Proceedings of the Third Seminar
on Pharmaceutical Public Policy Issues

IMPACT OF PUBLIC POLICY ON DRUG INNOVATION AND PRICING

Edited by:
Samuel A. Mitchell
Emery A. Link

2

The Effects of Regulatory Policy on The Incentives to Innovate: An International Comparative Analysis

HENRY G. GRABOWSKI, JOHN M. VERNON
and LACY GLENN THOMAS

The rate of new product and process innovation in an economy is a key determinant of its performance. As new products are developed to satisfy existing and potential demands and new processes are discovered to implement existing production techniques, an economy moves forward generating increases in real output and income per capita. Various studies by economists at the macro-economic level have pointed to innovation as the most important factor underlying the rising long-run growth in output per capita in the U.S. economy. They have estimated that between a third and a half of the total growth in real output per capita has been accounted for by product and process innovation.[1]

Innovation in the pharmaceutical area has particular significance because of its key role in improving the quality of human life and health. In this regard, pharmaceutical innovation is best seen as an integral part of a rapidly progressing technology of health. There are numerous examples where new pharmacological agents have produced enormous therapeutic benefits in the treatment of particular illnesses. It is also important to recognize that the cumulative advance in drug therapy, which often occurs in small incremental advances, has provided a relatively low-cost means of treating disease and producing good health. This is important because the

[1]See for example the analysis of this question in Edward F. Denison, *The Sources of Economic Growth in the United States and the Alternatives Before Us.* (New York: Committee for Economic Development, 1962).

health sector in general is characterized by scarce and expensive professional manpower, labor intensive activities and complex technical equipment — all contributing to a very high rate of cost inflation in health services over recent years. By contrast, the costs of ethical drugs have accounted for a relatively small percentage of total health costs and have been a relatively stable element in the presence of rapidly rising costs elsewhere in the health sector.

While a number of private and public institutions clearly contribute to technological advances in the pharmaceutical area, the ethical drug industry historically has played a central role in the actual discovery and development of new product introductions in the U.S. and elsewhere. This is confirmed by a number of studies that have formally studied the sources of pharmaceutical innovation. All have found that the majority of new chemical entities introduced into the U.S. over the post-war period have been discovered and developed by private ethical drug firms. This general result also holds when one focuses only on the class of "important" advances as ranked by physicians or medical experts.[2]

It is also true, however, that innovation in the ethical drug industry in recent years has been characterized by a number of adverse structural developments. In particular, there has been a sharp decline in the rate of new product introductions and the incentives for engaging in R & D activity have been negatively influenced by rapid increases in the costs and risks of developing new products. While there is little debate about the existence of these adverse trends, there is considerable controversy about the factors producing them. One position is that the increased regulation of the industry has been largely responsible for the declining rate of innovation and the related observed phenomena. An alternative hypothesis is that the industry has experienced a depletion of research opportunities.

In this paper, we present some new evidence on these alternative hypotheses regarding the decline of new product innovation in ethical drugs. Our new evidence is based on a comparative analysis of developments in the U.S. and U.K. In effect, we attempt to separate the impacts of increased regulatory controls in the U.S. from other factors such as research depletion by using the U.K. industry as a control. Since firms in the latter country have been governed by a very different regulatory system but are subject to

[2]The sources of innovation in the ethical drug industry have been examined in independent studies by Schnee, Schwartzman and Duetsch with basically similar findings; See Jerome E. Schnee, "Innovation and Discovery in the Ethical Pharmaceutical Industry" in Edwin Mansfield, *Research and Innovation in the Modern Corporation* (New York: W. W. Norton, 1971); David Schwartzman, *The Expected Return from Pharmaceutical Research* (Washington, D.C., American Enterprise Institute for Public Policy Research: 1974) and L. L. Deutsch, "Research Performance in the Ethical Drug Industry", *Marquette Business Review*, Fall 1973, pp. 129-43.

similar research depletion effects as U.S. firms, we feel that a comparative analysis is a very fruitful way of approaching this question.

The paper has the following plan. First, as background to our analysis, we discuss in detail the various inter-related structural changes that have characterized new product innovation in ethical drugs. We then review past empirical studies that have attempted to explain the causes of declining levels of new product introductions in the U.S. A model previously developed by Martin Baily[3] for this purpose is reformulated and employed in our comparative analysis of the U.S. and U.K. industries. In addition to analyzing the factors accounting for declining levels of innovation in ethical drugs, we also investigate the extent to which innovation is becoming concentrated in fewer and larger firms in both the U.S. and U.K. industries. The contrast in the trends observed for the two countries in this area provides further insights into the impacts of research depletion and increased regulation on innovational activity in ethical drugs.

I. Structural Changes in Pharmaceutical Innovation

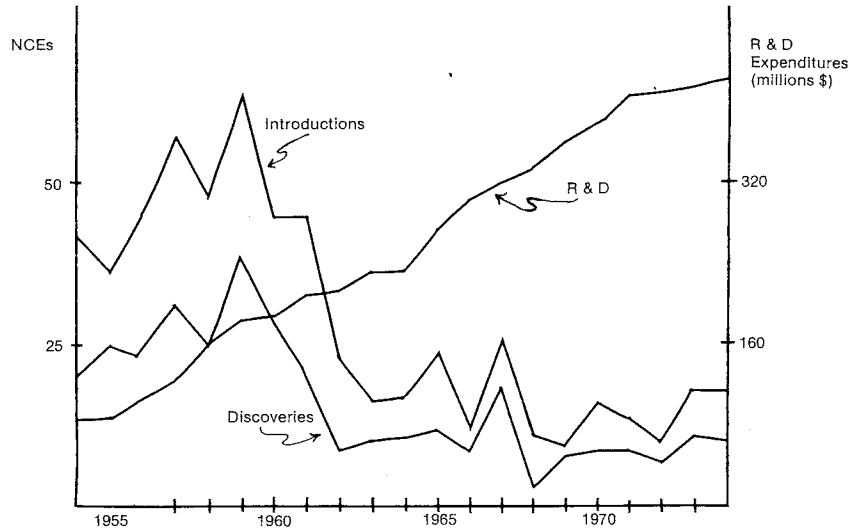
A number of developments attest to the fact that innovation in the pharmaceutical industry has undergone some rather fundamental structural changes over recent years.

A. The Rate of New Product Innovation

First of all, the annual number of new product introductions has declined significantly. This is illustrated in Figure 1. It shows the total new single chemical entities (NCE's) introduced annually into the U.S. over the period 1955-74 as well as the subset of introductions in each year that were discovered in the U.S. by the pharmaceutical industry.[4] New chemical entities are the most important category of new products because they represent new compounds not previously marketed and include all significant new therapeutic advances. Other new products involve combinations of existing products, new dosage forms or brand names.

[3]Martin N. Baily, "Research and Development Costs and Returns: The U.S. Pharmaceutical Industry", *Journal of Political Economy*, Vol. 80, January/February 1972, pp. 70-85.

[4]Data on NCE's and their years of introductions were obtained from Paul de Haen. Biologicals and diagnostics were deleted from the analysis. Information on the country of discovery was also obtained from de Haen and other supplementary sources. An NCE is regarded as discovered in a particular country if the research laboratory producing the entity was located in that country irrespective of the nationality of laboratory ownership. See the statistical appendix for details on the procedures used in this paper in this regard.



Introduction and Discoveries of New Chemical Entities by Domestic Firms and Constant (1958) Dollar Expenditures on Pharmaceutical Research and Development, the United States 1954-1974

Figure I

After reaching a peak in the late fifties and early sixties, the annual rate of NCE introductions has declined sharply. The rate of introductions over the most recent five year period, for example, is less than one-third the rate prevailing in a similar period a decade ago. A similar pattern characterizes NCE introductions discovered in the U.S. by the pharmaceutical industry.

New chemical entities of course are not homogeneous commodities. The sharp downward trend in the absolute level of NCE's could be a misleading indicator of new product innovation if the NCE's introduced over recent periods, while fewer in number, are of greater value than formerly was the case. Some data relevant to this question are presented in Table 1. In particular we investigate the market sales performance of NCE introductions in the U.S. over the period 1957 to 1971. We have grouped the data into three five year sub-periods for comparative purposes.[5]

The first column of data shows the total number of NCE's introduced in each period. There is a decline from 233 NCE's in the first period, 1957-1961, to 76 in the last one, 1967-1971. The second column shows annual domestic sales per NCE averaged over their first full three years of product life. While

[5]The choice of period here was dictated by the availability of sales data (no data were available prior to 1957) and the three year weighting procedure employed in the text. The sales data were obtained from Intercontinental Medical Statistics. The nature of these data are discussed in the statistical appendix.

the figures indicate that there has been an increase in average sales per NCE over each successive period, the increase is little more than commensurate with the general rate of market growth experienced by the pharmaceutical industry as a whole. In this regard the third column shows the aggregate (annualized) value of sales for all the NCE's introduced into each of the five year periods as a percentage of total sales of ethical drugs measured at the end of each period. This provides a rough measure of the importance of new versus old drugs. This figure declines from 20 percent in 1957-1961 to 5.5 percent in 1967-1971, a decline that is roughly proportional to the total number of NCE's (233 to 76) between the first and last period.

It is therefore difficult to conclude on the basis of market sales and share data that the NCE's introduced over more recent periods are of significantly greater value than formerly were the case. Rather Table 1 underscores the extent to which new product innovation has declined as a competitive factor in the total ethical drug market.

Table 1

Number of Sales of New Chemical Entities in the Pre and Post Amendment Period in the U.S.

Period	Total Number of New Chemical Entities (NCE's)	Average Annual Sales per NCE (During First 3 Years)	Sales of NCE's as a percent of total Ethical Drug Sales[1]
1957-1961	233	$1,745,000	20.0
1962-1966	93	$2,657,000	8.6
1967-1971	76	$3,187,900	5.5

[1]Average annual sales of all NCE's introduced during this period as a percentage of total ethical drug sales in the last year of the period.

Data Sources: Lists of New Chemical Entities in each year obtained from Paul de Haen *Annual New Product Parade*, various issues; all information on ethical drug sales obtained from Intercontinental Medical Statistics.

B. The Costs of Pharmaceutical Innovation

In Figure 1, annual R & D expenditures of the pharmaceutical industry for human ethical drug products are also plotted over time. Figure 1 shows that over the same time frame in which NCE's have significantly declined, industry R & D expenditures have increased severalfold. The trend in these

industry aggregates seem to imply that there has been a rather formidable increase in the costs of producing an NCE over time.

A number of studies that have formally analyzed the costs of innovation in the pharmaceutical industry support this hypothesis. For example, a recent study by Dr. Lewis Sarett[6] suggests that over the decade 1962 to 1972, development costs per NCE rose from 1.2 to 11.5 million dollars. This is an order of magnitude increase. In addition, he suggests that total development and clearance times for an NCE were $7^{1}/_{2}$ to 10 years in 1972 as opposed to $2^{1}/_{2}$ years in 1962. These large shifts in magnitude for development costs and times are supported in earlier independent investigations by Clymer and Mund.[7]

In addition, there also appears to be a corresponding increase in the risk and uncertainty associated with innovational activity. One measure of risk in this industry is the attrition rate for compounds that undergo clinical testing but fail to become commercial products. While there is little data publicly available on this question, Clymer and others have hypothesized on the basis of case studies that the attrition rate of clinically investigated drugs has significantly increased. Clymer estimates that in the 1950's, the attrition rate of drugs undergoing clinical tests was two out of three. The best estimate of the current situation appears to be that less than one of every ten new compounds entering IND trials become new products.[8]

In sum, data from a number of sources indicate that innovational activity in the pharmaceutical industry has been characterized by adverse structural shifts in a number of dimensions. On the input side, total development costs and times have increased. Furthermore, innovation has become subject to greater risks and uncertainty. On the output side, the annual rate of new chemical entities has declined in absolute terms and NCE's now account for a correspondingly smaller share of total market for ethical drugs. All of these trends appear related to or symptomatic of a more fundamental underlying change in the innovational process. In addition, all point to a weakening of the incentive for private investment in innovational activity in the U.S. pharmaceutical industry.

[6]L. H. Sarett, "FDA Regulations and Their Influence on Future R & D", *Research Management* (March, 1974), p. 18-20.

[7]Harold A. Clymer, "The Changing Costs and Risks of Pharmaceutical Innovation" and Vernon A. Mund, "The Return on Investment of the Innovative Pharmaceutical Firm", in Joseph D. Cooper, ed. *The Economics of Drug Innovation* (Washington, D.C.: American University, 1970).

[8]On this question see the papers by Clymer, "The Economic and Regulatory Climate: U.S. and Overseas Trends", and by Lasagna and Wardell "The Rate of New Drug Discovery" in Robert B. Helms, *Drug Development and Marketing* (Washington, D.C. American Enterprise Institute for Public Policy Research, 1975). Lasagna and Wardell in particular present some data (from a questionnaire survey of 15 large research oriented firms) that indicate only 7.1 percent of all NCE IND's filed by these firms between 1963 and 1967 had become approved NCE by April 1974 (the date of their study).

C. Further Implications

A number of further developments have occurred that are consistent with, and appear to follow directly from the structural changes discussed above. First, the rapid rate of growth in domestic R & D expenditures by the pharmaceutical industry that characterized the fifties and sixties has now ceased. The growth in real terms may even be negative. Second, and related to the first point, U.S. firms are beginning to perform an increasing percentage of their R & D abroad. Finally, innovation has become concentrated in fewer and larger firms. We shall comment briefly on each of these points.

Declining Growth Rates for Domestic R & D and Shifts in R & D Abroad

In Table 2, domestic R & D expenditures for human ethical drugs, measured in current and constant dollars, are presented for the period 1960-1973. Because no direct measure of the rate of inflation for pharmaceutical industry R & D inputs is available, we used the GNP implicit price deflator to transform current R & D expenditures to constant dollar terms. Since it is generally acknowledged that the rate of inflation characterizing R & D activity has exceeded the general economy wide rate, this constant dollar measure undoubtedly overstates the level and growth of real R & D expenditures, particularly over the most recent periods when the inflation rate has been more pronounced in nature.

Since 1970, our constant dollar measure indicates that the rate of growth has been a little less than 2 percent. The true rate of growth over this period could even be negative given the upward bias that arises from using the GNP price deflator. In any event the rate of growth in real domestic R & D expenditures has declined severalfold from the very high growth rates prevalent in the late fifties and sixties.

The declining rate of growth in domestic R & D over recent years would appear to signal a shift of resources by ethical drug firms into alternative investment activities offering a more promising rate of return. This has in turn taken the form of both increased diversification outside ethical drugs as well as shifts in pharmaceutical R & D activity abroad.

While the evidence concerning increased diversification across domestic activities arises largely from case studies, data on foreign R & D performance of U.S. firms have been systematically collected since 1961. These data are presented in Table 2. They show that foreign R & D expenditures of U.S. firms have historically been small (less than ten percent) relative to total domestic R & D outlays. However, in recent years foreign R & D

Table 2

Domestic and Foreign R & D Expenditures of U.S. Ethical Drug Firms, 1961-1973

Year	Domestic R & D in Current Dollars[1] (Million)	Domestic R & D in Constant Dollars[2] (Million)	Foreign R & D of U.S. Firms in Current Dollars[3] (Million)	Foreign R & D of U.S. Firms to Total Domestic R & D
1961	215.9	206.4	11.4	5.3
1962	224.8	212.5	13.0	5.8
1963	248.2	231.6	18.9	7.6
1964	254.3	233.6	24.0	9.4
1965	304.2	274.4	24.5	8.0
1966	344.2	302.0	30.2	8.8
1967	377.9	321.4	34.5	9.1
1968	410.4	335.6	39.1	9.5
1969	464.1	362.0	41.7	8.9
1970	518.6	383.5	47.2	9.1
1971	576.5	407.9	52.3	9.1
1972	600.7	411.1	66.1	11.0
1973	643.8	417.2	108.7	16.9

Notes:
[1]Company financed R & D outlays for human use pharmaceuticals expanded in U.S. by all PMA member firms.
[2]Data in column 1 converted to 1958 base by GNP price deflator.
[3]Company financed R & D outlays for human use pharmaceuticals expended by U.S. PMA member firms in foreign countries.

Source: Pharmaceutical Manufacturers Association *Annual Survey Reports*, various issues.

expenditures by U.S. firms have grown at a much more rapid rate than domestic expenditures. Over the period 1971 to 1973, for example, U.S. firms' foreign expenditures more than doubled.

From an economic standpoint, the incentives to shift R & D activity abroad could be provided by lower development costs and times as well as greater market opportunities for new products in foreign countries. There is evidence to suggest that both factors have influenced firm decisions. On the demand side, for example, Clymer[9] has shown that the aggregate sum of peak yearly sales of the NCE's introduced in the U.K. over the period 1966-72

[9]Clymer, ibid., p. 145-147.

were roughly equivalent to that of the U.S., even though the U.K. market is only one-seventh the size of U.S. market. On the cost side Sarett[10] has provided some rough estimates comparing the trend in development costs and times in European countries with those of the U.S. While he estimates that costs have significantly increased abroad since the early 60's, they remain considerably lower than those for the U.S. and the "gap" in R & D costs per NCE has been increasing.

In the section which follows, we perform a comparative analysis of R & D productivity in the U.S. and U.K. which provides some further insights into the incentives for firms to shift R & D abroad.

Concentration of Innovational Activity in Fewer and Larger Firms

On theoretical grounds, one would expect concentration of innovation to occur as the innovational process becomes costly and riskier in nature. This is because the minimum scale which R & D can be undertaken without exposing a firm to a high variance in earnings also will increase. In effect, a firm must pool a larger number of costlier projects to obtain a balanced total R & D portfolio that provides security against excessive risks of earnings fluctuations. Small firms with limited resource bases will have particular difficulty adapting to large shifts in costs and riskiness of R & D projects, unless they are especially confident about their comparative advantage in performing R & D. In addition, firms that are especially risk averse or ones with relatively lower expected returns fom R & D activities are also likely to transfer resources out of new drug development.[11]

Later in the paper we will present a detailed empirical analysis of the extent to which innovation in fact has become concentrated in fewer and larger firms. At this point, we note only that our analysis suggests some dramatic shifts have taken place in this respect. In effect, the number of independent sources of innovation has significantly declined over time as the costs and risks of producing an NCE have escalated.

II. The Effects of Regulation and Other Factors on Pharmaceutical Innovation

The explanation for the decline in new chemical entities introduced in the U.S. market has been the subject of much controversy. One position is that

[10]Sarett, op. cit., p. 18-19.
[11]A detailed theoretical analysis of this qustion is presented in our forthcoming paper, Henry G. Grabowski and John M. Vernon, "Structural Effects of Regulation in the Ethical Drug Industry", to be published in the *Festschrift in Honor of Joe Bain*, Ballinger Press, 1976.

there has been a depletion of research opportunities available to the industry, and that a return to the rapid rate of new product innovation of the fifties will require new research breakthroughs at a fundamental level. An alternative explanation is that the increased tightness of regulation required by the 1962 Amendment to the Food, Drug and Cosmetic Act has raised the costs and riskiness of new drug innovation. As a result, drug manufacturers have been unable to maintain the rate of innovation that prevailed in the fifties.

In this section we shall review the evidence supporting these explanations and report some new evidence that we have developed. Our new evidence primarily consists of a comparative analysis of the U.S. industry and the U.K. industry. The basic assumption is that while the depletion explanation should have affected the industries in both countries, the increased regulatory tightness that began in the U.S. in 1962 was not duplicated in the U.K. Hence, in principle, we should be able to use the U.K. industry as our "control group" in our attempt to identify the effect of regulation on the U.S. industry.

Before turning to some previous studies of this question, we should briefly explain the main changes that took place in FDA regulation as a consequence of the passage of the 1962 Amendments.

The 1962 Amendments

The 1938 Food, Drug and Cosmetic Act required all new drugs to undergo a pre-market approval process.[12] However, the 1938 Act was primarily concerned with the safety of new drugs. Under this law, the FDA further had to reject a new drug compound within a period of 180 days or the new compound was automatically approved for marketing by the manufacturer.

The 1962 Amendments extended the regulatory control of the FDA in several ways. First, it required firms to submit documented scientific evidence on a new drug's *efficacy* as well as its safety. This has normally led to a substantial increase in the number of tests that must be performed and submitted to the FDA. Second, the FDA was given discretionary power over the clinical research process. Thus, prior to any testing in humans, firms must now submit a new drug investigational plan (IND) which provides the results of animal tests and plans for human testing. Based on its evaluation

[12]The first law regulating drugs was actually the Food and Drugs Act of 1906 which prohibited adulteration and mislabeling of food and drugs sold in interstate commerce. Even within this narrow domain, implementation of this earlier law was plagued by a number of problems and proved generally ineffective. For an historical discussion see Clair Wilcox, *Public Policies Toward Business*, 3rd. ed. (Homewood, Ill., Ricard D. Irwin, 1966) pp. 587-589.

of the IND and subsequent reports of research findings, the FDA may delay or halt clinical testing. Finally, the new regulations provide for FDA approval of advertising claims.

Over the post-1962 period, therefore, there has been a significant increase in the degree and extent of regulatory controls on ethical drugs. Not only have the criteria for approval become more stringent, but the FDA also has become directly involved with the innovational process from the initial stages of development through the marketing of new drugs.

We shall now review briefly two studies that have sought the explanation for the reduced rate of new drug innovation.

The Peltzman Study

Peltzman's study was a cost-benefit analysis of the 1962 Amendments.[13] We shall restrict our review to only one part of his study: his analysis of the effect of the amendments on the rate and character of drug innovation.

A basic operating assumption in Peltzman's analysis is the supply of NCE's in any period will adjust over time to the expected market size and demand for prescription drugs. New drugs are treated as homogeneous commodities and shifts in demand are the exogenous variables to which this homogeneous supply of new drugs respond (with a lag). This is essentially a "demand-pull" model of technological change. It builds on the approach of Jacob Schmookler[14] who postulated that technological innovation generally followed demand rather than vice-versa. In his economic work, Peltzman uses moving averages of total out-of-hospital prescriptions and personal consumption expenditures on physicians services as demand variables determining the flow of new chemical entities in each period. His model also includes cumulative NCE's lagged one year as an explanatory variable.

A residual type approach is employed to calculate the impact of the 1962 Amendments. The model is first estimated on pre-amendment data (1948-1962) where it provided a relatively good fit of the data ($\bar{R}^2 = .80$).[15] The estimated coefficients from this regression are then used to predict what the number of NCE's would have been in each year in the absence of the 1962 change in regulations. The effects of the 1962 Amendments are then calculated as the residual difference in the predicted and actual flow of NCE's in each year in the post-amendment period.

[13]Sam Peltzman, "The Benefits and Costs of New Drug Development" in Richard L. Landau *Regulating New Drugs*, (Chicago: University of Chicago, 1973, pp. 113-212; also Sam Peltzman *Regulation of Pharmaceutical Innovation*): *The 1962 Amendments* (Washington, D.C.: American Enterprise Institute for Public Policy Research, 1974).

[14]Jacob Schmookler, *Invention and Economic Growth* (Cambridge: Harvard University Press, 1966).

[15]Peltzman, "Benefits and Costs", p. 124.

On the basis of this residual analysis, he presents the following results:

> I conclude from these data that: a) the 1962 Amendments significantly reduced the flow of new chemical entities and, what is perhaps more interesting, b) that all of the observed difference between the pre- and the post-1962 New Chemical Entities flow can be attributed to the 1962 Amendments.[16]

In effect, Peltzman's model suggests that the rate of innovation in the post-amendment period was more than halved as a result of the 1962 Amendments. However, his model never formally includes or considers any supply side factors relating to the depletion of scientific knowledge. Since the effects of regulation are captured only indirectly through a residual procedure in the post-amendment period, the effects of depletion of knowledge could obviously also be reflected in this residual if they are contemperaneous in nature. In effect, Peltzman does not investigate this latter possibility, even though Baily's analysis (to be described next) suggests it also has had a significant influence on the decline in NCE's since 1962.

The Baily Study

Baily's study made use of a "production function" model of drug development.[17] He postulated that the number of new chemical entities introduced by the industry in any period would be a function of i) past R & D dollars; ii) the stringency of FDA regulations; iii) the depletion of the stock of research opportunities available to the industry. Using this model, he analyzed the number of new product introductions for the industry over the period 1954 to 1969.

The model performed well and explained 95 percent of the variance in the ratio of industry NCE's to R & D expenditures. Both of the variables measuring regulatory "tightness" and the depletion of research opportunities had the postulated negative effect and were statistically significant. The regulatory variable had a large quantitative impact in explaining the observed decline in NCE's per R & D dollar invested. In particular, he found that the level of R & D expenditures necessary to generate a constant flow of new products was increased by a factor of 2.35 in the post-amendment period.[18]

A potential problem in the Baily analysis is that both the effects of regulation and research depletion were measured by proxy variables. Hence they are subject to considerable measurement error. The regulatory tightness

[16]Peltzman, ibid., p. 126.
[17]Martin Baily, op. cit., pp. 70-85.
[18]Baily, ibid., p. 77-78.

variable is captured by a simple intercept shift or "dummy" variable which takes on the value one over the post-1962 period and zero in the pre-amendment period. The depletion of research opportunities is measured by a lagged seven year moving average of NCE's introduced in the U.S. from all sources. It is quite possible that the effects of regulation and research depletion may be confounded when measured by these aggregate proxy variables in this time series analysis. The model also assumes there were no additions to the stock of knowledge over this period although a moving average formulation might implicitly capture some changes in this regard.

Since Baily's model at least conceptually provides a method for identifying the separate effects of regulation *and* depletion, we have re-estimated it with more recent data. Baily used data covering the period, 1954-1969, while we have employed data for the longer period, 1954-1974.

The estimated least squares equation for the 1954-74 period is:

$$(1) \qquad \log\left[\frac{N_t}{E_t}\right] = \underset{(2.21)}{-0.87} - \underset{(7.99)}{2.25\,D_t} - \underset{(0.22)}{.003\,P_t}$$

$$R^2 = 0.86 \qquad F = 56.3 \qquad D\text{–}W = 1.8$$

(t-statistics are in parentheses)

where: N_t = number of new chemical entities introduced and discovered by U.S. firms in year t

E_t = the average deflated R & D expenditure in the U.S. in t–4, t–5, and t–6, (it is assumed that there is a lag of 5 years from actual R & D to introduction)

D_t = a zero-one variable representing the effect of regulation (it equals zero through 1961 and unity thereafter)

$P_t = \frac{1}{7}\sum_{v=7}^{13} M_{t-v}$ where M_t is the total number of new drugs introduced from all sources (P_t is Baily's depletion variable)

Thus, Baily's model indicates that N_t/E_t, the number of NCE's discovered per dollar of expenditure, has been adversely affected both by the introduction of regulation in 1962 and by the depletion of research opportunities. As stated earlier, in Baily's own estimated equation for 1954-1969, both of the proxy variables for regulation, D_t, and depletion, P_t, were statistically significant. In our re-estimation for the longer period, the coefficient of the depletion variable has become statistically insignificant — though it does continue to have the expected negative sign. Furthermore, the explanatory power of our re-estimated equation has declined substantially from that obtained by Baily (the R^2 declined from 0.95 to 0.86).[19]

In view of these rather unsatisfactory results, we elected to re-examine Baily's proxy variable for depletion with the objective of devising a conceptually more appealing measure of this phenomenon. First, we should review Baily's own rationale for P_t more carefully:

> The variable P_t is a measure of the depletion of research opportunities. The research project is formulated six to seven years before introduction; thus, if a large number of new drugs were introduced in the period prior to this, we would expect some reduction in the number of directions for fruitful R & D. Variable P_t was therefore taken as a seven-year moving average of past total new drug introductions. . . . The variable added is rather one-sided in that depletion of opportunities is allowed for explicitly, while the flow of new knowledge opening up new opportunities is implicit. Some attempt was made to incorporate expenditure on pure medical research as a separate variable but without success.[20]

Given the one-sided nature of P_t, as observed by Baily, and its poor statistical performance, we concluded that the concept itself is so elusive that an alternative approach would be desirable. In brief, we decided to try to observe the *effects* of depletion in another country, the U.K. — a country in which depletion could be assumed to be at work but in which increased U.S. regulation would not. Hence, by making the admittedly strong assumptions that the effects of depletion in the U.K. and U.S. were the same over the 1960-1970 period and that the U.K. decline was due entirely to depletion, we have been able to obtain what we consider to be a more plausible measure of depletion.

Before turning to our actual measure of depletion and how we have used it to disentangle the effects of regulation and depletion on U.S. R & D productivity, we should examine the U.K. regulatory system and some comparative statistics of the U.S. and U.K. industries.

[19]We also explored a number of related functional forms with similar qualitative findings.
[20]Baily, op. cit., pp. 75-76.

Comparison of U.S. and U.K. Ethical Drug Industries

We should make explicit at the outset that the two industries are not independent. Most of the large drug firms are multi-national in character. For example, during the 1960's U.S. based firms had between 40 and 50 percent of the U.K. market.[21] Hence, increased controls in the U.S. can be expected to have had some impact on U.K. drug innovation. We shall consider this point in more detail shortly.

The system of regulatory controls in effect in the U.K. over the period since 1962 differs in a number of ways from that in the U.S. In terms of formal requirements both systems had a pre-market review of all new drugs on safety grounds over this period. On the other hand the U.K. did not require formal proof of efficacy until very recently and essentially left this task of evaluating a drug's efficacy to the market mechanism. In addition the U.K. IND procedure was on a voluntary basis over most of this period.

Perhaps the greatest contrast between the two systems lies in the institutional characteristics of the review process. Sir Derrick Dunlop, who was the head of the British system for many years, provided a detailed comparison of the two systems in a recent conference on drug regulation. He notes:

> The main difference between the two systems is that ultimate power to license medicines in the United Kingdom rests with the Licensing Authority (the Ministers responsible to Parliament) acting on the professional advice of the Safety Committees. The decisions of these committees are taken by professional men whose careers in no way depend on their membership of the committees on which they serve part-time in a virtually honorary capacity as an altruistic chore. They are assisted, of course, by a small staff of expert professional civil servants who do most of the preparatory work, but the decisions are taken by the committees. It is probable that the experience gained from the eight-years' informal Safety of Drugs Committee will tincture their subsequent official actions.
>
> In the United States, on the other hand, ultimate power rests with the full time professional civil servants of the FDA whose careers depend on the correctness of their decisions, and who are subject to formidable grillings by Congressional Committees. The FDA has to work under fairly rigid rules by Congress which seem to rely more on animal experiments than is usual in the United Kingdom.[22]

The greater use of external professional advice in the U.K. apparently has produced a regulatory incentive structure which is less prone to bias in the

[21]This is based on sales audit data in the U.K. by Intercontinental Medical Statistics. The changing U.S. share of the U.K. market is discussed more fully in Section III.
[22]Sir Derrick Dunlop, "The British System of Drug Regulation", in Richard L. Landau, ed. *Regulating New Drugs* (Chicago: University of Chicago, 1973) p. 235.

direction of caution and delay. This combined with the greater reliance on medical judgement rather than formal regulatory controls has meant a system with much shorter time lags in the introduction of new products than has been the case in the United States. William Wardell has provided some empirical evidence for this on the basis of a detailed analysis of introductions in both countries since 1962 for nine select therapeutic categories.[23]

One dimension in which the U.K. has apparently had much more stringent regulatory controls is in the area of post market surveillance. According to Wardell[24] post market surveillance is more seriously undertaken in the U.K. while being a relatively neglected area in the United States.

The British system of drug regulation therefore has been characterized by a less bureaucratic pre-market screening process for new drugs and has relied more on medical judgment and stronger post-market checks on drugs than is the case in the U.S. At the same time, some changes have been instituted in the British system in the last few years which have made it more bureaucratic in nature and closer to the U.S. situation. These were associated with the implementation of the Medicines Act which became law in 1971.[25] Because of this, we shall focus on the period prior to 1971 in our comparative international analysis presented below.

In Figure 2 we present trends in total NCE introductions, NCE discoveries, and R & D expenditures in the U.K. over the period 1960-74.[26] These are the same variables that we examined for the U.S. in Figure 1. Clearly, the U.S. and U.K. trends are operating in the same directions: NCE introductions and discoveries are both declining overtime while R & D expenditures are rising.

As FDA Commissioner Schmidt[27] has argued, the downward trend in NCE *introductions* in the U.K. — paralleling the U.S. trend — provides some evidence for a worldwide phenomenon which may be labeled research depletion. However, it is also true that the U.S. regulatory stringency beginning in the early 1960's probably has had some impact on U.K. introductions, given the large share of the U.K. market held by U.S. firms.

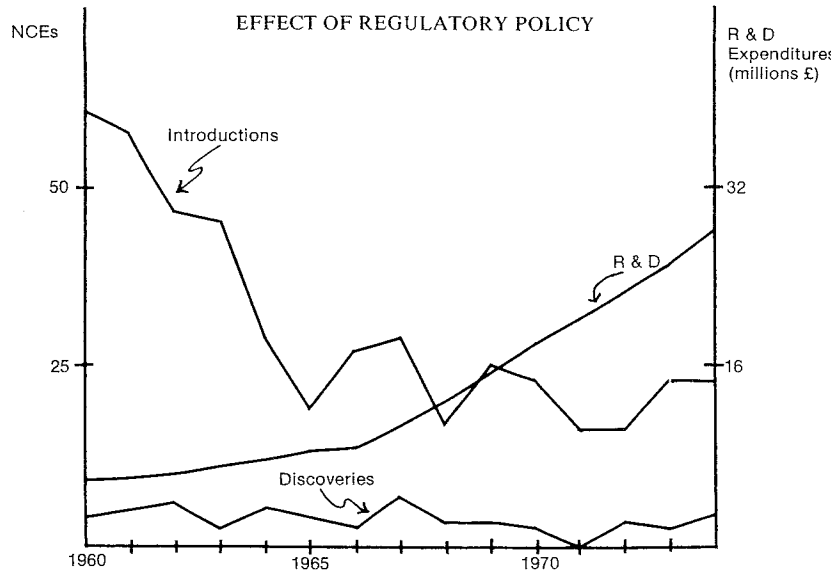
[23]His analysis in this regard is summarized in William M. Wardell and Louis Lasagna, *Regulation and Drug Development*, (Washington, D.C.: American Enterprise Institute for Public Policy Research, 1975), Part II, p. 51-126.

[24]Wardell, William. "Regulatory Assessment Models Re-Assessed". Paper presented to Second Seminar on the Dynamics of Pharmaceutical Innovation and Economics, American University, 1973.

[25]See Wardell and Lasagna, op. cit., p. 109-123 for a further discussion and analysis of U.K. developments since the Medicines Act went into effect in 1971.

[26]These variables are defined in comparable fashion to those for the U.S. case. See the statistical appendix for further details.

[27]Alexander Schmidt, testimony before U.S. Senate Subcommittee on Health of the Committee on Labor and Public Welfare, *Hearings on Legislation Amending the Public Health Service Act and the Food and Drug Cosmetic Act*, 93 Congress, August 1974, p. 30-47.



Introductions and Discoveries of New Chemical Entities by Domestic Firms and Constant (1958) Pound Expenditures on Pharmaceutical Research and Development, the United Kingdom, 1960-1974

Figure II

For example, U.S. law prohibits the export of any drugs that have not received regulatory clearance by the FDA. Hence, to the degree that U.S. firms had formerly performed their R & D in the U.S., introduced new products here first and then exported them to foreign countries, U.S. firms' introductions abroad should be adversely affected. The fact that the share of the U.K. market accounted for by U.S. firms has been declining steadily over the 1962-1973 period offers further support to this argument.

On the other hand, we believe that U.K. *discoveries* should not be particularly sensitive to increased regulation in the U.S. Hence, in order to separate the effects of regulation from depletion, we shall direct most of our attention to the comparison of U.S. and U.K. discoveries per R & D dollar. This is, of course, the variable used by Baily in his analysis.

In Table 3 we show the comparative "productivity" trends for the U.S. and U.K., where productivity is the number of new chemical entities *discovered* and *introduced* in each country per R & D dollar. This is precisely the variable Baily defined as N_t/E_t. Our calculations in Table 3 embody two strong assumptions made by Baily in his analysis. Specifically, i) *all* R & D expenditures in each country are allocated to discovery of new NCE's and ii) a five year lag is assumed between R & D expenditures and the actual introduction of an NCE. These have been applied uniformly to the data for both countries. Because we are primarily interested here in the relative trend in R & D productivities of the two countries rather than the

Table 3

Comparative Productivity of U.S. and U.K. in Discovered NCE's per Dollar of R & D Input

	U.S.		U.K.	
	Actual Value[1]	Index	Actual Value[2]	Index
1960-61	0.249	593	0.364	293
1966-70	0.042	100	0.124	100
1970-74	0.031	74	0.054	43

Notes:
[1]Number of NCE's discovered and introduced in U.S. per R & D input (Note: R & D is measured in millions of constant 1958 dollars)
[2]Number of NCE's discovered and introduced in U.K. per R & D input. (U.K. data measured in millions of constant 1958 dollars where pounds are converted to dollar basis here at exchange rate of $2.80/pound)

Data Sources: See Statistical Appendix.

absolute value of R & D productivity at a point in time, these assumptions are less limiting than they might first appear.[28]

Because of U.K. data limitations, we were able to obtain productivities for only two years prior to 1962 — the year 1962 was considered important because it marks the beginning of increased regulation in the U.S. However, for the latter periods we have measured productivity for five-year periods. These particular periods (1966-1970 and 1970-1974) were selected because of the increased U.K. regulation which began in 1971. In addition, there has been a significant increase in R & D performance by U.S. firms in the U.K. and other countries over the last few years making the assumption of independence in the discovery process less tenable.

Of course, there are many factors which affect the relative levels of N_t/E_t in the two countries. In particular, the higher U.K. value, 0.364, compared to only 0.249 in the U.S., in the initial period might be affected by differences in the average quality of NCE discovered in each country as well as differences

[28]David Schwartzman, op. cit., p. 26-28, has estimated that approximately 75 percent of the U.S. industry's ethical drug R & D expenditures over the period 61-67 were for the discovery and development of new NCE's as opposed to the development of other drug products (combinations, new dosage forms, etc.). Thus the assumption that all R & D is for new NCE's tends to understate R & D productivity somewhat in absolute terms (for both countries). On the other hand, the assumption of a constant five year development period is conservative and will tend to work in the opposite direction.

in market structures, pre-1962 regulatory environments, etc. Teeling-Smith[29] has performed an analysis of the relative quality of discoveries in each country for NCE's whose first worldwide introduction occurred between 1958 and 1970. He found that U.S. discoveries for this period on average achieved a somewhat higher rating in terms of a quality index based on worldwide sales[30] but a roughly comparable rating for a quality index based on medical importance (as evaluated by U.K. medical experts). He concluded that some modest adjustment of the raw productivity calculation is warranted in comparing the two countries because of the higher overall quality of NCE's discovered in the U.S. His findings in this regard are therefore consistent with the somewhat higher observed productivity for the U.K. for the initial period, 1960-61.

Since our primary interest here is in the relative trends in productivity over time, we have included in Table 3 an index of productivities for each country, with productivity in 1966-1970 arbitrarily taken as 100.

Perhaps the most important information given in Table 3 is the approximate six-fold productivity decline in the U.S. and three-fold decline in the U.K. between 1960-61 and 1966-70. One interpretation is that the more rapid U.S. decline is attributable to the increased stringency of regulation that took place in the U.S. beginning in 1962. If we assume that the 3 to 1 U.K. decline is a result of the depletion of research opportunities, then the depletion effect *only* in the U.S. would have led to a decline in the U.S. index from about 600 to about 200. The additional U.S. decline from 200 to 100 would then provide a very rough measure of the regulation effect. This halving of productivity in the U.S. due to regulation (from 200 to 100) of course implies a doubling of cost per NCE discovered.

We should also note the steeper decline in productivity in the U.K. compared to the U.S. between 1966-70 and 1970-74. A plausible explanation for this phenomenon might be the onset of tighter regulation in the U.K. beginning in 1971.

In the next part we shall report the results of an econometric analysis in which we incorporate a measure of depletion based on U.K. experience into a "production-function" model of the Baily type.

Econometric Analysis

As noted above, when we re-estimated the Baily model for the full 1954-1974 period, his measure of depletion (i.e., a moving average of total

[29]George Teeling-Smith, "Comparative International Sources of Innovation", Paper presented to Second Seminar on the Dynamics of Pharmaceutical Innovation. American University, 1973.
[30]In particular, Teeling-Smith found the weighted average market performance for U.S. compounds to be 2.8 million and for the U.K. it was 2.3 million.

introductions) became insignificant. The above comparative analysis of the U.S. and U.K. indicates, however, that some type of phenomena which may be labeled research depletion has taken place over the post 1962 period.

In the current analysis, we attempt to estimate the effects of depletion by the alternative method of fitting a time trend to the U.K. productivity data. We then employ the resulting estimate as an external measure of depletion in our analysis of U.S. data. Specifically we assume that in the absence of regulatory differences, U.S. productivity would decline at an identical percentage rate as that for the U.K. Hence, the estimated annual rate of decline on R & D productivity for the U.K. in effect becomes our estimate of research depletion for the U.S.

Of course, the estimated annual rate of decline in U.K. productivity is undoubtedly the result of other factors in addition to the depletion of research opportunities. However, by assuming that *all* of the decline was the depletion effect, we tend to overstate the depletion effect and thereby will, if anything, understate the impact of regulation. That is to say, by making the strong assumption that the depletion induced productivity decline in the U.S. is equal to the full U.K. estimated decline, we tend to understate the effects of other factors which may be causing declining productivity in the U.S.

Our first step in this approach is therefore to fit a time trend on U.K. productivity data for the 1960-1970 period. We would have preferred to have had U.K. data prior to 1960, but such data was unavailable. We elected to use 1970 as the end point year in order to avoid confounding the trend with increased U.K. regulatory effects which began in 1971.

Least squares regressions of the logarithm of N_t/E_t on time yielded an annual rate of decline of –0.15.[31] Using alternate starting dates of 1961 and 1962, the rates of decline of U.K. productivity were –0.16 and –0.15 respectively. Hence, the decline rate was relatively insensitive to the period selected for estimation.

Using the –0.15 rate of decline as the effect of depletion from 1960 onward, we must now consider the question of depletion effects in the pre-1960 period. Perhaps the simplest assumption is to assume that prior to 1960, depletion was not important. In other words, suppose as one polar case we take the effect of depletion on U.S. productivity to be a zero rate of decline from 1954 to 1960, and a –0.15 rate of decline from 1960 to 1974.

[31] The least squares regression equation estimated for 1960 to 1970 in the U.K. was

$$\text{Log } [N_t/E_t] = \underset{(3.73)}{297} - \underset{(3.74)}{0.15\,T} \qquad R^2 = 0.61$$

Imposing these time trends on the Baily model, and following Baily in using the dummy variable D_t to estimate the impact of regulation, we obtain:

$$(2) \qquad \log [N_t/E_t] = \underset{(6.52)}{-0.93} - \underset{(6.14)}{1.12\,D_t} - 0.15\,T60$$

$R^2 = 0.88$ (t-statistics are in parentheses) $D\text{–}W = 1.90$

where: N_t/E_t = NCE productivity in U.S. as defined previously

D_t = a zero-one variable equal to zero through 1961 and unity thereafter

$T60$ = 0 from 1954 to 1960, 1 in 1961, 2 in 1962, . . .

The coefficient of D_t is negative and highly significant, indicating the adverse effect of regulation on U.S. productivity. The size of the coefficient (–1.11) also indicates that the quantitative effect is substantial. A coefficient of –1.11 would imply that the cost per NCE increased by a factor of 3 as a result of the 1962 Amendments.

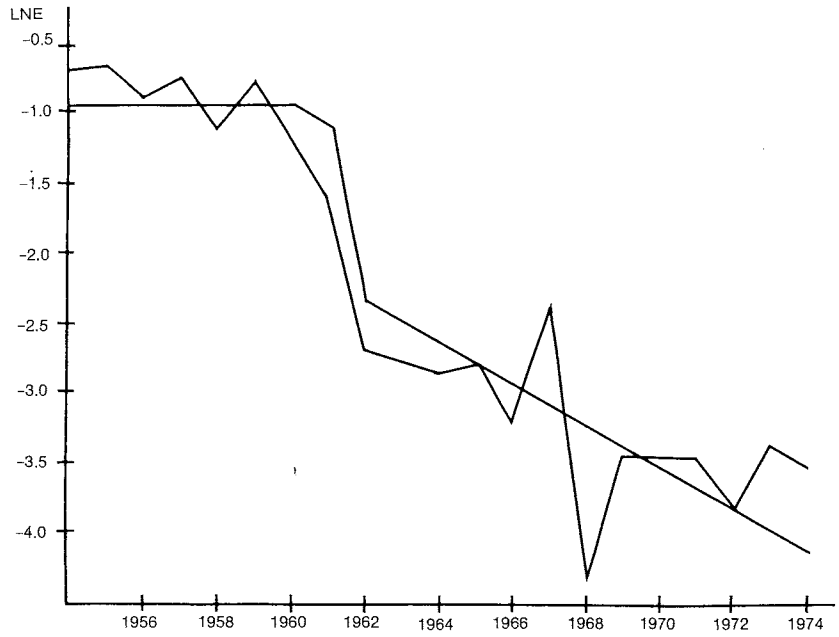
In Figure 3 we have plotted the actual U.S. productivity values against the estimated values given by equation (2). Since there does appear to be a downward trend in the pre-1960 period, our assumption of a zero depletion effect in that period should perhaps be modified. Hence, as an alternate assumption, we have estimated the U.S. time trend prior to 1960 — letting the estimated trend represent the effect of depletion for that period. At the same time, we continue to restrict the rate of decline in the post-1960 period to be –0.15. The resulting equation is given below:

$$(3) \qquad \log [N_t/E_t] = \underset{(2.28)}{-0.59} - \underset{(3.47)}{0.85\,D_t} - \underset{(1.54)}{0.10\,T54} - \underset{(0.75)}{0.05\,T60}$$

$R^2 = 0.89$ (t-statistics are in parentheses) $D\text{–}W = 2.03$

where: $T54 = 0$ in 1954, 1 in 1955, . . .
(other variables are as defined earlier)

Again we observe that the coefficient of D_t is negative and statistically significant. Its value has declined somewhat, however, indicating that the impact of the 1962 Amendments on cost per NCE is now to increase cost by a factor of 2.3. Although the high collinearity between $T54$ and $T60$ renders



Logarithm of (N_t/E_t), Actual and as Predicted by Equation Two, 1954-1974

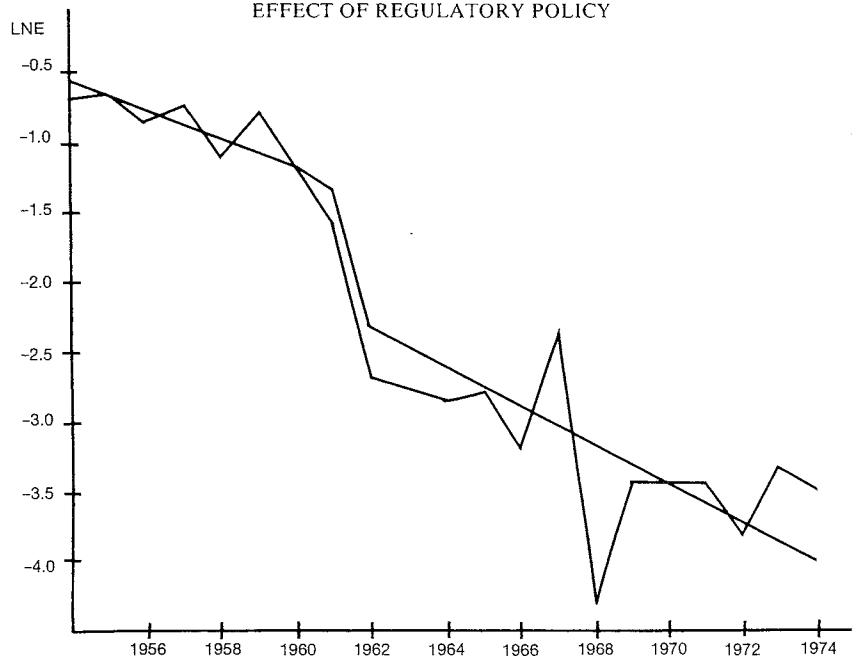
Figure III

their particular coefficients statistically insignificant, the restriction that the two coefficients sum to –0.15 *is* statistically significant. (Note that the sum of their coefficients equals –0.15, the assumed rate of decline due to depletion in the post-1960 period.)

Figure 4 shows the actual values of U.S. productivity against the values predicted by equation (3).

Both equations provide rather close fits to the data (both account for almost 90 percent of the variation in log $[N_t/E_t]$). However, the representation of the effect of regulation as a single sharp decline in productivity in 1962 might be regarded as less believable than a more gradual effect taking place over several years. Although the data do seem to support the sharp 1962 decline, we experimented with some other measures of regulatory effects. In particular we also estimated the above equation with a "regulatory stringency" variable, S_t, based on the average length of time from submission of an NDA (new drug application) to the FDA's final disposition of the NDA.[32]

[32]Because of data limitations the measure we constructed in this regard was subject to a number of approximations and therefore considerable potential measurement error. This may explain in part its somewhat poorer explanatory power compared to the D_t variable. See the statistical appendix for further details on the construction of this variable.



Logarithm of (N_t/E_t), Actual and as Predicted by Equation Three, 1954-1974

Figure IV

We report below the re-estimation of equation (2) in which S_t is substituted for the zero-one dummy, D_t.

$$(4) \qquad \log [N_t/E_t] = \underset{(3.55)}{-0.92} - \underset{(3.09)}{0.04\, S_t} - 0.15\, T60$$

$R^2 = 0.78$ (t-statistics are in parentheses) $D\text{-}w = 1.12$

Although the R^2 is 10 points lower than the same regression using D_t, the coefficient of the regulatory stringency variable is negative and statistically significant. This result tends to support the view that increased regulation did not necessarily all occur suddenly in 1962. On the other hand, given the somewhat better performance of simple D_t variable, it is difficult to avoid the conclusion that a large part of the decline in productivity did take effect in 1962 and that the new regulatory environment must have played a rather significant role.[33]

[33]We further tested the sensitivity of our estimated equations to alternative starting years on the D_t variable (i.e., 1961 and 1963) and found the R^2 was maximized when 1962 is the shift year.

In summary, our evidence — based on a comparison of productivity trends in the U.S. and U.K. — supports the view that both depletion of research opportunities *and* increased regulation have reduced the productivity of drug R & D. Furthermore, our evidence corroborates the findings of others that the regulatory effect alone has substantially raised the costs of new drug innovation. In the next section we turn to an analysis of the impacts of these developments on the relation of innovation to firm size for both countries.

III. Concentration of Innovational Activity in the U.S. and the U.K.

As noted in the first section, the increased costs of drug R & D in the U.S. have led to some important structural changes in the industry. In this section, we examine in detail one of the most important changes — the tendency over time for innovation to become concentrated in fewer and larger firms. We also perform a parallel analysis on this question for the U.K. economy. The structural trends observed in the latter country are quite different from those for the U.S. The contrast between the two economies provides further support for the hypothesis that regulation has had a significant independent effect on U.S. innovational activity, apart from any worldwide depletion of research opportunities.

The results reported in this section are a summary of findings from a more extensive analysis of this question to be published in a forthcoming paper.[34]

A. Changes in the Structure of Innovational Activity — The U.S. Case

As a first step in our analysis, we constructed "concentration ratios" of innovational output in the U.S. pharmaceutical industry over the three subperiods 1957 to 1961, 1962 to 1966, and 1967 to 1971. Innovational output for each firm is measured by its number of NCE introductions, weighted by their sales over the first three years of product life. In effect, because NCE introductions are not homogeneous commodities, we use sales weights as an index of an NCE's relative quality or value. This procedure has been employed in prior work as well as the alternative one of weights based on the rankings of experts on a new product's importance or quality.[35]

[34]Henry G. Grabowski and John M. Vernon, "Structural Effects of Regulation in the Ethical Drug Industry", op. cit.

[35]In general, past investigations of the size structure of innovation in the pharmaceutical industry have not found that results are qualitatively altered when different measures of

Our tabulations on the concentration of innovational output are presented in Table 4. The first column of Table 4 shows the total number of new chemical entities introduced in each of the periods. As previously noted, a sharp decline in aggregate NCE's occurred in the post-amendment period. Column 2 of Table 4 further reveals that the number of individual firms having an NCE has significantly declined over time. In particular the number of firms having at least one NCE declined from 51 in the 1957-61 period to only 23 in the 1967-71 period.

The last three columns of Table 4 show the "concentration ratio" of innovational output in terms of the 4, 8, and 20 leading firms (i.e., ranked in order of our measure of innovational output). The rather sharp increase in concentration of innovational output is clear. This is especially the case for the four-firm ratio which increases over 15 percentage points between the first and last periods.

As one might expect, we generally found some sensitivity in the numbers observed to the particular choice of time period. Nevertheless, whatever convention we employed in this regard, a distinct upward trend in the concentration of innovational output over the range of the top firms was unmistakedly observed in all instances. In other words, the percentage of innovation accounted for by the top four and eight firms always increased significantly, irrespective of the time period convention utilized.

A further important question has to do with the relationship between the size of the firm (as measured by sales of ethical drugs) and its level of innovational output. In Table 5 the firms are ranked by size (i.e., their total sales of ethical drug products) instead of by innovational output and comparison is made of the largest four firms' share of industry sales to their share of innovational output over the three periods. This table also shows some dramatic trends over the three periods. In particular, in the pre-amendment period, the largest four firms accounted for a slightly smaller share of total innovational output than their percentage of total sales (24% to 26.5%) whereas by the final period, they accounted for a substantially higher percent of innovational output than sales (48.7% to 26.1%).

For each period we also estimated linear, quadratic, and cubic regressions of innovational output on firm size. The regressions were based on a sample

weighting NCE's are employed. For example, David Schwartzman used five different weighting schemes (a simple count of NCE's as well as weights based on sales, chemical novelty, medical importance, number of prescriptions, and number of patents) in such an investigation and found that his results were not highly sensitive to the method of weighting innovation. David Schwartzman, "Research Activity and Size of Firm in the U.S. Pharmaceutical Industry", Paper presented to the Second Seminar on the Dynamics of Pharmaceutical Innovation, American University, 1973. In this paper we have used sales weights because they were readily available and have a somewhat more objective quality than some of the other measures used in the literature.

Table 4

Concentration of Innovational Output in the United States Ethical Drug Industry

Period	Total Number of New Chemical Entities (NCE's)	Number of Firms Having an NCE	Concentration Ratios of Innovational Output 4-Firm	8-Firm	20-Firm
1957-1961	233	51	.462	.712	.931
1962-1966	93	34	.546	.789	.976
1967-1971	76	23	.610	.815	.978

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

Data Sources: List of New Chemical Entities in each year obtained from Paul de Haen *Annual New Product Parade*, various issues; all information on ethical drug sales obtained frm Intercontinental Medical Statistics.

of 53 firms which includes all firms that introduced an NCE into the U.S. over the period 1957 to 1971.

During the first two periods, the best fitting relation was provided by a linear regression equation or a roughly proportionate relation between size and innovational outputs. In the 1967-71 period, however, the best fitting equation was a cubic one. Moreover, the estimated coefficients of this cubic equation imply that the innovational output increased more than proportionately with firm size over the upper size range of firms in our sample and that the highest values of innovational intensity was obtained by these firms.[36] This is consistent with the findings in Table 5 for the 1967-1971 period.

All of the results in this section therefore indicate that there has been a strong shift toward greater concentration of innovational output in the U.S. in the very largest ethical drug firms. Historically, most industries in the U.S. have not been characterized by a disproportionate amount of innovation

[36]The best fitting equation for the 1967-71 period was the cubic relationship

$$Y_i = \underset{(1.67)}{-11{,}647} + \underset{(3.17)}{0.94\,S_i} - \underset{(3.19)}{.00088\,S_i^2} + \underset{(3.81)}{.0000025\,S_i^3} \qquad R^2 = 0.63$$

where Y is the number of new chemical entities (weighted by their first 3 years of sales) of the ith firm and S_i is the total market sales of the ith firm in the midpoint year of the period. Note the cubic term is positive and statistically significant at the one percent level. The coefficients of this equation imply collectively that over the range of our sample, the highest value of Y/S occurs for the largest firm.

Table 5

Percentage of Innovational Output and Total Ethical Sales Accounted for by the Largest Four U.S. Drug Firms, 1957-61, 1962-66, and 1967-71

Period	Four Largest Firms' Share of Innovational Output	Four Largest Firms' Share of Total Ethical Drug Sales
1957-1961	24.0	26.5
1962-1966	25.0	24.0
1967-1971	48.7	26.1

Data Sources: See Table 4

being accounted for by the largest firms in the industry.[37] It has been observed consistently only in the case of the chemical industry. Nevertheless, in the light of the large upward shifts in ethical drug development costs over the post-amendment period discussed above, this shift in the structure of innovation towards the larger firms is not really surprising. However, the sizes of such shifts are quite dramatic in magnitude, considering the relatively short time periods being analyzed.

B. Structural Changes in the U.K. Industry

Our data for the U.K. industry are more limited than for the U.S. We were able to gather sales data for only the two most recent five-year periods, 1962-1966 and 1967-1971. Furthermore, the sales data apply only to drug stores and excludes hospital or other institutional purchases.[38] For this reason, drugs used exclusively or primarily in hospitals (e.g., injections) have not been included. Finally, we lost a higher proportion of drugs overall in the 1962-1966 period (31 percent) than in the 1967-1971 period (10 percent) primarily because the data sources tended to exclude drugs introduced in the earlier period with low or zero current sales.

Subject to these data limitations, we performed similar analyses for the U.K. to those presented above for the U.S. Table 6 presents some basic information on the concentration of innovational output for the U.K. for the periods 1962-66 and 1967-71. The first two columns of Table 6 show the

[37]See, for example, the survey of this question presented in F. M. Scherer, *Industrial Market Structure and Economic Performance* (Chicago: Rand McNally, 1970), Ch. 15.

[38]The data source on drug store sales is the U.K. subsidiary of Intercontinental Medical Statistics and the data is quite similar to that for the U.S. used above. See the statistical appendix for a further discussion of this variable.

Table 6

Concentration of Innovational Output in the United Kingdom Ethical Drug Industry

Period	Number of New Chemical Entities (NCE's)[1]	Number of Firms Having an NCE	Concentration Ratios of Innovational Output[1] 4-Firm	8-Firm	20-Firm
1962-1966	115	48	.631	.766	.941
1967-1971	95	44	.427	.664	.911

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

Notes:
[1]Based on NCE's introduced in U.K. for which we were able to obtain positive sales information. See Text and statistical appendix for further information on sample composition.

Data Sources: List of New Chemical Entities in each year obtained from Paul de Haen, *New Drug Analysis-Europe* and special reports by de Haen. All data on sales obtained from Intercontinental Medical Statistics.

aggregate number of NCE introductions and the number of firms having at least one NCE. As in the U.S. case, there is a decline over time in both these variables. However, the declines are much smaller in magnitude in the U.K. case. For example the number of firms having an NCE decreases only 10 percent in the U.K. over the two periods (48 to 44 firms) while it declined three times as much for the comparable time span in the U.S. (34 to 23 firms).

A really surprising result in Table 6 is the fact that the concentration ratios of innovational output for the U.K. exhibit a significant decline over the two periods. The 4 and 8 firm ratios decrease 21 percent and 10 percent respectively. This substantial downward movement in the concentration of innovational output is exactly opposite to what occurred in the U.S. case. This observed decline in the concentration of innovational output is surprising because our analysis in the last section clearly shows that R & D cost per NCE discovery have significantly increased in the U.K. Although the increases in R & D costs in the U.K. have been much less than for U.S. (with its tighter regulatory environment) nevertheless one would still expect the rising trend in R & D costs per NCE abroad to produce more rather than less concentration of innovation over time.

Table 7 presents an analysis of the relation of innovational output to firm size in the U.K. that directly corresponds to that performed for the U.S. This analysis further demonstrates that innovation in the U.K. has become less concentrated in the very largest sized firms (ranked by U.K. sales). Table 7 shows that in the 1962-1967 period the four largest firms had a significantly larger share of innovational output than their share of total drug sales (39.9% to 26.9%) while the reverse is true in the 1967-1971 period (14.5% to 29.5%). Similarly, a regression analysis for the U.K. shows that the best fit between innovational output and firm size in the 1962-1966 period was roughly linear. On the other hand, a quadratic relation offers the best fit for the 1967-71 period with innovational output declining with sales over the upper size range.[39] This is opposite in character to the relation that was observed in the U.S. for the upper size range in this period.

The source of much of this declining overall concentration of innovational output in the U.K. as well as the weakening relation of innovation to firm size becomes clear when the performance of U.S. firms and their subsidiaries is examined in the U.K. over these two periods.[40] U.S. firms historically have accounted for a large share of total market sales and innovational output in the U.K. For example, in 1962, U.S. firms collectively accounted for 47 percent of U.K. ethical drug sales and several U.S. firms were among the leading firms ranked by sales.

However, our analysis indicates that the U.S. leadership position in innovation in the U.K. declined dramatically over the decade 1962-71. This

Table 7

Percentage of Innovational Output and Total Ethical Sales in U.K. Accounted for by the Largest Four U.K. Drug Firms, 1962-66 and 1967-71

Period	Four Largest Firms' Share of Innovational Output	Four Largest Firms' Share of Total Ethical Drug Sales
1962-1966	39.9	26.9
1967-1971	14.5	29.5

Data Source: See Table 6

[39]The best fitting equation for the 1967 to 1971 period was the quadratic relation

$$Y_i = -53.3 + 0.86\,S_i - .00006\,S_i^2 \qquad R^2 = 0.24$$
$$(0.15) \quad (3.90) \quad (2.94)$$

and for 1962-66 it was the linear relation

$$Y_i = 10.57 + 0.54\,S_i \qquad R^2 = 0.19$$
$$(0.03) \quad (3.66)$$

with Y_i and S_i defined as above (see footnote 36)

[40]U.S. firms in the analysis of this section are classified on the basis of the nationality of the parent firm.

is demonstrated by the fact that U.S. firms and their subsidiaries accounted for 48 percent of the new product innovation in the 1962-66 period (as measured in Table 6 and 7) but only 15 percent in the 1967-71 period.[41] Thus the declining concentration in innovational output in the U.K. in large part can be explained by and is directly tied to the declining innovative performance of the U.S. firms. As one might further expect, U.S. firms also experienced a corresponding decline in their overall share of the U.K. ethical drug market over this 10 year period. By 1971, the share of the market captured by U.S. firms was only 38 percent, a 9 percent decline from the 47 percent share held in the first year, 1962.

The declining innovative performance by the U.S. firms in the U.K. in the post 1962 period in turn might be plausibly explained as a lagged response or "echo effect" to the tighter regulatory climate that took effect in the U.S. in the early sixties. Prior to the 1962 Amendments the prevalent strategy of U.S. firms apparently was to introduce their products first into the U.S. market and then introduce them with a lag into foreign countries.[42] Moreover, in accordance with the product trade cycle theory,[43] these new products were often manufactured here and exported abroad in the earlier stages of their life cycle. However, as the U.S. regulatory environment became more stringent and the number of NCE's cleared in the U.S. sharply declined, the stock of U.S. new product innovations available for subsequent introduction abroad also declined. Hence, one might expect that a corresponding decline would take place, somewhat lagged in time, in the innovational performance of U.S. abroad. This is precisely what was observed in the U.K. over the decade 1962-71.

The institutional practices and strategies of U.S. firms concerning foreign introductions of course are not immutable and there are now various strands of evidence that these traditional institutional arrangements are experiencing significant changes. A cursory analysis of recent new product introductions by U.S. firms in this country suggests that increasingly these products are being introduced abroad before they obtain FDA clearance in the U.S. Market.[44] Moreover, sizeable foreign investment by U.S. drug firms in the sixties and seventies has now provided U.S. firms with substantial

[41]This is based on an analysis of IMS data. See our forthcoming paper for a more extended analysis of this question. Grabowski and Vernon, op. cit.

[42]A preliminary analysis of de Haen data on the U.K. introductions of U.S. firms in the early 60's clearly indicates this to be the case. We plan to do further research into this question including an extensive analysis of time trends in other major European countries.

[43]For a discussion of the product trade cycle theory and some general evidence supporting it, see Raymond Vernon, *Sovereignty at Bay* (New York: Basic Books, 1971).

[44]Some data on worldwide discoveries and introductions consistent with this view has also been presented in a paper by Reis-Arnt and Elvers, "Results in Pharmaceutical Research. New Pharmaceutical Agents", *Drugs Made in Germany*, Vol. 15, No. 3, 1972.

manufacturing capacity abroad. As noted in the first section, U.S. firms also are performing more of their research and development and clinical testing in foreign environments. At this point, the long run impact and conseqences of this movement of technical and physical resources abroad by U.S. firms remains open to question. These resource shifts, which would appear on logical grounds to be a plausible long run consequence of more stringent regulatory environment in the U.S. relative to other countries, are clearly a high priority item for future research.

IV. Summary and Conclusions

Innovation in the pharmaceutical industry has been subject to number of adverse structural developments in recent years. There has been a sharp decline in the annual number of NCE introductions and rapid increases in the costs and risks of producing an NCE. In the initial section of the paper, we reviewed these and related structural developments in some detail.

In Section II, we turned to an analysis of the factors underlying this declining rate of innovation. The two main hypotheses advanced in the literature to explain it involve i) a depletion of research opportunities and ii) increased regulation of the industry associated with the 1962 Amendments to the Food, Drug and Cosmetic Act. In order to evaluate the validity and relative importance of these alternative hypotheses, we performed in Section II a comparative analysis of U.S. and U.K. innovative performance.

A principal finding that emerged from this analysis is that U.S. "productivity" — defined as the number of NCE's discovered and introduced in the U.S. per dollar of R & D expenditure — declined by about six-fold between 1960-61 and 1966-70. The corresponding decrease in the U.K. was about three-fold. Clearly, some world-wide phenomenon, which might be labeled a "depletion of research opportunities", seems to hold for pharmaceutical R & D. However, there is also strong support for the hypothesis that an additional factor is at work in the U.S. industry.

We contend that this additional factor, which has lowered U.S. productivity at a significantly more rapid rate, is the increased regulatory tightness resulting from the 1962 Amendments. On the basis of a more sophisticated econometric analysis presented in Section II, we estimate that the 1962 Amendments have roughly doubled the cost of a NCE. This estimate is actually quite close to that of an early study by Martin Baily using a very different measure of research depletion. However, the depletion measure used in the original Baily model proved to be quite unstable when his analysis was extended forward in time. This was a primary factor motivating the development of a new measure by us from international data on R & D productivity.

In Section III, we further show that, in accordance with the increased cost and riskiness of the innovative process, NCE introductions have become increasingly concentrated among the larger firms in the U.S. industry. As a consequence, there has been a significant reduction in the number of independent sources for new drug discoveries and introductions. On the other hand, we found that the U.K. has not experienced comparable changes in innovative concentration to that observed for the U.S. Innovation in that country became less rather than more concentrated in the largest sized firms over the period 1962-71. An analysis into the reasons for these opposite trends in the U.K. indicated that it reflected in considerable part a sharp decline in the share of total U.K. innovation accounted for by U.S. firms. This decline in innovative performance abroad by U.S. firms might plausably be construed as an "echo effect" of the increased regulatory controls in the U.S. However, in recent years there have been strong shifts in technical and physical resources abroad by U.S. multinational firms in an apparent effort to reverse their decline in foreign innovative performance and market shares.

Our general findings concerning the effects of regulation on innovation appear to reflect the basic incentives built into the U.S. drug regulatory process. Under this system, FDA officials do not have very strong incentives to be concerned about possible negative impacts of regulation on innovation. This is true for several reasons. First of all, the regulatory mandate is drawn in very narrow terms — to protect consumers against unsafe or ineffective drugs. There is no corresponding institutional mandate dealing with the positive encouragement of drug innovation. Similarly the reward structure confronting the individual FDA regulator is strongly skewed toward the encouragement of risk — averse behavior. The FDA official stands to bear heavy personal costs if a bad outcome occurs after a new drug is approved, but he appropriates little of the benefits from a good outcome. Moreover, the costs of delays in new drug approvals are borne entirely by outside parties.

Any adverse impacts of drug regulation on the costs and risks of innovational activity are thus largely "external" to the current regulatory decision making process. In terms of incentives, the process is structured to err on the side of safety and caution and does not really provide for an objective weighing of the costs associated with reduced levels of innovation against the benefits of greater drug safety and efficacy.

In principle there is a wide spectrum of policy options that could be considered to change this situation. These range from various measures designed to change the existing regulatory incentive structure in the area of innovation (i.e., through external reviews, greater institutional accountability, etc.) to much more fundamental reforms that would reduce the scope of

direct regulation and place greater emphasis on a decentralized decision making process.[45] The merits of these various policy options of course cannot be decided solely on the basis of how they influence the incentives for innovation. Nevertheless, the analysis presented above suggests that the adverse impacts of regulation on innovational performance have been quite substantial in magnitude. There are therefore sizeable potential benefits to be gained from improving this dimension of regulatory performance. In light of this fact, serious consideration and experimentation with these alternative regulatory procedures would clearly seem warranted.

APPENDIX

This appendix presents in summary form the sources and methods of computation for statistics used in the paper.

NCE Introductions and Discoveries

Data on new chemical entities and their years of introduction for both the U.S. and U.K. were obtained from the publications of Paul de Haen [1,2,3,4,5,6,7,8]. In a very few cases, information on British introductory dates was supplemented by the work of William Wardell [9]. Biologicals and diagnostics were here deleted from data lists and analysis due to problems of data availability and reliability prior to 1966.

Information as to which of these NCE's were also discoveries by industry research laboratories was obtained for the U.S. from Paul de Haen [1,2,3,4], for the U.K. in 1960-1970 from the National Economic Development Office [10], and for the U.K. in 1970-1974 from, again, Paul de Haen [7,8]. A NCE was regarded as discovered in a particular country if the research laboratory producing the entity were located in that country, irrespective of nationality of laboratory ownership. Thus the discoveries of Pfizer, U.K., are credited to Britain while those of Hoffmann-La Roche, U.S. are considered as American. It should be recognized that the discoveries of NCE's are denoted by year of introduction in either the U.S. or the U.K. (depending on origin) rather than first year of introduction on a worldwide basis (should these dates differ).

[45] An extensive discussion of these policy options is presented in a manuscript that is currently being prepared for the American Enterprise Institute For Public Policy Research by Henry Grabowski.

R & D Expenditures

Expenditures for research and development are here considered as those domestic outlays by the pharmaceutical industry for discovery of humanly usable ethical drugs. In the U.S., data were obtained from publications of the PMA [11,12] for worldwide human R & D expenditures, 1948-1974, of member firms. However, the breakdown of domestic vs. foreign expenditures in this total was available only for 1960-1974, from the same sources. By fitting an exponential trend for foreign R & D expenditures of PMA member firms against time, 1960-1974, estimates of this parameter were obtained for earlier years. Subtraction of these estimates from the worldwide total gave the data used in the text.

R & D data for the U.K. for 1954-1966 and 1973 were taken from releases of the ABPI [13,14]. For 1954 to 1965, data aggregated human and veterinary research expenditures. These statistics were multiplied by 86.15% (the 1966 value) to obtain estimates of expenditures for purely human research. For the years 1966 to 1974 an exponential trend on time was fitted to obtain R & D estimates for intervening years.

R & D estimates for both industries were deflated by the GNP deflator to constant (1958) dollars for the U.S. [15] and to constant (1958) pounds for the U.K. [16]. Statistics for deflated expenditures on R & D as well as introductions and discoveries of NCE's are plotted in Figures One and Two of the text. Additionally, segments of the U.S. R & D data are contained in Table Two of the text.

Pharmaceutical Sales

Data on U.S. sales of ethical drugs were obtained from the publications of a marketing research firm, Intercontinental Medical Statistics [17,18]. These data were based on a projection from a 1000 drug store sample to the population of all U.S. drug stores, and on a sample of about 10% of total hospital beds. Sales directly to other institutions, such as to the U.S. government are here excluded, but they account for less than 20% of U.S. ethical drug sales.

Data for U.K. sales are more limited than for the U.S. It was feasible to gather data only for the period 1962 to 1974. Furthermore, the sales data apply only to drug stores and exclude hospital or other institutional purchases. For this reason, drugs used exclusively or primarily in hospitals (e.g., injections) were not included. Finally, a higher proportion of drugs were lost in the 1962-1966 period (31 percent) than in later periods (10 percent) because the data sources tended to exclude drugs introduced in the earlier period with low or zero current sales. The data source on drugstore

sales was the British subsidiary of IMS [19] and the data is quite similar to that collected for the U.S. Data are based on an audit of 600 retail pharmacies in the U.K., and have been continuously collected since the early sixties.

FDA Stringency

Estimates of the mean time in months to FDA approval of NCE's introduced in the U.S. were taken from an unpublished dissertation of Joseph M. Jadlow [20]. Jadlow himself obtained his estimates through private communication with the FDA. The figures used in the text extrapolate from Jadlow's and are as follows:

1954-1961	7.0 months
1962	9.3 months
1963	11.6 months
1964	14.0 months
1965	19.0 months
1966	24.0 months
1967-1974	27.0 months

These values are used for Equation 4 of Section III.

REFERENCES FOR APPENDIX

1. Haen, Paul de, "Compilation of New Drugs," *American Professional Pharmacist* 33 (November, 1967) 25-62.
2. ———, *New Drug Analysis USA* Volume VII, 1966-1970, New York, Paul de Haen, Inc. 1971.
3. ———, *New Drug Analysis USA* Volume X, 1969-1973, New York, Paul de Haen, Inc. 1974.
4. ———, "New Products Parade", 20th edition, mimeographed, New York, Paul de Haen, Inc. (February, 1975).
5. ———, "New Single Drugs Marketed in England, France, Germany, and Italy 1960 to 1965", mimeographed, New York, Paul de Haen, Inc. (February, 1973).
6. ———, "New Single Drugs Marketed in England, France, Germany and Italy 1966", mimeographed, New York, Paul de Haen, Inc. (October, 1973).
7. ———, *New Drug Analysis Europe* Volume I, 1967-1971, New York, Paul de Haen, Inc. 1972.
8. ———, *New Drug Analysis Europe* Volume IV, 1970-1974, New York, Paul de Haen, Inc. 1975.
9. Wardell, William M., "Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison," *Clinical Pharmacology and Therapeutics*. Volume 14 (1973), pp. 773-790.

10. National Economic Development Office, "A List of 466 Pharmaceutical Compounds and Country of Discovery", (Prepared for NEDO by the Centre for the Study of Industrial Organization as part of the study "Innovative Activity in the Pharmaceutical Industry"), mimeographed, London, NEDO, 1971.
11. Pharmaceutical Manufacturers Association, *Annual Survey Report*, Washington, D.C., PMA, various years.
12. ———, *Prescription Drug Industry Factbook*, Washington, D.C., PMA, 1967.
13. Association of the British Pharmaceutical Industry, *Annual Report 1973-1974*, London, ABPI, 1974.
14. ———, "Pharmaceutical Research and Development Survey," mimeographed, London, ABPI, (January 17, 1975).
15. Council of Economic Advisors, *Economic Report of the President*, Washington, D.C., Government Printing Office, 1975.
16. Central Statistics Office, *Annual Abstract of Statistics*, London, Her Majesty's Stationary Office, various years.
17. Intercontinental Medical Statistics, *Pharmaceutical Market — Hospitals*, various years.
18. ———, *Pharmaceutical Market — Drugstores*, various years.
19. ———, *BPI Area Breakdown*, London, IMS, various issues.
20. Jadlow, Joseph M., Jr., "The Economic Effects of the 1962 Drug Amendments," unpublished Ph.D. dissertation, University of Virginia, 1970, p. 174.

Critique: J. E. S. Parker

I would like to say I enjoyed the paper a great deal and I found it most stimulating. I particularly liked the attempt to resolve the research depletion against regulatory effect question by using the United Kingdom as a control. I think the paper goes a long way towards reaching a sensible judgment. But I have a philosophical difficulty. This is not, in a sense, a criticism of the paper. It's a statement of my own prejudice, which I find undermined, and which therefore, I have to expose. My philosophical position is this: I don't believe the concept of research depletion. I find that an extremely difficult concept to swallow. Research depletion, as an idea, I find distasteful. Why? Because my thinking leads me to believe that, as a process, research generates knowledge. It generates more ideas, and so there is an accumulation and thus a deeper technological well, not one that's being exhausted. If one starts with such a philosophical position, then there is a tendency to be sceptical about figures which attempt to demonstrate that there is research depletion. I accept that it's extremely difficult to exhibit research depletion, but I also accept that, with the philosophical position I start with, I need to be fairly well satisfied that this has been demonstrated.

Now, what's the nature of my problem? Well, the figures used to show research depletion are the numbers of new chemical entities over time, and research and development expenditure. Neither of these, of course, is a direct measure of this concept of the technological well. They're approximates, and furthermore, they're circular. They're not independent of each other. Why? Because research and development expenditure is a measure of resources put to the search for new products and processes. New chemical entities discovered, on the other hand, reflect not only the amount of money spent on R & D but also, of course, the scientific ease or difficulty involved in making the discoveries. They are interrelated. The two measures cannot be treated as independent indicators of research depletion. The fact that the numbers go in a particular direction doesn't necessarily upset my preconceptions. One of the more technical reasons is that, if you look at the research costs, certainly at first sight, these would seem to rise dramatically, but I wonder if they would exhibit such a dramatic rise — in fact, I wonder if they would go up at all — if one used a deflator which was more appropriate to the circumstances. In other words, if one could have a deflator that was related, shall we say, to the cost of employing R & D personnel, rather than the more general ones that are used, perhaps we would end up with an R & D expenditure which has not risen, but has fallen. If this has in fact happened, then it would hardly be surprising that there has been a falling number of new chemical entities discovered. So you can see, I'm faced with a philosophical problem which makes me hypercritical about the figures used, and I also have some doubts about the actual indicators.

Having made that point, however, I must be sympathetic with Dr. Grabowski's approach. Ideal measures of research depletion do not exist ready made, and would take an enormous amount of effort to generate. Under these circumstances, the researcher has to be aware that the figures he uses are, at best, indifferent proxies. Nevertheless, he has to do whatever he can with them, and make his audience aware of the shortcomings. I'm merely pointing up shortcomings, and while being sympathetic to problems faced by the authors, I still don't find my philosophical position undermined. In other words, I don't feel there has been research depletion. If there hasn't been research depletion, then explanations for the fall in new chemical entities discovered must be sought elsewhere. Inevitably, government regulation will be high on such a list of alternative explanations.

To be more positive about the paper, what it does for me is to indicate how subtle and long-term the effects of regulation may be. There's now quite an amount of evidence building up to suggest that certain things happen if you have a particularly tight regulatory policy. A checklist looks something like this: The cost of R & D may be increased, fewer discoveries may be made, the use of new drugs may be delayed in particular countries;

the so-called "drug-lag", R & D may become more concentrated, and there may be a resource "flight." In other words, resources may move from a tight regulatory climate into a less tight regulatory climate. A tight regulatory policy may even lead to a reduction in productivity in other economies; the so-called "echo-effect." This list is a strong reminder that innovation is a tender process and that if it is regulated in too restrictive a manner, it will respond in a manner that may prove very costly in terms of future human welfare.

I thus conclude with a plea. It is this: I would like regulatory systems and authorities whose anxiety is to foster innovation, not to attenuate it. I would like to see the regulatory process as a joint venture between industry and government, where the emphasis is to increase the flow of innovation, not to stretch it out over time. I must expose the assumption underlying this plea. I believe that the benefits of innovation very greatly outweigh the costs. You have to accept that assumption, before you begin to take the position I have taken. But I think that position is extremely plausible.

Critique: Michael D. Sherman

The paper offers new evidence that supports two major points regarding the effect of the 1962 Amendments to the Food, Drug and Cosmetic Act on research and development in the pharmaceutical industry. First, the authors found new support for the contention that these regulations have reduced the productivity of industry R & D (in terms of new chemical entities developed per dollar of R & D expenditure). Second, they have developed a means of demonstrating for the first time that these provisions have also caused research to become concentrated among the larger members of the industry. The basis for their conclusions lie in a comparison of the differential experience of drug firms in the United Kingdom, where no such regulations exist, with similar companies in the U.S. under such controls.

While I support their contentions and feel that the approach they have used is well-founded, I am of the opinion that their model is not sufficiently developed to capture fully the extent of these effects. There are several reasons for this assessment. First, the model contains several proxy variables which are supposed to capture one event, but may in fact be a composite of a number of others as well. The variables D_t, $T54$, and $T60$ all are subject to this shortcoming. Second, their approach is based on several critical and relatively heroic assumptions that have been made in order to tie the model together. For example, they have assumed that the effects of research depletion in both the U.S. and the U.K. were the same throughout the 1960's.

They have also made the presumption that regulation in the United States had no effect on new drug discoveries in Great Britain. The latter is particularly unlikely since a number of U.S. companies operate in England either directly or through subsidiaries. Third, the model may not be specified completely. This is because the components of the phenomena being investigated are interactive. Thus, a simultaneous equations model would seem to be more appropriate in developing their analysis.

In addition to these problems, the presentation itself suffers in certain places from a lack of clarity in exposition. There are several examples of this throughout the paper. A few are particularly obvious. On page 67, discussion is offered regarding the relationship between the productivity coefficient for research (N_t/E_t), cost per NCE, and the regulatory dummy, D_t. However, the reader is not informed of the method by which the cost factor was calculated. Thus, it is difficult to understand the manner in which costs are affected directly by regulation and indirectly by the impact of the latter on research productivity. Statements made on pages 70 and 71 of the paper refer to the increasing relation between firm size and innovation that is unique to the U.S. pharmaceutical and chemical industries but not found in other domestic sectors of the economy. However, no data and/or analysis is offered which supports this allegation. Finally on pages 76 and on, arguments are offered that the declining innovative performance in the U.K. in the late 1960's is in large part a reflection of the lagged response of U.S. firms operating there to the 1962 Amendments. However, the declining concentration in the innovational output of U.S. firms in England could be caused by the changing operating characteristics of American firms in that country. For example, the decline in U.S. participation may be the result of the conversion from direct sales of new chemical entities developed in the U.S. to direct sales of new chemical entities developed in the U.K. and elsewhere by U.S. subsidiaries and jointly owned divisions operating in England and other European countries. No apparent attempt was made by the authors to screen out the effect of the general multinational movement of U.S. firms on British innovation, a factor that may be as important as the impact of the 1962 Amendments on U.S. research productivity in that country.

The second part of the econometric analysis, which deals with the differential concentration of innovational activity in the United States and England, seems to be much stronger. Both the data and the analytical methods applied to this portion of the study appear to capture in a more direct manner the phenomena being investigated. However, as noted in part above, the analysis does not fully recognize the impact of the movement of U.S. and other subsidiaries to the U.K. on innovation there. Because such firms are likely to be small and research intensive at entry and in the earlier

stages of their relocation, this phenomenon may account for the differential in the size-innovation relationship in the U.K. versus the U.S. However, it should be noted that at least in part, this movement probably has arisen from the favorable regulatory climate in Great Britain.

Having offered a number of criticisms of the paper but generally being strongly supportive of this effort, it is only fair that a number of suggestions be offered that might enhance the strength and impact of the investigation. To do less would be to subject this reviewer quite rightly to the criticism of taking "pot shots" at an excellent and major piece of work.

First, I would suggest that one or more variables be substituted for the regulatory proxy, D_t. As noted by the authors in a later version of their paper, one such alternative variable would be FDA approval time, a measure already used by Kendall. However, the parameter adopted by the latter was based on estimated data and, therefore, is itself somewhat of a proxy. A more carefully developed variable is thus necessary.

Approval time would appear to reflect more clearly and accurately the regulatory phenomenon experienced since 1962 in the U.S. In addition, it is more likely that such delays have been a primary cause of the poor research climate in this country. Another reason for the adverse trend in innovation may be the increased cost of finding new drug entities and of processing appropriate applications for their subsequent development and marketing. The addition of a variable to reflect this aspect of regulation might also enhance the realism and predictability of the model developed by Dr. Grabowski, et al.

Second, it is recommended that substitutes be found for the knowledge depletion proxies. More explicit variables such as IND applications and/or number of non-overlapping world-wide discoveries would seem to be better suited to the investigation, assuming that such information is obtainable. Such parameters would better reflect the state of pharmaceutical knowledge and would eliminate other factors that may be correlated with time (as expressed in the present proxies) that would systematically reduce innovation for other reasons than knowledge depletion, e.g., poor economic conditions.

Third, consideration should be given to altering the model itself. Two somewhat competitive approaches should be entertained. As previously indicated, the authors might explore the practicality and suitability of adopting a simultaneous equations model for use in their study. Such a model should explicity recognize the differential effects of regulation and knowledge on innovational productivity. Alternatively, the authors might consider the continued use of their present U.S.-U.K. model, but introduce additional variables and/or equations to enhance the realism and predicality of their analytical framework. The additions that are most apparent would

be those that would treat specifically some of the gross assumptions which mitigate the value of the results that have been obtained.

With more effort in these directions, it is the feeling of this reviewer that the research efforts of Dr. Grabowski, et al. would produce more meaningful results of greater statistical validity. Certainly, with the portent of additional regulation of this industry and the seeming lack of understanding of the impact of such controls, it is imperative that research along the lines of this paper be encouraged and assisted.

Discussion

DR. DEMSETZ: I also find this assumption about the depletion of research opportunities difficult to accept. I don't know of any theoretical justifications for it, and I suspect that there is somewhat of a bias in the statistical work, of a sort, that you sort of implicitly recognize, but not explicitly, in the paper, where you use the U.K. as an index of the amount of depletion. If the U.K. sold to the United States, and if the regulatory procedures made it more costly to sell to the United States, you would find a reduction in the new chemical entities per research dollar, which reflected merely the regulatory variable and not a depletion of research opportunities. Therefore, I think that the procedure used in Dr. Grabowski's paper leads to a lower-bound estimate of the effects of the regulatory variable in this picture.

Throughout this work, there seems to be an implicit judgment that what the FDA is doing is raising the quality of the pharmaceuticals consumed, by virtue of its tighter procedures, and also, although the reduction in number of chemical entities might be a part of the cost, nonetheless, there's an offsetting benefit. This implicit judgment, I believe, is founded on faulty reasoning. Making a drug sure of not having any defects in its application in my opinion is not equivalent to raising the quality of the drug. Let me give you an example. If we would put M.D.'s through 30 years of school in order to assure that when they come out, that they would be more highly-trained and less likely to make mistakes, we would have so raised the costs of doctoring services to the public that they would tend to self-administer and purchase more from quacks, and the quality of the services actually received by the purchasing public would go down, as a result of insisting on higher standards in the production of doctors. Quality of input does not guarantee quality of output; the two are not necessarily correlated with each other, although that is implicitly assumed in much of the analysis that goes on.

DR. GRABOWSKI: I guess I'm not as far apart from some of my critics as I might appear. I think we stated at a few points that our approach really

was understating the effects of regulation, that our depletion variable was a kind of umbrella-type variable that could be picking up other effects. One of the things we were most interested in was, if you loaded the analysis as we did, would you still get a significant effect for regulation. I think the analysis came out that we did. It varied between two and three times the effect for research depletion. I would agree with Harold Demsetz that that's probably a lower estimate. We spent a lot of time talking among ourselves of just what is this thing, really, we call depletion. In most research, one thinks of research building on itself. Now, on the other hand, having said that, I think if you look at gross trends for both the U.S. and the U.K., it's clear that there is no way that you could deflate these by a more appropriate deflator and get constant NCE introductions and discoveries per R & D dollar. There has been something influencing, causing steep trends, not only in the U.S., but the U.K., and what we are attempting to do is get some sort of a lower bound on the regulatory effect, loading the analysis somewhat by a comparative analysis with the U.K. In terms of the particular regulatory stringency variable, there is a discussion in the paper — perhaps Mike Sherman didn't see the last version — where we did some analysis with that particular proxy variable, similar to Kendall's analysis. That variable did perform in a statistically significant manner. It's not a completely satisfactory proxy, either, because there is, I think, considerable measurement error associated with those estimates of approval time. Approval time is only one dimension of what might be called regulatory stringency, and a more important dimension would look at, I think, things like the attrition rate in IND's. If we could get an empirical measure of IND discoveries, that would certainly be a fruitful way to augment our particular analysis.

I agree also that the next step would be to work in terms of a simultaneous equation approach here, in which R & D could be an endogenous variable in the system, and then one could proceed to make some of the kinds of estimates on the ultimate impact on NCE's. So I guess I'm not philosophically all that far apart from the others, although I think there's something occurring in the U.K. in terms of declining productivity, and I think we've chosen to make that our umbrella depletion variable, as a way of getting a lower bound on the effects of regulation, which are substantial, and roughly comparable to the Baily model, which as we started out by saying, became very unstable.

I think our approach is a significant advance over simply counting the number of introductions, and using a moving average. We found all sorts of effects, bizarre effects; for example, in experimenting with that kind of measure, we would find that it did very well in the U.S., but when applying it to the U.K. we would find a completely different effect. So, an attempt to get at this through some kind of moving average, I think, is just fraught with

a lot of problems, and I think this comparative international approach, at least conceptually, is a better way to proceed than some kind of simple count.

DR. DEMSETZ: Thank you.

MR. SCHANKERMAN: I have three comments on the paper, and on the paper on which it's based, namely Baily's analysis. First of all, I think I should make clear a couple of assumptions that I recall Baily made in his analysis which might merit relevant consideration. First is that Baily, as I recall, assumes constant returns to scale. Constant returns to scale means that there are no economies of scale that might be termed familiar. That may or may not be an acceptable assumption, but it is certainly implicit in his model and also in the model presented today.

The second thought is that none of the papers, for obvious reasons of data unavailability, separates out research expenditures from development expenditures. They're all lumped together, to get R & D. Now, it's my contention, although, unfortunately, I haven't yet gotten extensive data, that one can view the research and development process as, first, a kind of stock of innovational knowledge which comes largely from the research expenditures, and perhaps also, to a certain lesser extent, from development expenditures. The development process as opposed to the research process is akin to drawing from the resultant library of potential compounds. Each withdrawal is used to try to develop a marketable product.

The question of depletion, it seems to me, cannot really be conclusively answered until you have an idea of how the ratio of compounds researched to compounds developed has behaved over the period of observation, because it's quite conceivable, you see, that development expenditures have proceeded apace, or in fact, perhaps even quickened in the pace, while research expenditures have declined; for what reason, I'm not sure yet. If that's true, it's quite conceivable that, after a certain gestation period, you would find that the stock of ideas from which you can potentially draw is very much diminished. This point serves of course, to underscore the potential lags in the effects of regulation. In any case, until that ratio is calculated, however roughly, I don't have a conclusive answer. That's point number one.

Point number two relates to another assumption made here. That is that the lag structure, the gestation period, really, in research and development, has been constant over the observation period. Now, it seems to me that this assumption in all probability is patently false. The question we then fall back on is to what extent is the changing lag structure, that is, the changing gestation period, particularly the increasing gestation period over time, due to depletion in some sense, or regulation? You have to disentangle the effects on the lag structure which I think has not yet been done.

The last point is really an inferential problem. What policy conclusions can we possibly draw? From the result of the paper it seems clear there has been some increase in the concentration of innovational output, but we don't know much about inputs. It seems to me we have with the research based drug companies about the same problem as is present in making policy judgments about concentration in any industry or any market structural area: We don't know whether or not, or the extent to which it is due to increased efficiency. Now, it's quite conceivable, for example, that the top four firms have been gaining in innovational output share. Of course, that may be because they have responded more efficiently to whatever constraints were put on them by regulation, depletion, or whatever; that is to say, it's quite conceivable that the R & D productivity as stated by Professor Grabowski, for the leading firms, has been greater, or declined less than for the smaller firms. Now, I don't have any actual judgment about that, but it seems to me, you have to try and answer that question before you enter on policy decisions.

DR. DEMSETZ: Thank you very much.

DR. GRABOWSKI: I think we dealt with the first question about the constancy of the lag structure in a footnote. Clearly, there has been some change towards a longer gestation period. I think basically the question is "How does the lag structure we use affect our comparative international analysis?" I think the lags are longer. They've become longer in the U.S. than in the U.K. We apply the same uniform five-year lag to both countries, in the absence of hard knowledge on how they're changing. I think the bias that this produces is to overstate the depletion effect, and understate the regulatory effect. We are quite explicit that our estimates on regulation are conservative.

In terms of the question of what's been happening to R & D productivity, that's been answered, or it's been analyzed, I should say, by Vernon and Gusen in a paper that's come in the *Review of Economics and Statistics*. On the basis of what policy conclusions would one draw, the policy conclusion I draw from this is that regulation is leading to a lessened number of sources of innovational output, and that's an undesirable thing. But it's a result of the higher cost associated with doing research and innovation in this industry. But I wouldn't go on and carry things further than that.

DR. DEMSETZ: Questions? Yes.

DR. FELDMANN: I have two questions or comments that I would like to address to Dr. Grabowski. They relate to Figure 1. I understood him to relate, at least in part, the decline of new chemical entities, as well as introductions, to the 1962 drug amendments. Yet the '62 drug amendments were not signed into effect until October of that year and would not have

had any impact at least until 1963. Yet the 1962 levels for both discoveries and, to a slightly lesser extent, introductions, already had reached the point where they virtually plateaued between the years of 1962 and the present. So, while regulation may have a substantial effect on both of these factors, I can't personally directly attribute them to the '62 drug amendments.

The other question I had was, how he derived his figures for R & D. Mr. Schankerman correctly distinguished between research and development, but even within the general category of research, there are important distinctions. Research can relate to discovery of new chemical entities, as well as other types of research. There has been a decline, for example, in the amount of research expenditure for combination drug products, as combination drugs have met with less acceptance by prior regulatory bodies. On the other hand, there's been an increase in such things as duplicative drug products. Once an effort has been made to ascertain the precise segment of research expenditures that's related to new chemical entities, it would be difficult to make a direct correlation between those expenditures and the rate that the chemical entities have appeared on the market.

DR. GRABOWSKI: First, on the question of '62. We used that date when we employ a shift variable. We also use '63 as our shift variable, as well as '61. We experimented with that, and we got qualitatively similar results, although the factor in one case might be 2.3, and in another, it might be 2. But it doesn't change the quality of the effect.

In terms of when did the regulation take effect, or when did the increased stringency take effect, I've heard conflicting viewpoints on that. I've heard that nothing really occurred until 1965, by some observers. Other observers said that, as a result of the bill in the works, the thing took effect prior to the actual law, in terms of the incentives that regulators work under, and they had already become stringent before the actual signing of the bill. So I think it's difficult to pinpoint a date. What we did is try a few alternative dates around that period. Using alternative dates quantitatively alters the outcome, but not qualitatively.

In concerning ourselves with R & D, we followed Baily's, as I said, extreme procedure of just allocating all of R & D to the NCE's. This is an extreme assumption. What we could have done is changed it by some factor, say .75. As we note, David Schwartzman did an investigation in which, from case studies, he determined roughly three-quarters of research and development went for NCE's over a particular period.

If we deflated R & D by some uniform procedure, it would not affect the way the model is designed. It would not affect our time trend and our corresponding effects associated with it. In effect, we're estimating a shift factor, and the shift factor, provided the R & D were deflated by a common percentage in either country, wouldn't be affected.

Now, the key question is, how has the relationship between R & D and NCE's been changing? If the lags and the percentage of R & D going for NCE's have been changing markedly over time, that would affect our estimates. The shifts, however, have been so dramatic — we're dealing with a shift of six times and three times — that changes in lag time and percent of R & D on NCE's are not going to alter the direction of our results, but they could certainly alter the coefficient by some factor.

I certainly would like to have someone, perhaps the PMA, give us some leads on what are reasonable assumptions on the time series and the percentage of R & D being devoted to the discoveries of NCE. We just did the polar case, applying a comparable procedure in both countries. We could have deflated it by three-quarters. We could have deflated it by a common factor, and it wouldn't have changed the results. And what we really would like to know about is how it's been changing over time.

MR. SHERMAN: May I make a quick comment?

DR. DEMSETZ: Yes.

MR. SHERMAN: The regulatory period didn't really begin in 1962. If you recall, Senator Kefauver began his hearings in 1959, and I'm sure there was a very strong impact on R & D activities as a result of that.

DR. DEMSETZ: I would like to add some comments. I've already said that I thought that your results bias downward the effects of regulation, because of the handling of the depletion problem, but I think there's a point to be raised, to follow along the question here, that there might have been some tendency to bias upward the results of the impact of regulation. If, in fact, the industry anticipated the coming of regulation, they might have rushed out new chemical entities which might account for the peak in the data around 1962, entities which might have been brought out somewhat later. I don't know to what extent that actually happened, but that anticipatory effect would exaggerate the impact of the regulations.

Dr. Stauffer, do you have a question?

DR. STAUFFER: I think it might be interesting to proceed forward from the conclusions and analyses in the paper, rather than backwards. In a sense, the policy conclusions that might be drawn from this paper are independent of whichever interpretation one chooses as to why the yield out of pharmaceutical research has fallen, if it has fallen, indeed.

The paper starts from the systematic evidence as to the decline in output, and goes back and tries to determine whether or not this is due to either regulation or to depletion factors. But if we look forward at the implications of this for the industry, the same result follows from either proposal of interpretation. So, in that sense, the whole argumentation may be moot, as far as the industry is concerned, because if the output of R & D has really fallen, and if the attrition rate is increasing, and if the yield, in terms of the

revenue per new chemical entity is not increasing, then the expected return of continued R & D, everything else being equal, is falling, or indeed, is close to zero; which would then imply that, for the industry, at least, continued investments in the area may simply be unprofitable and unwarranted. That conclusion may indeed follow quite independently of whether it's depletion causing this, or whether it's regulation. And this may, in fact, be the most important consequence, looking forward, as I said, rather than retrospectively. I'd like to throw that out as a comment for the panel.

MR. SCHANKERMAN: While I agree that the empirical sum of our information indicates that the real rate of return may be falling, or near zero, I think it's true that the source of the decline, if indeed, there's been a decline, has some implication for our choice of familiar strategies. I mean, if it's just depletion, and that's just a case of divine intervention then it would strike me that there may not be a whole lot to do, certainly not to change the regulatory review. On the other hand, if it has been due — at least in large part — to regulation, then, of course, the strategy ahead of us is clear. So I'm only in partial agreement.

DR. GRABOWSKI: I think that I would agree with Professor Stauffer that there's a strong presumption that the rate of return has declined. To what extent are the rates of return sufficient to sustain continuing investment? If it is true that rates have been declining and if this continues, then we'll see a very different industry ten years down the line.

I would agree, in addition, though, that to try to develop to what extent this is related to either regulation or other factors is important, in terms of how one proceeds in a policy sense.

DR. ASHFORD: Let me offer quite a different possible interpretation of your figures, namely that, in fact, the rapid decline which appears over four or five years, from '59 to '63, was in fact, due to some sort of research depletion for reasons which may become clear over our luncheon address, or through something I may say tomorrow. It may be that what regulation has done has been to help the situation, rather than hurt it by increasing the R & D intensity, although along safety and efficacy lines. Increased R & D intensity of this sort may have expanded the dimensions under which one examines the product, and thus inhibited the industry from reaching the more precipitous, low levels that it otherwise would have done. This pattern has been followed in other areas of innovation, which I will talk about tomorrow. But it might be that regulation has, in fact, made the situation less worse than it would have been under what appears to be a real depletion in research function.

DR. DEMSETZ: Any reply or comment?

I will make one comment. Anything may be the case.

(Laughter.)

MR. WOODWARD: I very much enjoyed the remarks. One problem that I'm concerned with is the numerator of the dependent variables in chemical entities. You might come up with different results on the impact of regulations if you restricted yourself to chemical entities which are important therapeutically or moderately important therapeutically as your dependent numerator, rather than all new chemical entities, which included, according to FDA, in the pre-1962 data, a substantial number of very slightly important therapeutic advancements.

DR. GRABOWSKI: Well, as you're aware, there is more than one list of important innovations here. We do have, as further research is done in this area, to look at weights, other than sales weights. In our footnote on this matter, we noted that in some of the related analyses to our work, at least on the concentration issue, David Schwartzman did a fairly exhaustive analysis of all different kinds of weights, including important innovations from a number of sources, and there's a lot of disagreement among the different sources as to what constitutes an important NCE, medically. His general finding was that it didn't change the general qualitative nature of the results. We plan to look into that question. However, I think the fact that the market share, the average market share of NCE's has not increased over time, in terms of sales, raises a question. If one were to make the argument that essentially, the quality of NCE's, in terms of being medically important, has increased over time, and yet the market shares within a particular therapeutic category haven't (Table 1), then one is posed with a further question of explaining why that's so. Is it the case that, essentially, you're getting higher quality drugs for rarer diseases, or for smaller markets? That approach would seem to be an implausible kind of strategy for firms to be pursuing in this kind of environment.

DR. HINSON: I should like to throw out several caveats, one of which was raised by the last speaker from the floor. I think that the discussion this morning has failed to take into account, particularly in the U.S. and to a large extent, in the U.K., Scandinavian countries, Australia and Japan, the regulatory process. For example, when you try to segregate out research from development, and you try to generate some empirical data as between the two, you're totally failing to take into account — if I understand your remarks this morning — the amount of additional research that goes back into the product, as a result of the regulatory requirements, and also, the interdependence between research and development, in order to secure premarketing clearance of new products in the particular jurisdictions I've mentioned.

Secondly, if you generate a data base of new chemical entities, I don't think that really has any relationship at all to the research depletion or aggregation involved. I say that because you have an abundant amount of

new chemical entities that never see the light of day, for various and sundry reasons, economics being one, regulatory being another. So your data base, in order to establish the new chemical entities being generated throughout the world, is quite a different thing from the new chemical entities which are being presented to the regulatory agency.

Invariably, how you measure the significance of a new chemical entity is something that even the U.S. Food and Drug Administration has yet to finalize. For example, there are proposed guidelines at FDA with respect to how the FDA would establish a priority system on the processing of investigation of new drug applications — as well as new drug approvals. And the FDA has not been able to even establish how they would themselves establish such priorities. Therefore, in absence of taking all these questions into account, I fail to see how any policy decisions can be made based on the data base presented this morning.

DR. DEMSETZ: Any comments?

DR. GRABOWSKI: Well, a general one concerning scientific methodology. Scientific methodology requires abstracting from a lot of factors. And in addition, one has to deal with the data that's available. In general, I think most of the points you raise are not points that would necessarily change the direction of the analysis. They are qualifying points that one would put into a refined analysis, such as how much R & D actually goes to NCE.

The crucial thing for this kind of model is to what extent is it changing dramatically over time? If it is not, then one can get a reasonably accurate measurement of the impact of the variables from the procedures employed. I think some of the trends are so dramatic that, even if the model were changing over time, the change would necessitate a qualifying revision, rather than a revision that would change the whole nature of the results.

DR. DEMSETZ: I would think that there was so much noise in the data that that would bias the coefficients toward zero, rather than anything else. I would be even more surprised to get a significant relationship.