How Europe Regulates Its Genes

With 1992 fast approaching, the European Community is formulating its rules for biotechnology—rules that have some researchers in industry alarmed

Paris–FACED WITH DELAYS—SOMETIMES OF years—in getting genetically engineered products approved by the Food and Drug Administration (FDA), corporate officials and researchers in the U.S. biotech industry must occasionally turn a wishful eye on Europe. Consider the case of Centocor. In March 1988, the Pennsylvania biotech firm applied to the FDA for permission to market its monoclonal antibody preparation, myoscint, which is designed to detect myocardial damage in patients with acute heart disease.

Three months later Centocor applied to the European Community's (EC) Committee for Proprietary Medicinal Products for permission to market the same product. In the spring of 1989, less than 11 months after the European application, a positive decision came back from the EC. Meanwhile, in the United States, time is still hanging heavy on Centocor's hands: The FDA has yet to render a decision on myoscint. A company spokesman's best guess about when the FDA might decide was a wistful "in the second half of this year."

But U.S. companies' envy of their European counterparts could soon turn to sympathy. As Europe moves toward unification in 1992, more than two dozen regulations and directives that will affect biotech are working their way through the complex European legislative system. The result could mean tough scrutiny for genetically engineered products. One reason is that the EC has chosen to examine genetically engineered products as a special category—an approach the FDA has rejected. Another is that the EC is considering enacting regulations that would mandate consideration of the socioeconomic effects of biotech products in addition to their safety (see box on next page). In addition, some—particularly in industry—fear a nightmare of overlapping and contradictory regulations.

It's too soon to tell how well the European system will work, or how stifling the regulations might be. Indeed, in some countries—such as Germany and Denmark—that had already adopted their own stringent rules, the regulatory climate will actually be balmier when the European framework supplants national laws. In all likelihood the regulations emerging in Europe won't be demonstrably superior—or inferior—to the American ones, just different, with different strengths and weaknesses. But since many U.S. biotech companies are looking to the huge market that a unified Europe represents, the specifics of those strengths and weaknesses will ultimately be of more than passing interest from Boston to Berkeley.

One reason the European regulations are crucial for biotech is that, unlike in the United States, where many standards governing genetic engineering are voluntary, the European directives will be community-wide laws. Says Mark Cantley, director of the Concertation Unit for Biotechnology, the EC's central coordinating center for biotech research and communication: "In Europe we are still constructing our community. To create a uniform environment for biotechnology, we can't have different rules in each country. So there has to be positive action."

Indeed, almost all the EC biotech guidelines now being considered are in the form of directives—meaning that once the EC adopts them, member states are required to enact them into national legislation. To date, the EC has adopted four of the directives. The first was passed in 1987, when the Community enacted legislation requiring all so-called high-technology drugs to go through a Community-wide, centralized approval process. In the years since, many of the applications have zipped through this procedure at a speed unseen in the United States—including Centocor's myoscint.

The second directive was a set of guidelines for worker safety in biotech, which must take effect by November 1993. (Portugal, with its less developed scientific infrastructure, has until November 1995.) The last two were key directives governing the "contained use" and "deliberate release" of genetically modified organisms, which must come into force in the member countries by 23 October of this year. It is these last two directives—particularly the one on deliberate release—that are causing the most heartburn in the biotech industry.

"The new laws are not exactly in contradiction with biotechnology research," says Daniel Thomas, a biochemist at the University of Compiègne, north of Paris, and director of France's National Program for Biotechnology. "But I think they are truly at the limit of compatibility." And Kenneth Baker, head of biotechnology science and policy for the chemical giant Monsanto's European operations, argues that these regulations are "a bad piece of work. We're off to a bad start."

The directives governing contained use and deliberate release of genetically modified organisms cover everything from laboratory research to field trials of genetically altered plants to the marketing of products containing genetically modified organisms (GMOs in European parlance). In most cases the voluntary approach familiar to U.S. scientists has been shorn away. For example, the rules on contained use follow a containment and classification protocol similar to the National Institute of Health guidelines used in the United States, but they are not

EUROBIOTECH: RULES OF THE GAME

REGULATION	TAKES EFFECT	COMMENTS
Approval process for biotech products	1987	Centralized, Europe-wide process is considerably faster than in the United States
Guidelines for worker safety	1993 (Portugal has until 1995)	
"Contained use" of genetically modified organisms (GMOs)	October 1991	Similar to NIH guidelines—but mandatory rather than voluntary
"Deliberate release" of GMOs	October 1991	Has drawn critics' fire for being too stringent
Two dozen rules on everything under the biotech sun	Still in the pipeline	Industry fears overlapping and contradictory regs

voluntary or self-governing.

Nevertheless, a research laboratory doing recombinant work with a well-characterized, nonpathogenic microorganism need only register its installation with the regulatory authorities in its own country, adhere to good safety practice, and keep records ready for inspection. For work with higher risk organisms, the lab must notify the authorities in each case but can still go ahead if no disapproval is received within 60 days.

On the other hand, large-scale industrial work with such organisms requires explicit consent. And where the deliberate release of a GMO to the environment is contemplated, the rules are much stricter. Similar to ad hoc procedures in effect at the U.S. Department of Agriculture and the Environmental Protection Agency, all such releases must be evaluated on a case-by-case basis, and none are allowed without the approval of an evaluating committee. Yet in contrast to the U.S. regulatory scene, where applications must sometimes be approved by several different agencies, the European directive provides a unified set of rules for everything from small-scale field trials to the marketing of products containing GMOs.

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—Mark Cantley

Although the directives will be legally binding, they say little about enforcement. No "lab police" will be created to monitor what is going on. "With this sort of technology, you can't walk into someone's lab and say, 'Ah yes, that person is cloning x, y, or z,'" says John Beringer of the University of Bristol in England. "We're still basically working on goodwill."

Critics of the new laws have reserved most of their fire for the directive on deliberate release. The issue is particularly touchy in the agricultural arena, where European biotechnology is the most competitive vis-à-vis the United States and Japan.

"If they ask a company to write a 50-page file to get a trial done, and you think it's worthwhile to put in the money and resources, you will do it," says Willy De Greef,

One More Hurdle for Biotech

On 20 March, the Monsanto Company received a long-awaited approval from the European Community's (EC) Committee for Veterinary Medicinal Products (CVMP) for its version of recombinant bovine somatotropin (BST), a growth hormone that, when injected into cows, can increase milk production up to 20%. Under normal circumstances, the generally positive recommendation would have meant BST was headed for market.

But BST is no ordinary drug. Controversies have raged on both sides of the Atlantic, not only about its safety but whether it is needed at all during a time of surplus milk production—and whether its use would drive many small farmers out of when cheap, hormone-induced milk from agribusiness floods the market. That concern led the EC's Council of Agricultural Ministers in April 1990 to declare a moratorium on the marketing of BST. The ban, recently extended to the end of this year, is designed to allow completion of several studies—including a look at the effect BST would have on European agriculture.

The action by the European Community is an informal version of what has come to be known as the "Fourth Hurdle" for biotechnology products. Traditionally, in Europe and the United States, new drugs have been judged on three criteria: safety, quality, and efficacy. The Fourth Hurdle could add social and economic considerations to the list—at least in Europe. The EC's Agriculture Directorate recently circulated a proposed directive that would apply socioeconomic criteria to the evaluation of drugs for promoting animal growth. Although only a draft, the legislation, if adopted, would make the Fourth Hurdle a formal part of the approval process for this category of biotech products.

The idea for the Fourth Hurdle came from Ken Collins, a Scottish member of the European Parliament, which plays an advisory role in the adoption of EC legislation. Collins, chairman of the Parliament's Environment Committee, is generally regarded as sympathetic to the development of biotechnology (though the industry is not delighted with his advocacy of the Fourth Hurdle). He says application of socioeconomic criteria is particularly appropriate in the case of growth promoters or other agricultural productivity enhancers. "I have sought to distinguish between medicines and production aids," Collins says. "If you give an animal something that makes it get fatter faster, you're not curing it of anything or preventing disease. In this case you should provide a different standard, and that standard includes the Fourth Hurdle."

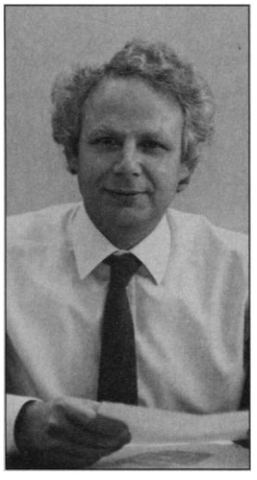
Most people in the biotech industry, however, argue that these decisions should be made in the marketplace. They are particularly fearful that introduction of nonscientific factors could open the floodgates to purely political considerations. "There are certain individuals who think that society should be saved from itself," says Ken Baker, head of biotech science and policy for Monsanto's European operations. "Personally, I am not very keen on people telling me what I should do or what I should buy."

Mark Cantley, director of the EC's Concertation Unit for Biotechnology, says that "establishing safety, quality, and efficacy is difficult enough. If we get involved in this kind of thing [the Fourth Hurdle], nobody's going to make a very good job of it. Many of the things we now accept as part of our daily lives, like aspirin or the motor car or glass, probably would not have gotten through an appropriately far-sighted socioeconomic impact assessment."

But Collins argues that "industry wants to have it both ways. On the one hand they call for rationality and objectivity, but on the other hand they say, 'Let the market decide it.' That's a contradiction. We need to set up a rational system under which new products can be measured. The present system erroneously supposes that safety, quality, and efficacy are the end of the story. But they're not, because BST, and the steroid hormones before it, went over these hurdles and then the race stopped. They have not been marketed."

For the moment, the debate whether there should be a Fourth Hurdle or not continues in Europe. But some of its advocates say that, in a sense, the heated debate misses the point. The Fourth Hurdle "is there whether you like it or not ," says Lars Hoelgaard, director of the Agriculture Directorate's quality and health division. "You can either have it the way it is now, on an ad hoc basis, unpredictable, with purely political decisions based on pressure groups—or you can have it the way I am proposing it, formalized and put into a proper structure." ■ **M.B.**

a plant geneticist at the University of Ghent in Belgium and former product development manager with the Belgian biotech company Plant Genetic Systems. "But there's an immense danger in this sort of overregulation, a tremendous potential for these rules to be ignored by scientists working in public institutions. You burden people with such a load of paper that it deters them from entering the field in the first place." Yet the directive contains one important feature that should make people in the biotech industry happy: Any product approved under its auspices in one member country must ultimately be allowed onto the market in the other member countries.



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Industry spokesmen are critical not only of specific rules—such as the deliberate release directive—but also of the underlying regulatory philosophy adopted by the EC, in which genetically engineered products are considered as a special category. They contrast that approach with the one they perceive in the United States, where the FDA has no special category for biotech products and where the White House Council on Competitiveness recently released a report urging regulators to continue focusing on the inherent characteristics of biotech products rather than on the processes by which they are made.

"The Community needs to sit down and say, What should be our approach to biotech regulation, how do we see it fitting into the existing structures?" says Brian Ager, director of the Senior Advisory Group on Biotechnology, made up of representatives from such multinational pharmaceutical giants as Rhône Poulenc, ICI, and Hoechst. "The environmental regulators are very much focused on the technique: 'This is genetic engineering, therefore we must regulate it differently.' What we would like to see is a nondiscriminatory policy."

But that isn't likely. Laurens Jan Brinkhorst, director general of the EC's powerful Environment Directorate, counters that "while the risks from biotechnology may be bigger or smaller, they are still different from the risks of other techniques. For example, I am also in charge of nuclear safety. The fact that nuclear energy produces electricity does not mean that it doesn't have different characteristics from the other means of doing this, like gas or oil or coal. I think people would be very surprised if we didn't take a specific look at nuclear power plants. Likewise with biotechnology."

Aside from the existing rules and the underlying philosophy, researchers and corporate officials are concerned that the regulations still in the pipeline could result in a maze of overlapping and contradictory rules. That concern is heightened by the complexity of the European administrative system—in which perhaps half of the 23 EC directorates could have a hand in regulating the work of biotechnology firms.

The two dozen additional directives still being developed cover everything from pesticides to "novel foods" to intellectual property. And in that tangle, basic questions remain unanswered. Would a new yogurt containing a *Lactobacillus* genetically altered to make the product creamier and tastier go through the procedure for novel foods, that for the deliberate release of an engineered organism, or both? And while the growing of potatoes genetically engineered to resist insect pests clearly falls into the category of a deliberate release, what happens when the potatoes are trucked to market? The directive on release specifically excludes transportation of engineered organisms, an area that's under study by the EC's Transportation Directorate.

While no one doubts that there are uncertainties and potential hazards in the emerging system for biotech regulation in Europe, it seems clear that some of the worries come simply from the shock of being faced with legally binding rules. In the past, depending on the country in which they worked, scientists in research and industry were rarely required to follow anything more stringent than the type of voluntary guidelines that continue to govern much biotech work in the United States. And conditions in some countries were even more lax: Italy, Greece, and Spain had no guidelines at all.

Furthermore, there's considerable difference of opinion as to how onerous the regulations will be. Many university researchers, for instance, seem sanguine. "On the research level," says Bristol's Beringer, "the additional burden is relatively small. In terms of contained work, in Great Britain at least, there will actually be a slight reduction in the amount of paperwork." And a scientist from France, where researchers have until now followed voluntary guidelines, comments: "We'll be able to do everything we did before, but with a little more paperwork."

What is more, in some countries the Community-wide legislation will lessen the burden of regulation. In Denmark and Germany draconian measures were adopted in the 1980s, partly due to pressures from the Green Party and other environmental activists. At that time much of the impetus for regulating biotechnology came from industry itself, which saw limited governmental regulation as a kind of benevolent protection from the virulence of the Greens. Now the threat from the Greens seems less: To a large extent, the new EC regulations represent a defeat for the more extreme segments of the Green movement, which failed in its attempts to put a straitjacket around biotech research.

This history is the reason that some EC officials are bitter about industry's complaints. "When industry was afraid it was going to be banned," complains one EC official, "it came to us and said, 'Please pass a law to stop them from banning things.' Now that there's no danger of that, they are saying we don't really need the laws at all."

"Industry often prefers not to be regulated," says Brinkhorst. "But the most important thing is to have predictability, and a standardized process. People should be thankful that there is this European legislation, because otherwise there would still be a patchwork of national laws, which in many cases were stricter than what we found necessary in the Community."

"The uncertainties are still great," says Mark Cantley. "We are in a period of intensive legislative effort to create the common market. Some sectors of industry have taken a beating, and scientists in Europe have seen safe techniques with a 100% track record being stigmatized....We have to learn our way out of these grosser stupidities. The Community is trying to achieve some sort of democratic compromise, to restrain the wilder excesses, in the course of creating a rational regulatory structure."

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