that could be brought on line by 1990 would not exceed 500,000 barrels per day. With an informational program, he says, daily production probably would be no more than half that.

Perry notes that there simply has been no case of a synfuels plant ever having been built before on the scale—50,000 barrels per day or larger—contemplated in President Carter's proposal. Nazi Germany's maximum daily production of synfuels during World War II was, he says, 110,000 barrels, with the largest plant producing 17,000 barrels.

Early this summer, prior to the President's announcement of his proposal, there was a strong push in Congress for a major national synfuels effort. A bill was passed by the House of Representatives to establish, through a program of price and loan guarantees, a 2 MBPD synfuels industry by 1990. Since then, however, an attitude of caution has become evident, especially on the part of the Congressional Budget Office. When Congress returns from its Labor Day recess, the kind of advice now being heard from the Harvard Business School team and RFF may contribute to a reshaping of synfuels strategy.—LUTHER J. CARTER

Dollars for Drug Research Flow Overseas

U.S. firms now sink millions into testing new drugs in Europe, partly because of strict limits on human experimentation at home

During the past decade, U.S. pharmaceutical companies have made a little-noticed but significant shift in where they sink their research dollars. Increasing amounts of money are flowing into Western Europe, especially into France, Switzerland, the United Kingdom, and West Germany. According to the Pharmaceutical Manufacturers Association (PMA), U.S. drug companies in 1970 spent $47.2 million or 8.7 percent of their total R & D budget in foreign countries. By 1978, those figures had climbed to $229.6 million and 16.8 percent. A large part of the money goes into clinical trials, in which clinical pharmacologists in many European countries give experimental drugs to groups of patients and healthy volunteers.

Why these studies are increasingly done abroad and what the U.S. drug giants do with the results of the research are questions currently under much debate. Industry executives say stiff federal regulations have put drug development in this country on the decline. To sidestep the regulations, they move their R & D overseas and then send the results back here.

Federal regulators at the Food and Drug Administration (FDA) say it is not that simple. While admitting that tough new rules are a factor, they also point to the decline of the dollar, to different tax structures in other countries, and to various economic incentives overseas, including the underwriting of research risks by some foreign governments. They also say that much of the research done by U.S. firms overseas is never used in the United States but instead goes for product development in expanding foreign markets.

The debate is diffuse, for there are few hard facts available to support either side's contentions. The pharmaceutical firms are loath to release any information that might tip off a competitor, and the FDA in most cases does not have the economic data to back up its views. Differing opinions are nonetheless significant. They touch on industrial innovation, a hot political topic that is currently the subject of an Administration domestic policy review. They also touch on the so-called drug lag—the alleged delay between marketing new drugs in Western Europe and getting them on pharmacy shelves in the United States. And the debate over pharmaceutical innovation is being closely followed by Senator Edward M. Kennedy (D-Mass.), who recently sponsored legislation that would, among other things, speed up the process of new drug approval.

Some FDA officials are quick to admit the adverse economic impact of their regulations. "The whole overview and federal supervision of research has increased substantially in the past 5 years," Jerome A. Halperin, deputy director of the bureau of drugs, told *Science*. "FDA now has a comprehensive bioresearch monitoring program. We evaluate toxicology laboratories through our 'good laboratory practices' regulations. We've proposed regulations on sponsors and monitors of clinical trials. We've got regulations covering the clinical investigators. We're proposing new regulations on Institutional Review Boards, and on informed consent. . . . It all increases the burden on a drug company doing research in the United States."

Confirming this view is a statistic from the National Science Foundation (NSF). In a study issued last April, NSF noted that the greatest growth in overseas expenditures occurred between 1974 and 1975, when the foreign R & D budgets of U.S. drug companies almost doubled. This, the study noted, was probably in response to a new FDA regulation that was proposed in 1973 and passed in 1975. It said for the first time that FDA would accept test results from studies made in foreign countries.

Many U.S. drug companies say the NSF assertions are correct. Barry M. Bloom, president of central research at Pfizer, which in 1978 put a total of some $113 million into R & D, told *Science* that since 1973 their R & D budget in Europe has grown about four times faster than their domestic R & D budget. Much of it, he said, was in response to the FDA foreign-data regulations. But when asked for specific examples of European data submitted in support of a U.S. drug application, Bloom waxed noncommittal. "There is sort of a time lag," he said. "Whereas in the future I fully expect we are going to have some important cases where the pivotal studies will be European, I can't say that yet." Bloom also concedes that the FDA position on expanding foreign markets is at least in part correct. "Today, the United States only constitutes a quarter of the world's market. Not so many years ago it used to be half. So regardless of whether that foreign R & D expenditure goes back to the U.S., it will certainly contribute to a company's foreign marketing organization."

With some companies, foreign data have already helped pave the way for acceptance of a drug in the United States.

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In 1974, Abbott Laboratories came to FDA with a drug known as valproic acid, an anticonvulsive for the treatment of epileptic seizures. The drug had long been used in Europe, and groups such as the Epilepsy Foundation lobbied extensively for its introduction into the United States. In addition, when Abbott submitted its completed application to FDA in September 1977, more than 200 studies from overseas were included, 30 of them clinical. In Februray 1978, FDA approved the drug for use in the United States. This total time of 5 months from submission to approval is far from the norm. By FDA's own estimates, processing the new drug applications that were approved in 1978 took, on the average, 34 months.

It is the prospect of quick clinical trials that lures many firms into overseas research, according to industry executives. Several who spoke with *Science* noted that the United Kingdom has no federal regulations for studies on normal subjects. In these studies, called phase I in the United States, a new drug is administered to a few healthy volunteers in order to see how it is metabolized and excreted and to see if it will produce any adverse effects. In the United States, a researcher must get an Investigational New Drug (IND) clearance from the FDA before starting this type of testing—and getting an IND can sometimes take years. "My impression," says Robert Temple, director of FDA's cardiorenal unit, "is that companies are screening their molecules abroad. The numbers always tossed about are that for every ten drugs that go into man, only one ever makes it to the filing of a New Drug Application [NDA]. The companies can do a quick phase I study overseas and if the drug has potential then do a larger study here. They save themselves a lot of time and trouble."

During the past year, even FDA has come to believe that its phase I requirements are a bit too burdensome. "In all the years that we have been regulating phase I research, we can't find a single instance in which FDA intervention made a damn bit of difference in terms of safety of subjects," says William Vodra, a Washington, D.C., attorney who recently resigned as FDA's associate chief counsel for drugs. "It's the Institutional Review Board and the quality of the scientist that makes the difference." In recognition of this, Senator Kennedy, through his drug reform bill, proposes to cut much of the federal red tape surrounding phase I studies. It is hoped that this will increase pharmaceutical innovation in this country.

If the bill passes Congress, the legislation may diminish the incentive to go overseas. The incentive is already shrinking, according to FDA officials, because many countries are beginning to abide by U.S. research standards. "There is a great effort going on internationally to harmonize requirements," says Halperin. "The EEC [European Economic Community] countries are working on what data elements ought to be in a drug application. They are also developing guidelines for preclinical and clinical tests on drugs. . . . More and more of the major differences between requirements from one country to another are going to disappear." The FDA also plays a part in this trend. For the past 2 years, it has been making site visits to various European toxicology laboratories. The FDA inspectors check to see if any unknown factors or contaminants might be influencing the data being generated—in short, to see if the laboratory is up to U.S. standards.

One incentive for U.S. pharmaceutical companies to send their research overseas is not likely to diminish. This is the ability to avoid industrial espionage. For several years it has been apparent that very few Freedom of Information (FOI) requests at FDA come from private individuals or the press (*Science*, 4 July 1975). Instead, most requests come from corporations seeking information about their competitors and from lawyers seeking information regarding liability suits. But not in Europe. "As long as you don't make an IND or NDA submission to FDA, those data are yours," says Donald van Roden, president of Smith Kline & French Laboratories. "The degree to which you think that exposure might injure you is the degree to which you will do your development abroad."

FDA officials admit that the problem is perennial. "We really have a government-in-the-sunshine process where what we do is available for the public to look at through the Freedom of Information Act," says Halperin. "Many of these things are not available until after a decision about a drug is made. Yet documents and data are available in the United States that are not available in other countries. In the United Kingdom it is just the opposite. They have an Official Secrets Act."

The lure of economic incentives, though not much discussed by industry spokespersons, figured quite clearly in the remarks of several FDA officials and academic pharmacologists. One university researcher noted that West Germany recently passed legislation that minimizes the cost of research risks. With it, all firms conducting pharmaceutical research pay into a central pool. Any compensation to patients or healthy volunteers injured in the course of clinical investigations are paid for out of this fund. He compared it to no-fault insurance. And an FDA official noted that in the United Kingdom pricing policy for drugs was linked to the amount of research a pharmaceutical firm did in that country, thus encouraging U.S. firms to do research there.

Does the flight of R & D to other countries lead to less pharmaceutical innovation in the United States—in short, does it help fuel the "drug lag"? Not if data developed overseas are eventually used here. It is too early, however, to say that such data will routinely influence the U.S. drug approval process. So far, foreign studies have been presented as pivotal evidence in only a few instances, and pharmaceutical companies are quick to point out that the studies were not always given much weight by the FDA.

Some say the flight of R & D has already contributed to the drug lag. William Wardell of the Center for the Study of Drug Development at the University of Rochester notes that about four times as many new drugs are introduced into Great Britain as into the United States. Recently resigned FDA Commissioner Donald Kennedy does not agree. He recently told the House subcommittee on science, research, and technology that, in terms of "therapeutically significant new chemical entities," there is not a lag. He noted that between 1975 and 1977 Great Britain approved about 26 significant new drugs while the United States approved 37.

Why hundreds of millions of dollars in pharmaceutical R & D are going overseas is clearly a complex question—especially in light of such limited hard evidence to help answer it. A host of economic and regulatory forces is obviously at work.

To hear some people tell it, however, the story is simple. Even though foreign economic factors clearly contribute to the shift of R & D overseas, one would never know it from some of the hue and cry raised over U.S. regulations. And not just from industry. "Federal regulations," says Gilbert McMahon, a clinical pharmacologist at the Tulane University School of Medicine, "have become so pervasive, picayune, and difficult that today 40 percent of all new drugs discovered in U.S. companies are first studied outside of the United States." He called it a "national tragedy."

—WILLIAM J. BROAD