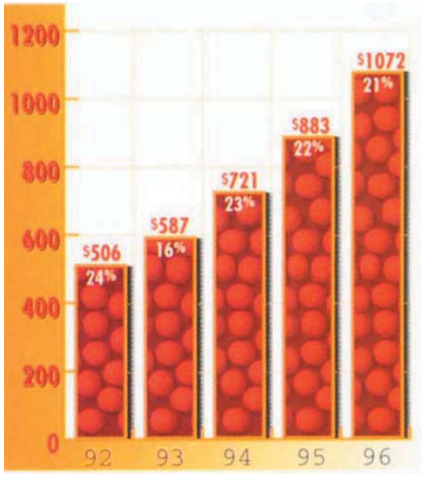
Amgen's NESP heats up competition in lucrative erythropoietin market

Amgen's (Thousand Oaks, CA) next generation "erythropoietin" is currently in phase III trials in Europe and the US. If it comes through successfully, it could allow the company not only to maintain its current supremacy in markets for blood cell growth stimulants, but also significantly extend them. The company hopes to make substantial in-roads in Europe. It expects that its new compound falls outside its agreement with Johnson and Johnson (J&J; New Brunswick, NJ), potentially providing it with exclusive access to markets outside the US. However, the intricacies of patent law in Europe may yet serve to thwart it, in Germany at least.

The product in question is known as novel erythropoiesis-stimulating protein (NESP), a preparation of one or several high-activity isoforms of erythropoietin (EPO). Amgen's European patent (EP 0 428 267 B1) demonstrates, by fractionating native EPO preparations, that the number of sialic acid residues on the molecule profoundly effects its in vivo activity measured in several assay formats; molecules with 11–14 sialic acids, for instance, exhibit activities 3–4 times those of molecules with 8–9 sialic acids.

NESP has moved rapidly through clinical trials—less than 12 months for all phases. Barbara Hoffman, an analyst with Vector Securities (Deerfield, IL) says this is because the endpoints of the trial—an increase in the blood cell count—are "very straightforward and do not take a long time to demonstrate." Phase III trials began only in August and the results will be announced at the American Society of Nephrology meeting in San Antonio, Texas, in November of this year. Unofficial sources suggest that, in early trials, NESP's serum half-life and its effective biological activity are three time greater than those of EPO.



Sales in millions ($) of Amgen's EPO over the past five years.

"The drug was primarily designed to conquer the European market," says Kevin Sharer, president of Amgen Europe. While Amgen and its α-EPO licensee, J&J, dominate the EPO market in North America, they have strong competition in Europe from Boehringer Mannheim (Mannheim, Germany), which is the licensee for Genetics Institute's (Cambridge, MA) β-EPO. Boehringer's annual EPO sales amount to around $400 million and most of that is in Europe. Hoffman says that it is yet to be established that NESP is novel—which would mean that it falls outside Amgen's agreement with J&J. A legal arbitor is now examining the case.

Even if things go Amgen's way in that judgment, NESP's path to the European markets may not be straightforward. Hoechst Marion Roussel (Frankfurt) has abandoned its generic project because, according to spokesman Joachim Pietzsch, "Me-too products no longer match HMR's strategy." However, it is still supporting Transkaryotic Therapies (TKT; Cambridge, MA) in its development of gene-activated EPO. The gene activated EPO has already entered clinical phase I trials. The approach allows the large-scale production of therapeutic proteins without requiring the cloning of structural genes and their subsequent insertion into nonhuman cell lines. Amgen has filed suit for patent infringement against TKT and HMR (*Nature Biotechnology* 15:486–487, 1997).

Boehringer Mannheim has become a licensee to a patent on EPO granted to researchers from what was formerly East Germany. According to Herbert Fuquét, Boehringer Mannheim's head patent lawyer, a hearing scheduled for October 21 at the German Federal Supreme Court (Karlsruhe) could decide that Genetics Institute/Boehringer Mannheim have the exclusive right to market EPO in Germany, currently a $160 million market. Furthermore, according to Fuquét, application of legal continuance (Rechtsbeständigkeit) to the East German patent could mean that it would dominate Amgen's European patent on NESP.

Matters may be complicated still further by the emergence of another potential competitor in the EPO market. Ulm-based Merckle recently won a victory in the German Federal Supreme Court, allowing it to conduct phase II clinical trials with EPO despite objections from Amgen. Siegfried Merckle, head of the licensing department at Merckle says that the court's decision made legal history but that the three-year delay while the matter was in dispute set Merckle's development back substantially. The company will to decide within the next year whether to drop its development of EPO or to pursue new chemical analogs of the growth factor.

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