

INNOVATION AND INVENTION

Consumer Protection Regulation in Ethical Drugs

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A number of studies by economists have emphasized that government regulation often produces undesirable or unintended side effects. In this paper, we examine some effects of this nature on the structure of innovation in the pharmaceutical industry.

In the first section of the paper, we review recent changes in the regulatory environment in ethical drugs and show that they have been a major factor leading to higher costs and risks in pharmaceutical innovation. In the second section, we show that significant shifts have also occurred in the structure of innovation in this industry. Namely, innovation has become more concentrated in large multinational drug firms. These firms are apparently in a better financial position to deal with the higher costs and risks of innovation and also can shift resources on a worldwide basis to offset some of the adverse impacts of regulations in this country. Some evidence concerning these international transfers is presented in last part of the paper.

I. The Effects of Regulation in Ethical Drugs on the Costs and Risks of Innovation

In 1938, with the passage of the Food, Drug and Cosmetic Act, Congress authorized the Food and Drug Administration (*FDA*) to perform a premarket safety review of all new drug compounds. Despite these new regulatory controls, innovation in ethical drugs flourished over the next two decades. Several notable therapeutic advances were achieved in antibiotics, psychotropic medicines and other fields. Fur-

thermore, drug industry *R & D* expenditures increased dramatically along with the annual volume of new chemical entities (*NCEs*) introduced commercially. While the premarket safety reviews of the *FDA* obviously resulted in time lags for all drugs and deterred some new drugs from the marketplace, regulatory review times were still quite short (7 months on average) and the annual volume of *NCE* introductions was at record levels (over 50 per year) at the end of the decade of the 1950's. (See Grabowski, 1976, Ch. II.)

In the early 1960's, following the thalidomide tragedy, *FDA* regulation of ethical drugs became much more stringent in character. A major factor in this regard was the passage by Congress in 1962 of the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act. This new law required firms to demonstrate the efficacy as well as safety of all new drugs to the *FDA* and also imposed regulatory controls on the clinical research process and on drug advertising and labeling.

One would expect the more stringent regulatory environment that evolved after 1962 to have some adverse effects on costs, risks and development times of new drug innovation. In fact, a number of studies have indicated that significant shifts took place in the economics of new product innovation in ethical drugs in the post-amendment period. In particular, studies by V. A. Mund, L. H. Sarett and others indicate that development costs and times increased severalfold after 1962. By the early 1970's, Sarett estimated that the introduction of an *NCE* required more than ten million dollars in development costs and a gestation period of 8 to 10 years in length. In addition, data developed by

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W. Wardell and L. Lasagna indicate a high attrition rate on new drug candidates in the post-amendment period. This is reflected in the fact that less than ten percent of the drugs entering clinical testing on humans after 1962 have become commercially available drugs. These adverse developments on the input side have been accompanied by a sizeable decline in the annual rate of *NCE* introductions in the post-amendment period. (See Table 1.)

While there is little argument that innovational activity in ethical drugs has been characterized by significant adverse structural trends, there has been considerable debate about the role of regulation in explaining this situation. Previous studies by Martin Baily and Sam Peltzman indicate that the 1962 Amendments had a strong negative effect on the rate of drug innovation. However, their analyses have been criticized by the *FDA* and others for not adequately discriminating between the impacts of regulation and other factors (see the discussion in Grabowski, 1976). An alternative hypothesis advanced in the literature is that a "depletion of research opportunities" has occurred in ethical drugs as a result of the rapid rate of innovation in the earlier postwar period; and that this has produced the adverse trends attributed to regulation.

In a recently completed study, we have attempted to disentangle the effects of regulation from nonregulatory factors like research depletion, through a comparative international study of the United States and the United Kingdom (Grabowski, Vernon and L. Thomas, 1976). International comparative analyses would seem to offer one of the most promising methodological approaches for analyzing this question. This is because a depletion in basic research opportunities influences innovational activities in all countries in a common way, whereas regulatory procedures have differed considerably across countries. This type of analysis therefore offers one of the closest things available to a natural experiment for distinguishing between these two hypotheses. Of course one must also recognize the multinational character of the firms in this industry in structuring this type of comparative international analysis.

Our comparison of the United States and *U.K.*

focuses on the number of *NCEs* discovered and developed in each country, per dollar of *R & D* investment, in both the pre- and postamendment period. We found both countries experienced significant increases in the total *R & D* investment expenditures necessary to produce an *NCE* in the postamendment period. However the increase was relatively greater in the United States, where regulatory controls were much more extensive. On the basis of a production function analysis using these data, we estimated that increased regulation, by itself, roughly doubled the cost of producing and introducing an *NCE* in the United States in the postamendment period.

In summary, our analysis (along with several other studies) points to increased regulation as an important factor underlying the higher costs and risks of drug innovation in the United States.

II. Structural Changes in Drug Innovation

In this section we examine various supply side shifts and structural changes that have occurred as an apparent consequence of the much higher costs and risks of drug innovation in the United States (see also Grabowski and Vernon).

A. Innovation and Firm Size

The first issue we consider is whether innovation has become more concentrated in fewer and larger firms. Some data on this question are presented in Table 1. The first two rows show the total number of *NCEs* and the number of firms having at least one *NCE* over three successive five-year periods, 1957 to 1961, 1962 to 1966, and 1967 to 1971. These data clearly show that the number of independent sources of new drug introduction has declined significantly over time, along with the rate of total introductions.

The third row of Table 1 gives the dollar value of "innovational output" in each period. This is the total number of *NCEs* introduced in each period, weighted by their sales during the first three years after introduction. This measure of innovation, like the simple count of *NCEs*, also shows a significant downward movement over time. Table 1 next presents 4-firm and 8-firm concentration ratios of innovational output. These data indicate that the leading

innovative firms have been accounting for increasing percentages of total innovation in successive periods, and reinforce the point that the number of independent sources of innovation is declining.

The final question considered in Table 1 is whether innovation has become more concentrated in the largest drug firms. The last two rows show the share of innovational output and the share of total drug sales accounted for by the four largest drug firms (ranked by ethical drug sales) for each of these 5-year periods. Thus, in the preamendment period, 1957-61, and in the first postamendment period, 1965-66, the largest four firms accounted for a roughly equal amount of innovational output and sales. In the final period, however, the four largest firms accounted for 48.7 percent of innovational output, which was much greater than their share of sales (26.1 percent).

TABLE 1—CONCENTRATION OF INNOVATIONAL OUTPUT IN THE U.S. ETHICAL DRUG INDUSTRY

	Periods		
	1957-61	1962-66	1967-71
(1) Total Number of New Chemical Entities (NCE's)	233	93	76
(2) Number of Firms Having an NCE	51	34	23
(3) Total Innovational Output ^a (millions \$)	\$1,220.3	\$738.6	\$726.8
(4) Concentration Ratios of Innovational Output:			
4-firm	46.2	54.6	61.0
8-firm	71.2	78.9	81.5
(5) Four Largest Firms' Share of Innovational Output	24.0	25.0	48.7
(6) Four Largest Firms' Share of Total Sales	26.5	24.0	26.1

Sources: List of new chemical entities obtained from Paul de Haen *Annual New Product Parade*, various issues; all data on ethical drug sales from intercontinental Medical Statistics.

^aInnovational output is measured as new chemical entity sales during the first three full years after product introduction

These findings were also consistent with a polynomial regression analysis of innovational output on sales for 51 drug firms for the three periods. In the first two periods, a linear relationship between innovational output and sales offered the best statistical fit whereas in the third period a cubic relation offered the best fit, with innovational output increasing at an increasing rate over the upper range of size. Two regressions from our analysis are given below. Equation (1) is the linear regression for the preamendment period and equation (2) is the cubic regression for the most recent period.

1957-61:

$$(1) \begin{cases} Y = 359.35 + .74 S, R^2/F = .51/50.52 \\ (.07) \quad (7.11) \end{cases}$$

1967-71:

$$(2) Y = -11467 + .94 S - .88 \times 10^{-5} S^2 + (1.67) \quad (3.17) \quad (3.19) \\ .25 \times 10^{-10} S^3, R^2/F = .64/20.7 \\ (3.81)$$

where: Y = innovational output (\$000); S = total ethical drug sales in middle year of period (\$000); and t -statistics are in parentheses

It is interesting to note that the cubic regression equation in the 1967-71 period contributed .19 incrementally to R^2 compared with a linear regression and .11 compared with a quadratic regression.

The hypothesis that the largest firms in an industry will be the dominant sources of innovation dates back to Joseph Schumpeter's pioneering analysis. However, most empirical studies (including those for the drug industry) have not provided much support for the Schumpeterian hypothesis. Nevertheless, the results reported here are quite consistent with the trends in pharmaceutical innovation discussed in the first section. Given the much higher costs and risks of drug innovation in the postamendment period, it is plausible that the structure of innovation would shift in the direction of the

Schumpeterian hypothesis.

B. Innovation and the Multinational Activities of Pharmaceutical Firms

The most innovative firms in the ethical drug industry are not only relatively large in terms of domestic sales, but also tend to have a strong multinational character. For example, the eight leading innovative firms in the 1967–71 subperiod (which accounted for over 80 percent of innovative output in that period) have a strong multinational orientation. Each of these firms had manufacturing plants in at least eight foreign countries, and seven of them has foreign sales in excess of 100 million dollars in 1970. While past studies of the Schumpeterian hypothesis have not considered this aspect of firm structure, it would appear to be highly relevant in the current context.

Multinational firms have some significant advantages in their ability to respond to the more stringent regulatory conditions that have evolved in this country. First, they can introduce new drug products into foreign markets (where regulatory conditions are less stringent) prior to (or in lieu of) introduction in the United States. This allows them to gain knowledge and realize sales revenues while a new drug compound remains under regulatory review and development in this country. While a firm with no foreign operations could in principle do the same thing through licensing, significant information and transaction costs exist in this situation to reduce the gains from a licensing arrangement.

In addition, multinational firms also can perform *R & D* activities in foreign countries in order to reduce time delays and the overall costs of developing new products. Some important institutional barriers do exist to this strategy however. Historically, the *FDA* has been unwilling to accept data from foreign clinical trials or patient experiences. Because of this, *U.S.* firms have incentives to perform their *R & D* in this country, even if they choose to introduce their new drugs first and in greater numbers abroad. Nevertheless, it should be borne in mind that only a small fraction of compounds entering

clinical testing in the United States ever become commercial products (as noted above, Wardell and Lasagna indicate this fraction is now less than 10 percent). Multinational firms therefore have the option of screening new drugs abroad and performing duplicate *U.S.* trials on the relatively small fraction of drugs for which New Drug Applications are submitted to the *FDA*. They also can perform different phases of development alternatively here and abroad in order to reduce regulatory lags and bottlenecks.

Some descriptive statistics serve to illustrate the extensive shifts that have occurred in the behavior of multinational firms with respect to foreign introductions and clinical testing over the postamendment period. In Table 2, data on all *U.S.* discovered drugs introduced in the United Kingdom over the period 1960–1974 have been assembled in order to consider whether *U.S.* discoveries are now being introduced there before here. A *U.S.* discovered drug is defined as one originating in a *U.S.* laboratory.

Table 2 shows that in the early 1960's, the vast majority of *U.S.* discovered *NCEs* introductions in the *U.K.* become available there only after here. However, a rather dramatic shift in this situation has occurred over time. By the final subperiod, 1972–74, approximately two-thirds of the United States discovered *NCE* introductions in the *U.K.* were either introduced later, or have yet to become available, in the United States. Preliminary analysis of data on France and Germany suggest similar patterns.

The shift in firm behavior depicted in Table 2 would seem to be strongly tied to regulatory differences in these countries. We might also point out that the *U.S.* firms share of *U.K.* total ethical drug and new product sales declined in the post-1962 period (Grabowski and Vernon), thus amplifying the incentives operating on firms to modify their traditional practices of introducing new products abroad only after *U.S.* introduction.

It would seem important to note that the behavior of pharmaceutical firms in recent years represents a significant departure from the pre-

TABLE 2—INTRODUCTION OF U.S. DISCOVERED DRUGS IN THE UNITED KINGDOM, 1960–74

Period	Number of <i>NCE</i> Introductions in <i>U.K.</i> of <i>U.S.</i> Origin ^a	Number (Percent) of these <i>U.S.</i> Discovered <i>NCEs</i> :			
		In <i>U.S.</i> Before	In <i>U.S.</i> Same Year	In <i>U.S.</i> Later	Not In <i>U.S.</i>
1960–62	57	38 (66.6)	13 (22.8)	5 (8.7)	1 (1.8)
1963–65	33	16 (48.4)	5 (15.1)	10 (30.3)	2 (6.1)
1966–68	24	10 (41.6)	4 (16.7)	8 (33.3)	2 (8.3)
1969–71	21	9 (42.8)	4 (19.0)	3 (14.2)	5 (23.8)
1972–74	28	8 (28.5)	2 (7.2)	6 (21.4)	12 (42.9)

Sources: Information on *NCE* introductions in the United Kingdom and the origin of each *NCE* introduction were obtained from data compiled by Paul de Haen, Inc., and the National Economic Development Office of Great Britain. In cases of conflict between these two sources on the country of origin, the drug was not included in the above sample of *U.S.* discovered introductions.

^aDrugs of *U.S.* origin defined as an *NCE* discovered in *U.S.* research laboratory.

dictions of the product life cycle trade theory proposed by Raymond Vernon and others. Not only are these new drug innovations being introduced first in foreign countries with much smaller markets than the United States, but they must also be produced in their initial stages of product life in foreign plants as well. This is because *U.S.* regulatory law prohibits drugs not yet cleared by *U.S.* authorities from being exported to foreign countries. Indeed, this provision of the law would appear to provide substantial incentives for direct foreign investment by *U.S.* firms.

Data recently developed by Lasagna and Wardell also suggest some significant shifts have taken place in the location of clinical testing by *U.S.* firms. They have recently completed a study of the new drug compounds clinically tested by 15 large *U.S.* ethical drug firms over the period 1960 to 1974. (These firms accounted for 80 percent of *R & D* expenditures in the United States.) Their results suggest an increasing tendency for *U.S.* firms to perform clinical testing of new drug compounds first in foreign locations. Specifically, they found that in 1974 these firms clinically tested approximately one-half of all their new drug compounds

first abroad, whereas before 1966, they performed virtually all their clinical testing first in the United States. Although industry *R & D* expenditure data indicate that the percentage of total *R & D* outlays expended in foreign countries by *U.S.* firms is still small (15.4 percent in 1974), foreign outlays are growing much more rapidly than domestic expenditures and this percentage has doubled in the space of a few years (Grabowski, Ch. III).

In summary, the data analyzed in this section indicate that *U.S.* based multinational firms are increasingly testing and marketing new chemical entities abroad before the United States. As discussed above, the option to engage in such foreign activities offers multinational firms significant advantages in dealing with the more stringent regulatory situation that has evolved in this country. It is therefore perhaps not surprising that large multinational firms now account for such a dominant share of innovation in the *U.S.* ethical drug industry.

III. Summary and Conclusions

Our results indicate that *FDA* regulation of ethical drugs has had some significant adverse effects on the structure of pharmaceutical inno-

vation. In effect, the higher costs and risks of drug innovation in the more stringent post-1962 regulatory environment have operated as a barrier to competition through new product introduction. Consequently, the supply of new drugs has not only declined, but it has also become more concentrated over time in the larger multinational firms better able to deal with this more stringent environment. Given the rapid spread of health and safety regulation controls throughout all sectors of the economy, further attention to the adverse effects of regulation on industry competitive structure would seem highly desirable. They constitute a potentially important source of long-run indirect costs to society that must be weighed against the benefits of these new regulatory controls.

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