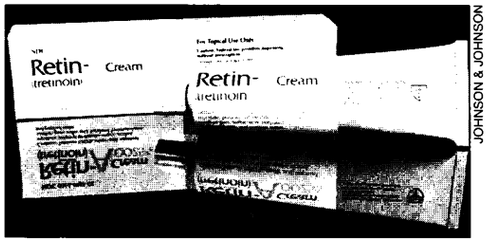
that the compound is effective in treating severe acne, and he and Penn both benefit from the patent for that application. What drove the marriage onto the rocks was the fact that when Kligman later filed for a patent on the use of Retin-A for treating "photoaged skin," he didn't include the university as a co-owner and assigned exclusive rights to the invention to Johnson & Johnson.

Penn filed suit, charging that Kligman had used junior faculty members and hospital facilities to conduct the studies that established the drug's value. Kligman and Johnson & Johnson disputed these charges, claiming that Kligman did the work in his own time (*Science*, 2 March 1990, p. 1028). The dispute never went to trial. Instead, after 26 months of wrangling, the university dropped its suit in March, permitting Kligman to retain the patent in return for a share of the antiwrinkle cream profits.



JOHNSON & JOHNSON

Billion-dollar drug? An FDA panel has voted to approve Retin-A to fight wrinkles.

The truce has come at a good time for everyone involved. Just weeks after the settlement, Retin-A cleared a key hurdle at FDA. An independent panel of experts gave the product a favorable review in a meeting at FDA on 9-10 April—even though the panel was apparently not persuaded that the compound actually heals damaged skin. According to panel chairman Arnold Schroeter, a dermatologist at the Wright State University School of Medicine, Johnson & Johnson "only had data to support the claim that there was improvement in the appearance of mottled pigmentation, roughness of the skin, and fine wrinkling"—not healing. Rather than reject the application entirely, Schroeter says, the advisory committee decided that FDA should simply change the label to emphasize that the cream has cosmetic benefits only.

If this leads to FDA approval the product could become extremely lucrative. One attorney involved in the litigation between Penn and Kligman says marketing experts believe it could earn $600 million to $1 billion a year. Schroeter agrees that it's no exaggeration to speak of potential annual revenues of $1 billion or more.

Penn's press release says the university is "particularly grateful for the opportunity to repair its relationship with Dr. Kligman." No wonder.

–Eliot Marshall

BIOTECHNOLOGY

Swiss Drug Giants Seek Antidote to Activists

BASEL—Kaspar von Meyenburg, head of pharmaceutical biotechnology research at Ciba-Geigy in Basel, has only to glance out of his office window to be reminded of what might have been. Fifty yards from his desk is the site once earmarked for Ciba-Geigy's Biotechnikum—a state-of-the-art pilot production plant that would have brought 120 new jobs to the city and high-tech drugs to the rest of the world. Last December, though, company managers abruptly abandoned their plans to build the $125 million facility in Basel. It will now be constructed in Huningue, less than half a mile away but on the other side of the border with France. The reason? Activists opposed to genetic engineering had promised to fight the building permit all the way to the Swiss federal court—a process that could have taken more than 2 years. France, it seems, provides a more secure home for biotechnology than Switzerland these days.

Threatened from one side by a vocal minority of environmentalists who oppose genetic engineering, and on the other by the Swiss public's ambivalence toward animal experimentation, the nation's world-renowned pharmaceutical giants are getting increasingly nervous about investing at home. And it's not merely production facilities that are at risk; research and development facilities are just as controversial. Executives at Hoffmann-La Roche, for example, are battling critics over the company's plan to build new research laboratories in Basel, and Sandoz officials are keeping an anxious eye on the local administration in Bern, which is expected to draft a law this year governing animal experiments. And while they are fending off such local threats, the drug companies are bracing for a campaign by foes of genetic engineering to impose strict national regulations on the technology.

As bad as it sounds, company officials haven't sounded maximum alert yet. They are encouraged that Ciba-Geigy's move into France in the midst of an unprecedented (for Switzerland) recession has provoked something of a backlash against the anti-genetic engineering activists. Nevertheless, they are warning that if the climate for biotechnology sours in Switzerland, the Swiss drug industry will be forced to shift its benchwork to newer laboratories abroad, such as those already established in the United States and Japan.

Were some or all of the behemoths to be hounded out of Switzerland, the impact on Basel would be catastrophic. The city's population is only 200,000, and its economy is dominated by Ciba, Roche, and Sandoz—each on the list of the world's top dozen pharmaceutical firms (see table). The trio have helped Basel become one of Europe's leading centers for biological research, and not solely because of their own labs—the city's academic research centers have become world famous, in part because of proximity to the giants. Take the Basel Institute for Immunology and the Friederich Miescher Institute. Both are supported directly by industry (by Roche and Ciba, respectively), and although the University of Basel Biozentrum has no direct financial links with industry, Biozentrum director Thomas Bickle says: "You shouldn't underestimate the intellectual contact." Swiss academic laboratories also face a direct threat from the opposition to genetic engineering and animal research. University of Zurich molecular biologist Charles Weissmann fears that if the climate gets any worse, "the best people will go to the United States and not come back."

Given that Switzerland's opponents to genetic engineering are no more numerous than those in the United States, why should the drug industry feel so threatened? For a start, say industry sources, Switzerland's affluence has bred complacency among those who don't oppose genetic engineering. "People forget where the money comes from," says E. Karl Weibel, who runs Roche's Basel biotech plant. Then there is Switzerland's constitution, which not only gives a strong measure of control over environmental and safety regulations to the cantonal, or regional, governments, but also allows minority groups to challenge the cantons' decisions through the courts. Moreover, under Switzerland's unique system of direct democracy, only 100,000 signatures are required to force a national referendum on any issue, and initiatives that pass must be implemented by the federal government.

The Top Twelve

	1991 sales* ($ billion)
Merck and Co. (US)	6.60
Glaxo (UK)	5.68
Bristol-Myers Squibb (US)	5.36
Ciba-Geigy (Switzerland)	4.49
SmithKline Beecham (UK/US)	4.21
Hoechst (Germany)	4.18
American Home (US)	3.67
Lilly (US)	3.66
Hoffmann-La Roche (Switzerland)	3.63
Johnson & Johnson (US)	3.60
Pfizer (US)	3.47
Sandoz (Switzerland)	3.33

*Sales of prescription drugs, year ending September 1991.

SOURCE: GLAXO

The power this system gives to special interest groups was demonstrated recently when the Swiss Animal Protection League forced a national vote on animal experimentation. The initiative would have given animal welfare groups the right to challenge in court licenses for specific animal research projects—a right similar to that exploited to block Ciba's Biotechnikum. The proposal was defeated in February by a 56% to 44 % vote, but only after an emotionally charged debate during which the drug companies argued that if it passed, many research programs would have to be moved abroad.

Although that message came across in areas such as Basel, where voters rejected the initiative by a margin of 2 to 1, four of Switzerland's 26 cantons approved the measure. And that could be troublesome for Sandoz, which has a 150-person research institute in Bern, one of the cantons that voted yes. Later this year, the Bern administration is expected to draft its own law, mirroring the Animal Protection League's proposal. The move will provoke a stormy debate in the cantonal parliament, but Sandoz is already contemplating moving animal research out of Bern, should the law pass.

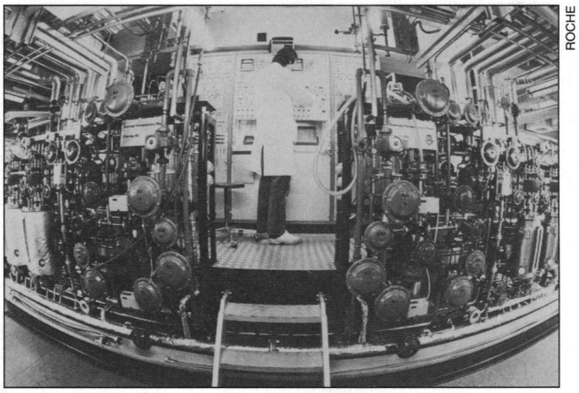
Ironically, the activities that are now attracting the critics' attention have been carried out in Switzerland for years without opposition. Ciba's Biotechnikum, for example, will produce recombinant hirudin (an anticoagulant) and alpha-interferon, yet Roche has been producing recombinant alpha-interferon at its biotech plant in Basel since 1984. So why worry about a facility that does more of the same? Ciba's von Meyenburg draws on a hunting analogy to explain his company's misfortune: "If you have a lot of deer in the wood," he says, "as long as they are standing there, you don't see them. But if one moves, you see it." In proposing a new facility, Ciba was "the deer that moved," says von Meyenburg.

Indeed, and the hunters pounced. They were led by ex-schoolteacher Florianne Koechlin. Despite a recent opinion poll showing that more than 60% of Basel's population wanted the Biotechnikum in the city, she and her activist colleagues exploited a basic democratic right to challenge a building permit. Why? Koechlin, a former antinuclear activist, admitted to *Science* that she targeted Ciba-Geigy because the Biotechnikum planning application gave her group, Basel Appeal—and its ally, the Swiss branch of the World Wide Fund for Nature—a "legal tool" to oppose all three companies' work in genetic engineering. "We took this case as an example to get the whole discussion on the risks of gene technology started," she says.

Now they're after new quarry: Roche. The company applied in summer 1991 for permission to build a new 8-story laboratory block, designed, in part, to house a 100-person molecular biology team that is now spread over Roche's Basel site. Permission came through last month, but Koechlin's group has already protested the construction of a small high-containment laboratory that is integral to the company's plans. Roche is making contingency plans to build the entire facility abroad, if necessary. "You cannot invest millions of Swiss francs and then find you can't use it," says Stefan Ryser, who is heading Roche's effort to win public support for its research plans.

At the moment, Koechlin and her allies have few weapons to challenge research at existing labs—only plans for new facilities. But they are hoping to change that by mounting a major campaign to impose strict regulations on all genetic engineering in Switzerland.

Their opening will come on 17 May, when Swiss voters are expected to approve an initiative that will place restrictions on human in vitro fertilization (IVF) and require the federal government to draft laws to regulate gene-splicing technology. Although some researchers are not happy about the proposed IVF rules (which would, for example, prevent the frozen storage of fertilized embryos), industry isn't opposing the initiative because it wants national regulations for genetic engineering, says Arthur Einsele, Sandoz's assistant vice president for corporate strategy in biotechnology. Companies now abide by the NIH guidelines for recombinant DNA research, but they are not required to do so, and this allows activists to argue that there is a legal vacuum, Einsele notes.



ROCHE

Hunter and quarry. Genetic engineering critic Florianne Koechlin and Roche's long-running alpha-interferon plant.

The companies may want regulation, but their main preoccupation now will be to ensure that the Swiss legislature doesn't follow the restrictive approach taken by neighboring Germany, which is causing a major headache for German genetics laboratories (*Science*, 31 January, p. 524). Koechlin and her allies have already upped the stakes: The Swiss Working Group on Gene Technology (SAG)—an umbrella organization representing all the Swiss groups opposed to genetic engineering—will begin gathering signatures this summer to secure a public vote on its own draconian set of regulations. These include banning the release of genetically engineered organisms into the environment, halting the production of transgenic animals, and preventing the patenting of plants and animals. It could be 5 years before SAG's initiative is put to the vote, but if it passes, says Roche's Ryser, "this is the death of research in Switzerland."

Galvanized by that threat, Switzerland's three pharmaceutical giants are joining forces in a public relations offensive to try to convince the Swiss that genetic engineering research is both safe and necessary. They are jointly bankrolling a lobby group, Gen Suisse, consisting of politicians and academic researchers, which this summer will send an exhibition promoting the merits of the technology on a tour of the country. "If we win round the public, then the [opposing] groups will fade away," Ryser predicts.

If he's wrong, expect Swiss drug companies to make most of their new research investment abroad. Already Swiss-based companies are expanding their research facilities in the United States and Japan—Roche, Ciba, and Sandoz all have thriving laboratories in New Jersey—and at Sandoz, says Daniel Hauser, the company's Basel head of preclinical research, the slogan is: "Grow West. Go West." The company will double its preclinical research activity in New Jersey over the next 3 years, he says. Significantly, Roche's head of international research and development, Jürgen Drews, moved from Basel to Nutley, New Jersey, at the beginning of 1991. Drews says that the decision to relocate was made for a number of reasons, including the need to coordinate research with Roche's recent U.S. acquisition, Genentech. But he says that the more favorable public attitude toward genetic engineering in New Jersey was a factor. In that respect, says Drews, "Switzerland is really in pretty bad shape at the moment."

So perhaps the handwriting is on the wall. Romeo Paioni, Ciba-Geigy's Basel head of pharmaceutical research, suggests otherwise: "Basel and Switzerland remain a key place to do research," he says. Even Roche's Drews believes that it's just a question of "riding out the storm" in Basel for the next 10 years or so until public doubts about the companies' research recede. But 10 years is a long time, especially for researchers who would be on the receiving end of any cuts in Basel. They will be looking for more immediate results in the coming public relations battle.

–Peter Aldhous