

## Hoechst production of recombinant human insulin finally begins after 14-year battle

After a 14-year struggle, and 16 years after recombinant insulin first appeared in the United States, Hoechst Marion Roussel (Frankfurt, Germany) finally started to produce recombinant human insulin in March 1998. Ironically, Jürgen Rüttgers, Germany's Minister of Science, assured attendees at the opening ceremony on March 16 that "there is no biotechnology location in Europe that offers better conditions for research, development, and production than Germany." The inauguration of the world's most modern human insulin plant was, he said, a seal of approval for Germany's status as a place to do [biotechnology] business."

Following the launch of insulin by Eli Lilly in 1982, Hoechst applied to German local authorities for permission to produce recombinant insulin in 1984. "If everything had run smoothly, we could have hit the German market with our insulin in 1989," says Hoechst technical manager Rainer Dickhardt. As it was, Hoechst had to stand by and watch not only Lilly's product flourish in the United States, but also the then-separate Danish companies Novo and Nordisk launch their products in Europe in 1987 and 1989, respectively. Hoechst met with considerable resistance from the German public, which, fearing the escape of genetically modified organisms into the environment, argued that there was no existing German law suitable to regulate gene technology.

The delay was slow and painful. Hoechst's insulin production facility comprises three plants—one for each step of the process—each of which required permission to be built and run. If objections are made, the process is suspended until an official decision is reached. In June 1985, permission was granted to build the first plant ("Fermtec"), which contains the fermenters in which bacteria are grown. Following April 1986 application, permission to build the second plant ("Chemtec"), in which bacteria are lysed, was granted in October 1987. However, permission for this and the Fermtec plant was suspended the following month after local groups objected to both plants. "There was no sufficient law governing the use of gene technology," says Thomas Schlimme, a member of the Hoechst

Schnüffler und Maagucker resistance group, the law for emissions that was applied was not suitable. If a chemical gets into the environment, it has a certain half-

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life. However, if an organism gets into the environment it can multiply. Hoechst requested an immediate continuation, which was granted in July 1988. After appealing the decision at a higher court, local groups succeeded in stopping Hoechst again. Fortunately for Hoechst, objections to the third plant ("Insultec"), in which insulin is purified, were rejected by the local and higher courts.

In 1990, Germany's gene technology law, Gesetz zur Regulierung der Gentechnik (Gentechnikgesetz GenTG)—strict guidelines covering the use and release of genetically modified organisms—came into force, following European directives 90/219 and 90/220. However, Schlimme explains that Hoechst wanted to change its procedure to remove a heat-treatment step that was unnecessary, according to the new gene technology law. The change resulted in a protocol different than that for which permission was originally granted, causing further delay until it got the go-ahead from local authorities (Regierungspräsidenten Darmstadt und Giessen) in 1994. In addition, during the years of struggle, Hoechst made several improvements to its production method: As well as a strain of *Escherichia coli* that folds insulin correctly, the company developed an enzymatic cleavage of the initial fusion protein using trypsin instead of chemical treatments. Permission for the new method was granted by local authorities in October 1996.

"I would estimate that [the whole strug-

gle] cost us more than 100 million DM [\$54.9 million]," says Dickhardt. In the late 1980s and early 1990s, while other German companies moved recombinant-protein production to different countries, insiders joked that Hoechst owned the world's most expensive biotechnology museum. (Bayer, for example, moved its factor VIII production to the United States, citing a better climate for biotechnology.) "Companies that want to be innovative also have to be pioneers," points out Dickhardt. "In this way we also achieved a goal for German biotechnology." However, he recognizes that Hoechst underestimated the emotional nature of the public's fears, and regrets that an open dialog with the public was too late coming.

Hoechst has a final hurdle to jump. In September 1997, the company applied to the European Medicines Evaluation Agency (EMA; London) for permission to market insulin. EMA permission is expected in the second half of this year.

*Ellen Peerenboom*



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*Ellen Peerenboom is a freelance writer working in Munich, Germany.*