controls beyond the normal sphere of classified research," she argues.

Allan Adler of the American Civil Liberties Union questions the legality of applying Freedom of Information exemptions in a situation for which they were never intended. Moreover, he argues that the new regulations themselves represent a worrisome extension of Defense Department authority over information that it does not own.

It is by no means clear that the Defense Department sees this episode as a model. Young notes that the procedures "worked well in the panic situation we were in," but says he would like to see a lot more discussion before they are applied routinely. "We can't use this as a model and put it in place without realizing what problems it creates for the societies," he says. "I don't know how it's going to end up."

SPIE officials believe, however, that technical societies may be forced to accept such controls. According to Lewis Larmore, the society's president, SPIE's governing committee held a meeting during the conference at which "all of us agreed that if we are going to stay in business we are going to have to kowtow to these rules." Although the bulk of the contested papers were salvaged by shifting them into restricted sessions, "we've lost our virginity," Larmore noted.

The incident also sent a shiver of apprehension through parts of the academic community because it threatened to undercut a policy worked out last year under which no restrictions would be placed on the publication of results of basic research funded by the Defense Department on university campuses (*Science*, 26 October 1984, p. 418). The policy was spelled out in a memorandum written by former Under Secretary for Research and Engineering Richard DeLauer and reiterated in a letter from Defense Secretary Caspar Weinberger to the head of the Institute of Electrical and Electronics Engineers. It applies to all Defense-funded research in the 6.1 budget category (essentially basic research), and on-campus research in the 6.2 category (essentially applied research) unless "there is a high likelihood of disclosing performance characteristics of military systems, or of manufacturing technologies unique and critical to defense."

Administration officials have been quick to deny that the SPIE episode has any bearing on the basic research policy. They point out that only one of the papers had academic authors and none was derived from basic research. (Although the budget categories under which the research was funded could not be ascertained, several observers suggested that the bulk of the projects would probably fall in the 6.2 or 6.3 categories.)

The Association of American Universities sought assurances from the Defense Department and the Office of Science and Technology Policy (OSTP) that the policy on the publication of basic research results has not changed. The association subsequently sent out a letter, which was cleared with Defense and OSTP officials, stating that "the Administration has no intention of using the new [regulations] to restrict the publication of fundamental research results or their presentation at scientific meetings."

The university community would, however, feel happier if the policy rested on a foundation more secure than a memo from a former Pentagon official and a letter from the Secretary. A draft statement establishing the policy government-wide has, in fact, been sitting in the National Security Council for more than 6 months with virtually no sign of movement. According to deputy OSTP director John McTague, "there is no disagreement on it in principle."

The SPIE episode may therefore have little direct impact on academic research. But the implications for researchers in Defense Department laboratories and defense contractors—and for the scientific and technical societies to which they belong—could be more worrisome.—**COLIN NORMAN**

Generics, Roche Joust for Valium Market

Roche claims differences in diazepams as generics race for FDA approval

On 27 February, after 22 years of patent protection and at least $3 billion of sales, Valium went off patent, starting a race among generic drug manufacturers to get a copy of the top-selling tranquilizer to market. Two weeks prior to Valium's patent expiration, however, Hoffmann–La Roche, the maker of Valium, petitioned the Food and Drug Administration (FDA) to block the agency's approval of any generic versions of the drug. Asserting that FDA's methods for judging the equivalency of copies of Valium are flawed, Roche argued that generic versions of the drug may not deliver correct therapeutic doses.

FDA officials and generic drug companies contend that the chief purpose of Roche's petition is to delay for as long as possible the marketing of competitors to Valium. They say Roche's line of argument is particularly significant because it foreshadows an escalation in rivalry between brand name and generic drug companies as the patents of other big money-making drugs expire.

The stakes are enormous. The National Council of Senior Citizens estimates that the introduction of more generic drugs could cut the nation's health care bill by $1 billion over the next dozen years. Last year's generic drug market rose to $4 billion, accounting for 20 percent of total prescription sales, according to the Generic Pharmaceutical Industry Association. But the amount is small change compared to potential future sales. Last year, patents expired on three major drugs with sales totaling $700 million. (The drugs were Inderal and Aldomet, used to treat hypertension, and Diabinese, used for diabetes therapy.) In the next 5 years, patents on 11 drugs, which individually had sales of $50 million to $173 million in 1982, will expire.

That generic drug manufacturers can now copy these off-patent drugs with relative regulatory ease is a result of a major bill passed by Congress last year (*Science*, 27 April, p. 369). After a long and bitter contest between generic and brand name companies and infighting among the brand name companies themselves, Representative Henry Waxman (D–Calif.) and Senator Orrin Hatch (R–Utah) pushed through compromise legislation designed to speed up the FDA approval process for generic drugs and at the same time give brand name companies additional patent protection for their drugs. Valium is the first major drug to go off patent under the legislation and is

regarded as a test of the FDA's ability to carry out the Waxman-Hatch bill.

By law, generics must contain active ingredients identical to the brand name product, but the formulation with inert ingredients may vary. Roche argues that FDA is using the wrong test to measure the rate at which various diazepams, the active ingredient in Valium, are absorbed by the body. FDA maintains that measuring blood levels of diazepams made by different companies is a reliable way to analyze bioequivalency. Roche contends that the agency instead should require computerized brain wave tests. The company says that the agency at least should require not one, but several dose levels of diazepams to be tested using the blood tests. Either recommendation, if adopted, would be much more costly and time-consuming for generic companies.

Roche bases its argument largely on a company-sponsored study that was completed shortly before Valium's patent expired. The study was conducted by Turan Itil, who is a professor at New York Medical College and heads his own consulting firm. Itil tested Valium, two generic diazepams marketed in Canada and Turkey, and a placebo on a group of 16 men. Roche argues that Itil's brain wave study showed that the generic diazepams did not produce the same effects as Valium on the central nervous system and are therefore less effective. Itil used computerized electroencephalography (EEG) to measure 22 variables, whereas conventional EEG methods analyze 4 variables. Blood tests conducted on the same group of men did not distinguish between the generics and Valium. "The result of these disparities [in the brain wave tests] among different brands of diazepam could well lead to less than optimal therapeutic effects or untoward reactions," Roche said in its petitions.

But two scientists at the National Institute of Mental Health, who were asked by *Science* to review Roche's description of the study, said that there were insufficient data to draw such a conclusion. In theory, computerized EEG's may very well be useful to test for bioequivalency, they say. But Richard Coppola, a senior investigator at the institute who specializes in EEG and psychopathology, says that from the data presented in the petition, "it's unclear whether EEG's can distinguish between diazepams." Roche "hasn't really done the bottom line test—a clinical test," Coppola says.

Furthermore, says Wallace Mendelson, a specialist in benzodiazepines, the class of drugs including diazepams, there is "no established way to predict Valium's effects on a normal person's EEG's and its ability to relieve anxiety, relax muscles, or treat convulsions." Mendelson adds that at best the brain wave tests would be used as a supplement, not a replacement to measuring blood concentrations. Testing the blood "is a valuable and classical way to measure bioequivalency," Mendelson says.

Itil acknowledged in an interview that no study has yet been conducted to replicate his work and that "we don't know what the clinical importance is." He says, "I am . . . just saying that there is an inequivalency in central nervous system effects." It is "premature" to say either that there is or is not clinical bioequivalence. Roche has contracted with Max Fink of the State University of New York at Stony Brook to replicate the study and with Itil to conduct a follow-up clinical trial.

FDA official Seife says Roche's arguments are "gobbledygook."

Although the FDA has not yet officially responded to Roche, it is expected shortly to reject the company's claims. Marvin Seife, director of FDA's division of generic drugs, says the company's petitions are "gobbledygook." Seife speculates that because several companies had filed applications before February to market diazepams, Roche apparently thought that FDA was ready to approve a generic version of Valium as soon as the patent expired. "It turns out they were wrong," Seife says, noting the applications to make generic diazepams are still under consideration. (These companies are different from the makers of the generics that Itil tested.) Last year Roche, presumably anticipating stiff generic competition, went so far as to trademark a new shape to Valium pills—a V-shaped hole in the center of tablets.

Even though FDA may eventually approve a generic version of Valium, any delay in the approval process has a major financial impact. In 1983, Valium sales reached $250 million, so every day of delay means thousands of dollars to Roche. Seife says that petitions like Roche's "have to be answered and it's money in the bank" for the brand name companies. "It's tedious work. If we didn't have to answer these [kinds of] petitions we would be processing more generics."

Roche spokesman John Doorley says that the timing of the petition filing and the patent expiration were "a coincidence. We'd like FDA to judge the petition on its scientific merits. The study clearly shows there is a difference in Valium and two generic diazepams."

This is not the first time that a brand name company has raised the issue of bioequivalency. FDA, in fact, does allow a variation of plus or minus 20 percent in bioavailability, but Seife says that this variation does not make much difference therapeutically and notes that brand name manufacturers are allowed the same variability. "Innovators don't hit 100 percent all the time. They waffle around," he says.

The Waxman-Hatch bill was intended to swing open the doors to the generic market, but petitions like Roche's may hamper approvals. Two weeks ago the Federal Trade Commission (FTC) began a preliminary look into whether Roche is playing fairly. An FTC attorney says, "The reason it caught our attention is that there are cases where competitors use the governmental process to keep others out of the market. We haven't found anything one way or the other. We have to gather a lot more facts."

Asked about FTC's interest, Doorley responded, "This is news to us. We know nothing about the FTC matter. If the FTC were to look at Roche's petition, we are sure that the agency would quickly conclude that the science was valid."

Companies that invest a lot of money in research and development deserve patent protection, the generic drug industry acknowledges. But representatives say enough is enough, citing Valium's 22 years of protection as an example. In fact, several brand name drug manufacturers themselves have stepped into the generic business as either makers or marketers of off-patent drugs. Lederle Laboratories, for instance, has applied to FDA for approval to produce a generic Valium in addition to generic drug companies. Other large drug houses that either produce or market generics include Eli Lilly, Parke-Davis, Smith Kline & French, and Pfizer, according to the Generic Pharmaceutical Industry Association. Deputy director of FDA's office of drugs and biologics James Morrison says that the contest for Valium's market is only a taste of the competition likely to develop over the next several years as the patents of more top-selling drugs expire. "Now you're going to see a step up," he says. "The stakes are higher."—**MARJORIE SUN**