FROM: M. REIMERS xcc Norm Latker (both sides) + ret.

PATENT BRANCH, OGC
DHEW

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The hidden cost of drug safety

Evidence that FDA rules to protect consumers gravely harm the industry

"The Food & Drug Administration regulates health policy, not economic matters. We do not pay any attention to the economic consequences of our decisions," says J. Richard Crout, director of the FDA's Bureau of Drugs. But economists are marshaling evidence to show that the economic effects of stringent regulation by the FDA are seriously hindering innovation by the pharmaceutical industry. And they are warning that passage of the proposed drug safety amendments of 1977 may well mean that regulation itself will become the nation's most serious health problem. The amendments would add yet another layer of regulation by limiting the sale of a new drug to a small group, which would be monitored for signs of adverse reactions before general marketing of that drug could begin.

Since the passage of the 1962 Kefauver-Harris amendments to the Food, Drug & Cosmetic Act of 1938, the FDA has seen its mandate as requiring more intensive efforts to protect consumers from potentially unsafe drugs. This in good part has led to an increase in the average time required for clinical study and agency approval from 2.7 years in 1966 to 6.6 years in 1973. Accordingly, the number of clinical study applications by drug companies fell to 41 in 1973, less than half the 85 filed a decade earlier. And the number of new drugs approved has averaged 17 a year in the post-Kefauver period, compared with more than three times that in the five years before the amendments were passed.

While not all of the sharp drop in drug innovation can be laid at the doorstep of regulation, economists argue that by ignoring the economic impacts of regulation the FDA is having a devastating effect on the drug industry. As they point out:

- The rate of return on research and development has plummeted, perhaps to one-third its 1960 level, and companies are therefore cutting back on research projects. So, while the nation clamors for better health care, the major source of cost-effective care—the development of new and better drugs—is being seriously undermined.
- Since 1960 the costs of discovering and developing a new drug have soared eighteenfold, with about half the increment attributable to FDA regulation. Smaller companies are being priced out of the market, and an important source of innovation is fast disappearing. And even large companies are moving their R&D efforts overseas to take advantage of the less stringent regulations there.

Development costs. David Schwartzman of the New School for Social Research is the economist who is creating quite a stir over his work on the expected rate of return for drug R&D. In his just-published book, *Innovation in the Pharmaceutical Industry*, for which Pfizer Inc. provided some financial assistance, he estimates that drug companies on the average are earning only 3.3% after taxes on their R&D spending. This 3.3%, he finds, contrasts sharply with an almost 12% aftertax return that they enjoyed in the early 1960s.

To calculate an expected rate of return on the total costs of developing the new drugs that were introduced between 1966 and 1972, Schwartzman estimates the R&D expenditures that went into producing them and the current and future profits that they will generate. Assuming a 30% pretax profit margin and a 15-year commercial life, he estimates a net profit of $1.4 million a year for each drug. He puts the average cost of discovery and development at $24.4 million, or $12.2 million after taxes, which is spread over a 10-year estimated development period. This works out to an expected aftertax rate of return of 3.3% on R&D investment, according to Schwartzman.

Even when he uses a higher gross profit margin and a longer commercial life, Schwartzman's computations produce rates of return that are still surprisingly low. At a 40% margin and 20-year life, for example, he estimates only a 7.5% rate of return. Based on the same assumptions, this compares with an 18.4% rate in 1960, when the average cost of R&D for an approved drug was only $1.3 million.

Says Schwartzman: "If the drug industry is to maintain its investment in R&D, the return it expects must be at least equal to that obtainable elsewhere. And it simply is not."

Irrelevant data. Schwartzman's study has come under sharp criticism from his fellow economists. Long-time FDA critic Sam Peltzman of the University of Chicago, who estimates that half of the eighteenfold increase in the cost of discovery and development is due to regulation, nevertheless says: "If the rate of return is so low, why do drug firms continue to invest in R&D?" Fredric M. Scherer, former chief economist of the Federal Trade Commission, and now at Northwestern University, puts it even more pointedly: "Either the drug companies are stupid or they know something that Schwartzman doesn't know." Scherer argues that Schwartzman is using historical data that are no longer relevant. "The very fact that R&D costs have soared has engendered new and adaptive measures by the drug companies, which means that the old gross margins are no longer applicable in estimating the expected rate of return on new R&D expenditures," he says.

Schwartzman, however, does not find the behavior of the drug companies all that baffling. Some companies think that they can do better than the industry average. Others have already invested huge sums in R&D and cannot economically discontinue their research activities. Still others are banking on a major breakthrough—another Valium—that may lead to a host of new innovations. Schwartzman insists that these expectations will only last in the short run. In the long run, the low rate of return spells, if not an absolute decline in R&D spending, then clearly a continued reduction in the number of research projects that companies undertake. "Some companies may have adapted to strict regulation, but that means putting their chips on projects that have the greatest chance of a payoff," he says. "Scores of projects that would have been undertaken in the early 1960s are no longer economical. And the big loser is the American public."

The right track. Although economists may question the precision of Schwartzman's rate-of-return estimate, they nonetheless agree that he is right about the downward course the rate has taken over the past decade. Says Duke University's Henry G. Grabowski: "It may not be 3.3%, but the rate has fallen sharply since the 1960s. And that poses a serious threat to drug innovation by the industry." *

Drug companies are close-mouthed about the number of projects they are working on, but Dr. Lewis H. Sarett, senior vice-president for science and technology of Merck & Co., notes that his company reduced research projects 10% from 1969 to 1973, and over the last 10 years three major drug companies showed a 15% to 25% shift away from basic research toward development. Furthermore, while total R&D expenditures have increased by 50% during the past five years in inflation-bloated dollars, the development cost for a single drug, according to the experts, has risen by more than 225%. This means that the industry has sharply curtailed its research projects. "There's no doubt

Grabowski: 'Research is a game that the smaller firms can no longer play'

about it," says Harold A. Clymer, retired vice-president for research at SmithKline Corp. "In the U. S. the industry has cut back."

The FDA claims that the sharp decline in innovation in the post-amendment period, as measured by the number of new drugs approved, is not a consequence of more FDA regulation, but is rather in large part due to the depletion of opportunities caused by rapid innovation in the 1950s. As FDA Commissioner Alexander M. Schmidt puts it: "In many areas of biomedical knowledge, we are on a plateau. We have temporarily exhausted the exploitation of known concepts and tools."

Declining innovation. Economic evidence indicates this explanation is wanting. A recent study by Grabowski and his colleagues John M. Vernon and Lacy Thomas shows that while R&D productivity declined about sixfold in the U. S. between 1960 and 1971, the decrease was only half as great in Britain, even though regulation there was also tightened over that period. The Duke economists, therefore, "attribute the more rapid decline for the U. S. to differences in regulatory procedures associated with the 1962 amendments."

Not only has there been a decline in innovational output by the drug industry, but this output has become more concentrated in the largest drug companies. In a study to be published in the February issue of the *American Economic Review*, Grabowski and Vernon show that between 1957 and 1961, the four largest drug companies' share of what they call innovational output—the sales of new drugs during the first three years after introduction—amounted to 24% of the total industry's innovational output. Between 1967 and 1971 this share jumped to 48.7%. Says Grabowski: "The sources of innovation are declining. With the costs of developing a new drug soaring, research is a game smaller firms can no longer afford to play."

The FDA claims that the only drugs it is keeping off the market are those that are either unsafe or of little therapeutic value. However, such noted pharmacologists as Louis Lasagna and William M. Wardell, professors of pharmacology and toxicology at the University of Rochester School of Medicine, have documented that scores of drugs used successfully in the U. K. for many years, like all but one of the "beta-blockers" used in cardiovascular therapy, are still not available in this country. Say Lasagna and Wardell: "The FDA's definition of protection is hopelessly myopic, since the public is only being protected from drug hazards and not from disease and discomfort."

Running away. During the past five years, there has been a marked shift of R&D dollars overseas. While domestic R&D expenditures have grown at an annual rate of only 2.3%, adjusted for inflation, expenditures by U. S. companies abroad have risen at an annual 19% rate. Clymer argues that this shift is mainly due to an adverse regulatory climate in the U. S., and that it seriously threatens the leadership of the domestic-based R&D activities of the technology-intensive U. S. pharmaceutical industry.

'The FDA has gone too far,' says Scherer, former chief economist of the FTC

Economists of all ideological persuasions seem to agree that the FDA and Congress are overregulating the drug industry. Even liberal Scherer says, "The FDA has gone too far." Ironically, in its testimony before Congress last year, the drug industry favored adding the regulation that once a drug is approved it can temporarily be sold only to a restricted group because this might lead the FDA to give quicker approval to new drugs. Based on the FDA's past performance, however, most economists view the proposed drug safety amendments as another handicap to the industry's ability to innovate.

Scherer, like Grabowski and Schwartzman, would like to see a two-tier market: FDA-approved drugs coexisting with not-yet-approved drugs. This would allow the patient and his doctor greater freedom in choosing what drug to use. "I would not prohibit a company from selling a drug just because it can't get some bureaucrat to put his stamp of approval on it," says Scherer. "The bureaucrat is so worried about safety and keeps asking for more proof. He fails to consider that there may be people out there dying for want of the drug." ■