies, it was introduced first into normal volunteer subjects and then diabetic patients.<sup>11</sup> The results were very good. In a double blind study in which 121 of 243 patients were transferred from either purified pork (PPI) or mixed beef-pork (ISP) insulin to BHI therapy (following one month of baseline observation), three months later the BHI patients' daily insulin dosage "remained at baseline levels with no evidence of a shift in total daily dosage."

FDA's approval letter went out on October 28, 1982, for recombinant human insulin (HUMULIN-R). FDA Endocrine Division Director Dr. Sol Sobel signed the letter. He was not unaware of the historical significance of this letter. "Except for my marriage license," he recalls, "that was the most important document I ever signed." Humulin as well as subsequent designer insulins, he notes, have had a great impact on the care of diabetics and there have been an accelerating curve of r-DNA approvals since the first one he signed for Humulin. The field accelerated rapidly with subsequent approvals of crucial products including the r-DNA form of an enzyme to treat Gaucher's disease, thyroid stimulating hormone (TSH) for diagnostic use in thyroid cancer, and many products for the production of monoclonal antibodies for the treatment of cancer. Other outgrowths of recombinant DNA technology currently in clinical trials include gene therapy with engineered plasmids, custom-made viral vectors, siRNA therapy, genetically altered cells, controlled differentiation of embryonic stem cells, and cell profiling.

Despite early reservations about the technology, r-DNA derived proteins actually have an enhanced safety profile as illustrated by FDA's experience with children suffering from growth hormone deficiency. Three years after the introduction of Humulin, there were critical concerns about the safety of human growth hormone. At that time, human growth hormone was derived

only from the pituitary glands of human cadavers. In early 1985, FDA received in close succession three reports of a fatal neurological disease in young people receiving human growth hormone to treat their growth retardation. This disease known by its eponym Creutzfeldt-Jacob (C-J) syndrome is caused by a sub-viral particle called a prion which also causes mad-cow disease. It is extremely rare occurring as a cause of death in only one in a million individuals and almost never diagnosed in children.

FDA responded by mandating the withdrawal of the cadaver derived growth hormone from the U.S. market in May 1985 while simultaneously stepping up its approval of the recombinant form of human growth hormone which did not carry the risk of C-J disease. FDA's quick action clearly prevented many more cases of C-J. France, for example, continued to use the cadaveric growth hormone for a longer period and reported 74 cases of CJ in contrast with 33 from the U.S. and 35 from Britain.

In its Millennial issue, Time magazine cited FDA's approval of r-DNA insulin as one of the 100 milestones in medicine of the 20th century, and it was the only FDA achievement listed in their "top 100." This achievement, however, came about only through close cooperation and collaboration with scientists and production engineers at Lilly, which, in turn, established a foundation for the practical utilization of recombinant DNA technology to produce human insulin and many subsequent r-DNA therapeutic advances. And, "at the present time," concludes FDA's Sobel, "I can't imagine producing a new therapeutic protein by any other means."

---

## Endnotes

1. Nature, April 25, 1953, Letter to the Editor. Watson and Crick also drew upon crucial evidence provided by researcher Rosaline Franklin, who died before receiving the Nobel Prize awarded to others sharing in the discovery of the helical structure of DNA.

2. The first draft of the human genome genetic blueprint was published Feb. 11, 2000.

3. Diamond v. Chakrabarty, 447 U.S. 303 (1980)

4. Bayh-Dole Act, Pub. L. 96-517, 94 Stat. 3019 (1980)

5. James D. Watson, "In Defense of DNA," 1976 Annual Report, Cold Spring Harbor Laboratory, reprinted by Center for Study of Drug Development, Department of Pharmacology and Toxicology, University of Rochester Medical Center, Rochester, NY, 1978.

6. Id., p. 3.

7. Watson commented on Asilomar: "I, for one, saw no way to decide whether work on Drosophila DNA, or yeast DNA or mouse DNA should be more or less restricted, if at all, and so found the Asilomar experience an exercise in the theater of the absurd. Particularly misguided was the placing of work with human DNA in the highest potential risk category, thereby restricting it to biological-warfare like facilities and insuring that almost no one in pure research could work with it. (p. 10)" Watson felt that the fears of creating monster microbes, in particular, were overblown. "To be sure," he quipped, "you can argue that such novel killers would be just the thing for CIA or

Mafia types, but I failed to see why they could not continue to pursue Castro with our ordinary pre-existing bacterial pathogens. (p. 7-8)."

8. According to Dr. Sol Sobel, Division of Metabolic and Endocrine Drugs, this idea of the structure of the end product being the prime consideration rather than the process by which it was produced is currently at the center of the debate concerning biogenerics or "follow-on" biologics. FDA considers the key issue to be accurate characterization of the final product rather than differences in production methodology.

9. Proposed legislation called the "Access to Life-Saving Drugs Act," would permit the generic pathway for biological drugs under the PHS Act including those produced by recombinant DNA technology. Biotech companies have taken the position that the only "biologicals" that have a legal pathway for generic replication are hormones; the other biological drugs, at present, have no generic pathway

10. Early recombinant DNA technology used bacterial cells that have no nuclei (prokaryocytes) but rather direct cellular activities by DNA-containing plasmids in the bacterial cytoplasm (plasmids – ring like structures in the cytoplasm of bacterial cells and containing chromosomal material composed of strands of DNA. Such plasmids substitute for the functions of the nucleus of cells found in higher species).

11. Clinical Trials – 43881, p.2 Humulin NDA Section 3.B.5. IND Protocol 6