At Bayer's Berkeley plant, site manager Paul Heiden in an R&D fermentation laboratory

Growing drugs is a tricky business

When it tried to roll out a hemophilia drug, Bayer learned the hard way that its factory wasn't as good as its labs. **by Stuart F. Brown**

BY THE TIME A VISITOR TO THE BAYER drug plant in Berkeley is allowed to step onto the factory floor, he makes a bunny-suited microchip worker look like a slob. Among the exotic raiment he has to put on: a surgeon-style top and bottom; a zippered jumpsuit; two different hair coverings; a surgical mask; an eye guard and face shield; latex gloves that cover the ends of the jumpsuit sleeves; and three—that's right, three—pairs of booties.

Why the elaborate getup? Because this isn't any ordinary drug factory: It's a biopharmaceutical plant where Bayer scientists grow products from living creatures. They don't want a single bacterium or fleck of dandruff or any other "bio burden" that lives on someone's skin to find its way into their sensitive processes. So fanatical are the people who tend the stainless-steel vessels and pumps and instruments in these areas that they say hospital operating rooms seem like pigsties to them.

Bayer's Berkeley plant—a sprawling

PHOTOGRAPH BY LENNY GONZALEZ

1,400-employee complex that recently received a $300 million sprucing-up—is one of only a few dozen on earth that make therapeutic proteins: drug molecules far larger and much less stable than those produced by traditional chemical synthesis. Hypercleanliness is just the most obvious manifestation of the mind-numbing complexity of biopharma, which is among the most technically challenging industries in the world and certainly the most closely regulated outside of the construction and testing of nuclear bombs. The FDA not only approves biopharma products through the painstaking clinical-trials process but also polices every step of production. The scrutiny safeguards the public from shoddy drugs but raises costs and complicates a manufacturing process that is tricky to start with. If you make mistakes, the FDA can make your life miserable, as Bayer learned firsthand.

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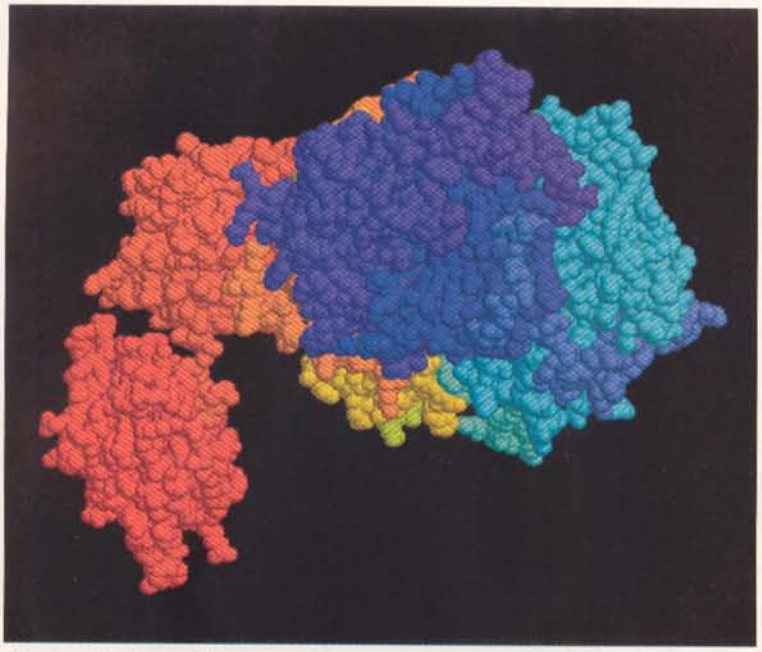


The massive factor VIII molecule is designed by nature to fall apart.

At its Berkeley plant the $27-billion-a-year German drug and chemical giant makes a hemophilia treatment called Kogenate FS, which contains a clotting protein known as factor VIII. For hemophiliacs, factor VIII is a lifesaver; untreated, many die before adulthood. It is also a natural marvel. Until the early 1990s drugmakers could get factor VIII only by extracting it from human blood. Now factor VIII is most commonly produced with so-called recombinant technology—from cultures of living cells into which human genes have been inserted. To make Kogenate, Bayer uses cells from the kidneys of baby hamsters. According to the Marketing Research Bureau in Orange, Conn., recombinant factor VIII sales hit $1.1 billion worldwide in 2000; Bayer's estimated share was 34%, vs. 59% and 7%, respectively, for rivals Baxter and Wyeth.

Things weren't always rosy at the Kogenate plant. Bayer suffered public humiliation and a blow to its business two years ago when FDA inspectors blasted the plant's manufacturing methods. The company had to take corrective steps that involved a drastic slowdown of Kogenate production and led to a rationing of supplies, infuriating and frightening hemophiliacs and their families.

Now that it has regained good standing with the FDA, Bayer agreed to share its Manufacturing Story from Hell with FORTUNE, in part because it helps illustrate why factory problems and capacity constraints plague the nascent biopharmaceutical business. Mike Fournel, senior VP for R&D at Bayer's biological products division, explains that while biotech scientists have raced down the path of discovery in recent years, people on the manufacturing side have lagged. "In the 1990s we were so excited about the idea of producing therapeutic proteins that we didn't fully appreciate some of the issues critical to manufacturing competence," he says. "The science is elegant and I love to talk about it, but at the end of the day we have to be able to put a product into a bottle that we can get out to the patients. And that ended up requiring a lot of sophistication in areas the research scientists don't normally think about."

Factor VIII is the biggest, most complicated drug molecule there is. Although its essential role in blood clotting has long been understood, the molecule's three-dimensional structure was mapped and published only this year. Readily produced in the bodies of people who don't suffer from hemophilia, factor VIII molecules are designed by nature to fall apart after they've played their part in blood coagulation. This innate fragility makes them devilishly hard to manufacture; look at them crosswise, as it were, and they begin to degrade. As a result, producing them requires constant testing for quality control.

Bayer's Berkeley plant started making the original Kogenate drug in 1993. The product was a big success, and by 2000, Bayer was gearing up for a second version, Kogenate FS. The original Kogenate contained a stabilizing agent derived from human plasma. Worry in the hemophiliac community about the possible transmission of diseases like West Nile virus through human-blood products led Bayer to develop the new formulation, which uses sucrose as a stabilizer.

The company was excited by the prospects for the new drug; hemophilia patients were clamoring for it. Bayer's plan called for an orderly transition in summer 2000, during which the older process at the plant would be shut down and a new Kogenate FS line would quickly ramp up. A smooth handoff was essential, because interest in the old drug was waning in anticipation of the new. "We expected to make a rather heroic shift," sighs Fournel.

But one uncertainty in the drug business is the timing of FDA product approvals. Bayer's plans hinged on getting an FDA signoff for the new version in January 2000. As things turned out, the green light didn't come until July 2000. In the meantime Bayer had continued making old Kogenate, and stopped when it thought it had a sufficient stockpile to last through

the transition. But as Bayer would soon find out, it guessed wrong.

In November, just as production engineers were bringing the new process line up to speed, the FDA showed up for a periodic inspection—unannounced, as is the agency's normal practice. Four inspectors began combing through the plant and its voluminous records. They ended up staying for six weeks, even working weekends. Attending to their document requests and to the issues raised by the inspectors sometimes stopped the manufacturing process cold. By January 2001 shipments of Kogenate FS began to grow sporadic; soon supplies were so short that Bayer announced to distributors that it was rationing the drug. In all, Bayer's shipments for the year were only 50% of 2000 levels. Wyeth and Baxter couldn't fill the gap, and some hemophiliacs were forced to use factor VIII derived from blood.

This did not sit well with the patients, who may be captive customers but are also demanding and vocal, as only people with a life-and-death dependency on a product can be. At a summit conference for hemophiliacs in June, a Bayer senior vice president apologized profusely for the distress the shortage had caused but was then forced to make a humiliating admission: "If you ask for a prediction for Kogenate FS supply for the coming year," she told the conference, "then you must count on nothing."

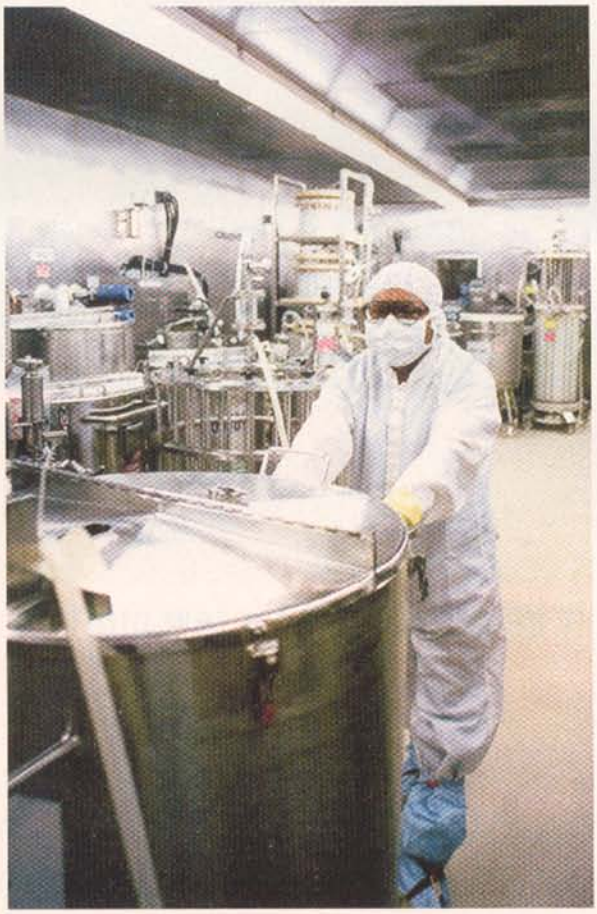
The final blow for Bayer came the following month when the FDA issued a formal warning letter citing key shortcomings in the plant's worker training, record keeping, and statistical analysis of samples to spot troubling trends.

Bayer's biological products division in Research Triangle Park, N.C., and parachuted into Berkeley to supervise what would turn out to be an 18-month, $30 million overhaul of the factor VIII manufacturing operation.

The process by which Bayer makes Kogenate FS involves three principal steps: fermentation, purification, and freeze-drying and packaging. Bayer's choice of production methods complicates its task. Most companies in the biotech industry are batch manufacturers: They ferment their protein drugs in large stainless-steel bioreactors, some big enough to hold 40,000 liters of brew. But a minority, including Bayer, use a so-called continuous-flow process. For Kogenate FS, Bayer uses a series of small 200-liter bioreactors. Workers constantly add protein supplement, growth factors, and other secret ingredients—think of it as cell food—to the colonies of baby-hamster kidney cells that live and multiply in high-purity water. The resulting protein-laden fermentation products are drawn off continuously for further processing.

A continuous-flow production run takes a long time—six to nine months—and lets drug companies make large quantities at lower costs. In the course of a normal year at the Berkeley plant, Bayer will mix 12 tons of cell food into five million liters of culture media to produce a half-pound of ultra-pure, powdered factor VIII—enough for the annual needs of 10,000 to 15,000 patients. (Doctors mix the powder with sterile water for administration by injection.)

Gowned to the nines, a Bayer worker tends purification solution.



The lengthy time frame gives Bayer a lot to keep track of and plenty of chances for missteps—and that's where it ran into problems with the FDA. Living conditions for the cell cultures in the fermenters have to be just right to grow a good yield of factor VIII. Sterility of materials, nutrient balance, temperature, pH, oxygen levels, and other variables must be monitored carefully and adjusted to keep things on track. This is especially true because of factor VIII's complexity. The molecule has more than 20 sites on its surface where sugar chains form. The branching of these chains is influenced by environmental conditions, and proper formations are essential to making molecules that won't trigger an unwanted immune response in patients. Hence the constant sampling and tweaking of the brew.

One of the FDA's principal beefs was with the way Bayer was handling "discrepancy evaluation reports"—warnings that are generated when testing shows the process is still within the product specifications but is drifting toward the limits. FDA inspectors pointed out that Bayer wasn't adhering to its own stated procedure of resolving discrepancies within 30 days. Instead the company was letting reports pile up till the end of the production run—a delay that could take months. "This was obviously a very broken process and a poor business practice as well," says Four-

"If you ask for a prediction for Kogenate FS supply for the coming year," said Bayer, "then you must count on nothing."

Failure to act could mean fines or a shutdown. As the scope of its regulatory and commercial headaches became apparent, Bayer replaced the plant's top managers and assembled a team of 25 experts from throughout the company, ranging from veteran production-floor workers to vice presidents. Fournel took a leave of absence from his research-director post at

nel. "In some cases we were trying to pull all the documentation and people together to resolve a fermentation discrepancy that had occurred six months earlier."

To fix the problem, Bayer hired dozens of new quality-control staffers and changed the way the plant ran. "We had traditional organizational silos like manufacturing, engineering, and quality control that only talked to each other at formal meetings," says Fournel. "These people now work together every day. We've learned a lot of lessons from other industries, frankly. Because we were very enamored of our science, we weren't necessarily paying attention to good manufacturing practice." A major change was the institution of quality-control points after every major process step instead of at the end of the line. The result has been a quicker response to changing conditions in the brew.

The regulators pressed Bayer to reduce the opportunity for human error. They wanted frequently used forms, such as the records accompanying the product as it moves along the line, to be written in language that wouldn't confuse production workers with a high-school education. "We had the process so this roomful of Ph.D.s could operate it," says Fournel. "But then we needed to make it bulletproof so that normal operators could run it too."

Bayer also had to find ways to avoid drowning in data. To keep its drugs in spec, the Berkeley operation conducts 120,000 product assays and tests 170,000 water and air samples per year. That works out to 1,200 assays for each lot of material moving through the plant. But numbers don't mean anything unless you can see the patterns in them, and the FDA was critical of Bayer's analysis routines.

Putting a better trend-spotting system in place wasn't just a matter of calling up a software supplier. Bayer had to develop an orderly, documented process for what Paul Heiden, Berkeley site manager since early 2001, calls deviation management. "It defines how we investigate changes from normal process limits, determine the root causes, and take corrective action," he says. "The FDA validates the total system and the software programs we use."

Nowhere was the need for a well-oiled system more important than in the complex and delicate purification process. In preparation for this phase, workers draw tissue-culture fluid from the bioreactors and store it in plastic pouches. These pouches are frozen and kept until enough have accumulated for an efficient purification run. Then the fluid is thawed and passed through five different chromatography columns of chemically treated beads that extract one impurity after another. The process removes leftover nutrients and the baby-hamster kidney cells, leaving only the factor VIII behind. But the stabilizing ingredients are eliminated too, making purification a stage in which the touchy factor VIII molecules are particularly vulnerable to going sour. Speed is thus essential.

That is where Bayer fell down. Because of poorly trained workers and an inefficient arrangement of production equipment, it was taking far too long to purify the drug and losing too much of its output. Bayer has since rejiggered its gear and stepped up its training regime. "In 2001 we had purification times that got way out of hand, up to 60 hours," says Heiden. "We've now got it down to about 35 hours." Streamlining the process has been a key to getting Kogenate FS production back on track.

Based on a follow-up inspection last March, the FDA formally lifted its warning letter. Bayer has managed to get its Kogenate FS shipments up to 80% of the 2000 level. The company plans to surpass that level next year. It will then add plant capacity so it can satisfy a factor VIII market where demand still exceeds supply. (According to the World Federation of Hemophilia, only 25% of hemophiliacs globally get adequate treatment.)

The other thing Fournel and his colleagues plan to do is avoid any more costly blunders. "We're an example of getting hit on the side of the head and recognizing that we needed to address all aspects of the business." A big stick is still a good motivator. F

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TIMOTHY BELL

Mike Fournel, here with his team, helped get the Berkeley plant back on track.

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