PRODUCT QUALITY REGULATION AND INNOVATION IN THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

This thesis examines the effect that federal regulation of the product quality of new drugs (through safety and efficacy requirements) has had on the flow of new drugs onto the market place. The approach is to econometrically estimate these effects using disaggregated therapeutic class data from the 1970's.

There are two primary estimations. First, the current effects of regulation on the production function relation between introductions and research expenditures are estimated. Second, the indirect effects of regulation on research effort are estimated in a research expenditures equation. These estimates are then combined to estimate the overall effect of regulation on introductions in the current era.

In addition to the basic estimations described above, several important subsidiary issues are treated in the thesis. One is a discussion of the decline in new drug introductions of the 1962 era in terms of its individual therapeutic class components. This discussion gives strong support to the position that nonregulatory factors precipitated that decline in the rate of product introductions. Also, the project selection process of major pharmaceutical companies is examined in great

detail. That discussion, and some econometric tests of hypotheses generated, clearly demonstrates that in order to predict how firms will respond to changes in environmental factors affecting profitability, one must first understand how firms collect, evaluate, and apply information concerning those factors.

Thesis supervisor and title: Peter Temin, Professor of Economics

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Product Quality Regulation and Innovation in the Pharmaceutical Industry

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Chapter 1. Introduction

Section 1.1. Introduction

Direct federal control of the quality of products in individual markets is a relatively recent phenomenon in this country. The oldest and best developed form of this regulation exists in the pharmaceutical industry. For practical purposes this regulation began in 1938 with the passage of the Food, Drug, and Cosmetic Act, which required that new pharmaceutical products be proven safe for human consumption before they could be placed on the market. In 1962 the Act was amended to further stipulate that substantial evidence be presented that products are effective in their intended uses before marketing.

These requirements have created a great deal of controversy among those interested in this area. One of the more intriguing and important aspects of this controversy concerns the effects of this regulation on innovation in this industry, which it is important to understand for a number of reasons.

First, pharmaceutical products have played a major role in the rapid advancement of our health care system's ability to mitigate the effects of many diseases over the past 40 years.[1] The rate of introduction of new products will be related to the continued advance in the quality of drugs available. Second, not only is product quality regulated in this industry, but the process of innovation itself comes under the scrutiny and supervision of government agencies. And, as other research intensive industries are being considered for similar

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[1] See Silverman and Lee, Pills, Profits, and Politics, pp. 1-23.

regulations, it is important to understand the full social implications of this regulation. Only in this way can society make informed decisions about the types of controls it wishes to impose on those introducing new products into the market place.

The interest level is also high in this area because there are enough data and hard facts available to begin to give some answers to these pressing issues. So far, however, not enough information has been provided to give definitive answers.

One of the most pressing issues concerning regulatory effects on innovation is the impact of regulation on the current rate of new product introductions. Related issues have received significant attention in the literature concerning the effect of the regulations on innovation. However, to date there has not been an attempt to examine the effects of regulation on introductions in the 1970's, as previous estimations have focused on data from the 1950's and 1960's.[2]

The estimation of these effects will form the core of this thesis. Since it is desirable to estimate the current effects of regulation, abstracting from possible short-run adjustments to the new regulations in the post-1962 era, the estimations will concentrate on data from 1970 to 1976. Thus the resulting estimations can be clearly interpreted as estimating true regulatory effects rather than measuring the effects of a decline in research opportunities that may have occurred in the early 1960's (see Section 1.2.).

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[2]See the Literature Review below. The one exception is Grabowski, Vernon, and Thomas (see footnote 11 in this Chapter) who carry out some estimations on a 1954-1974 data base. However, even here the driving force in their estimations is the drop in introductions of the 1962 era (see Stylized Facts).

In order to estimate the overall effects of regulation on introductions, it is necessary to estimate both the direct effect of regulation on the rate of introductions and its indirect effect on the production of new drugs through its effect on research spending. To estimate regulatory effects in these two areas, for the current period, will require that data on introductions, research expenditures, and other variables be disaggregated into individual therapeutic class components for use in the estimations. This will be the first use of therapeutic class data for these purposes and it will greatly clarify the role of various factors in changes in the rate of introductions. However, at this point it is worthwhile to formalize the goals of the thesis to add clarity to the current and later discussions.

The question that is to be answered is "What are the direct and indirect effects of regulation of product quality on the overall rate of new product introductions in the pharmaceutical industry?" Mathematically, what is:

$$(1.1) \qquad \frac{dNCE}{dReg} .$$

where:

NCE = the number of new drugs marketed annually, and

Reg = the overall stringency of government safety and efficacy standards.

Others (see below) have established the following mathematical relationship:

(1.2) $NCE = f(Res, Reg)$

where:

Res = the research expenditures of the pharmaceutical industry.

Thus the stringency of government regulation of the quality of new drugs coming onto the market will have a direct effect on the number of drugs marketed. In addition, regulation affects the profitability of pharmaceutical research. It should therefore affect the level of research expenditures and thereby have an indirect effect on the rate of new product introductions. So the mathematical system has the additional relationship:

(1.3) $Res = g(Reg, \bar{X})$

where:

$\bar{X}$ = a vector of nonregulatory factors that will affect the level of research spending.

In order to estimate the overall effect of regulation on introductions it is necessary to estimate both the direct and indirect effects. Mathematically, returning to (1.1), there is the following relation:

(1.1) $$\frac{dNCE}{dReg} = \frac{\partial f}{\partial Reg} + \frac{\partial f}{\partial Res}\,\frac{\partial g}{\partial Reg}\,.$$

The core of the thesis is to estimate the various elements of (1.1) and thereby arrive at an overall estimate of the current effects of regulation on new product introductions. In the estimations there are several sharp departures from previous work in this area.

First, previous work rests entirely on estimating the historical drop in overall new product introductions that occurred in the 1962 era (see Sections 1.2. and 1.3. below). Besides resting on a single historical drop in introductions, these equations stop in 1971. To the extent that previous estimates are relevant for current policy analysis, it must be assumed that what happened in history is still happening. This deficiency is corrected by estimating equations over the 1970's period.

Second, other estimations have been carried out on aggregate data. The current work examines the way in which new product introductions in specific therapeutic classes respond to changes in the stringency of regulation. As will be seen throughout the thesis, disaggregating aggregate industry data and examining changes in individual therapeutic classes greatly clarifies the underlying effects of regulation and other factors. For instance, disaggregation permits the estimation of the effects of regulation on new product introductions in the 1970's (i.e. using disaggregated data will permit the estimation of (1.2) for the 1970's which has not previously been possible).

Finally, previous work has not analyzed the effects of regulation on the level and allocation of research expenditures in the industry. Thus, the research expenditures equation, (1.3), has not received formal treatment and only passing attention in the literature. However, using the disaggregated data cited above we will be able to estimate the effects of regulation on research.

The plan of the study is as follows. First, a few stylized facts concerning the flow of new products onto the market and the accompany-

ing changes in regulation will be presented. Next the existing literature will be presented and critically evaluated. This will complete the first chapter.

Chapter 2 will present new estimates of the direct effects of regulation on new product introductions using data from the 1970's (Equation (1.2) will be estimated). Chapter 3 will present a model of the pharmaceutical R&D process. The basis of the model is a series of interviews with high-ranking R&D decision makers in major drug firms. In Chapter 4 the model from Chapter 3 is formalized and econometrically tested and the overall effect of regulation on the level and allocation of research funding is estimated (Equation (1.3) is estimated). Finally, in Chapter 5, the estimates of Chapters 2 and 4 are combined to arrive at an overall estimate of the effect of regulation on new product introductions (Equation (1.1) is estimated.) In addition, there is a re-examination of the traditional position that regulation caused a major fall in the rate of new product introductions in the period immediately following the 1962 amendments.

Before proceeding, a disclaimer needs to be made. Generally, the information presented in this thesis is an attempt to measure the trade-off between greater stringency in the safety and efficacy standards enforced by the Food and Drug Administration and the rate of introduction of new products. The reader should keep in mind that the purpose of safety and efficacy requirements is to lower the rate of introduction of new products (by keeping ineffective and unsafe products off the market). Thus, for most of the measurements carried out in the course of this study, it is difficult to determine if we are socially

better or worse off if the numbers turn out to indicate large trade-offs, as usually happens in the succeeding chapters. Until more is known about the kinds of drugs that regulation is keeping off the market, it is difficult to conclude on the basis of the evidence presented here, whether the efficacy requirements are too stringent or not stringent enough.

Section 1.2. Some Stylized Facts

The modern pharmaceutical industry has its roots in the period between the two World Wars. The discovery and clinical application of the sulfanilamides and penicillin set in motion the events which would transform the industry.[3] The industry was changed from primarily producers of very high grade chemicals into the research-intensive producers, packagers, and marketers of modern pharmaceutical products. The needs and problems of wartime therapy contributed significantly to the growth of the industry and by the end of the Second World War there was a "great mushrooming of drug research."[4] Basically, there developed a consensus in the industry that there was money to be made by investing funds in research efforts designed to find new therapeutic compounds. Thus began the pharmaceutical industry as we know it today.

As can be seen from Table 1.1 there followed a dramatic revolution in the number of products available on the market. There were a sig-

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[3]See Temin, "The Evolution of the Modern Pharmaceutical Industry," M.I.T. Working Paper, 1978, for a good discussion of this transformation.

[4]Temin, "The Evolution," p. 13.

nificant number of new products introduced annually in the 1940's and this number escalated sharply in the 1950's.

Table 1.1: Annual Introductions of New Chemical Entities

1941	20	1952	37	1963	12
1942	14	1953	55	1964	19
1943	10	1954	36	1965	18
1944	14	1955	44	1966	16
1945	14	1956	44	1967	18
1946	20	1957	53	1968	7
1947	24	1958	32	1969	10
1948	27	1959	56	1970	17
1949	42	1960	47	1971	13
1950	33	1961	36	1972	9
1951	47	1962	26	1973	17

For data from 1950-1973, data are New Chemical Entities excluding new salts and esters of previously marketed products, source: Henry Grabowski, Drug Regulation and Innovation, AEI, 1976, p. 18. Data excluding salts and esters are not available for the 1940's, thus the data from 1941-49 include these derivative products, source: Paul de Haen, Nonproprietary Name Index, 1974.

In the late 1950's Senator Estes Kefauver opened hearings to investigate the pricing practices in the industry. It seemed unlikely that new legislation would emerge from this activity until mid-1962. At about this time the scandal and tragedy of thalidomide burst upon the scene. This raised the issue of the safety and efficacy of pharmaceutical products. The bill, which had been languishing in committee,

was resurrected, amended, and passed.[5] Among other requirements, the new amendments forced manufacturers to provide "substantial evidence" that their products are effective in their intended uses before being permitted to market them.

At the same time, there was a drop in the rate of introduction of new pharmaceutical products onto the market. The annual number of introductions is graphed in Figure 1.1.[6] It is easy to see that there is a considerable difference between the period beginning in 1962 and the period of the 1950's. It is this difference that forms the heart of the controversy in this industry. Essentially, the controversy relates to whether regulation is responsible for the drop in introductions that occurred in 1962 or whether it was due to some other cause.

The traditional position has been that regulation was the primary factor in this decline (see the next section for specific references). This interpretation has been the driving force behind previous estimations of the effect of regulation on introductions of new products.

This is not the motivating factor in the estimations carried out in this thesis. Instead, the work presented here is an attempt to

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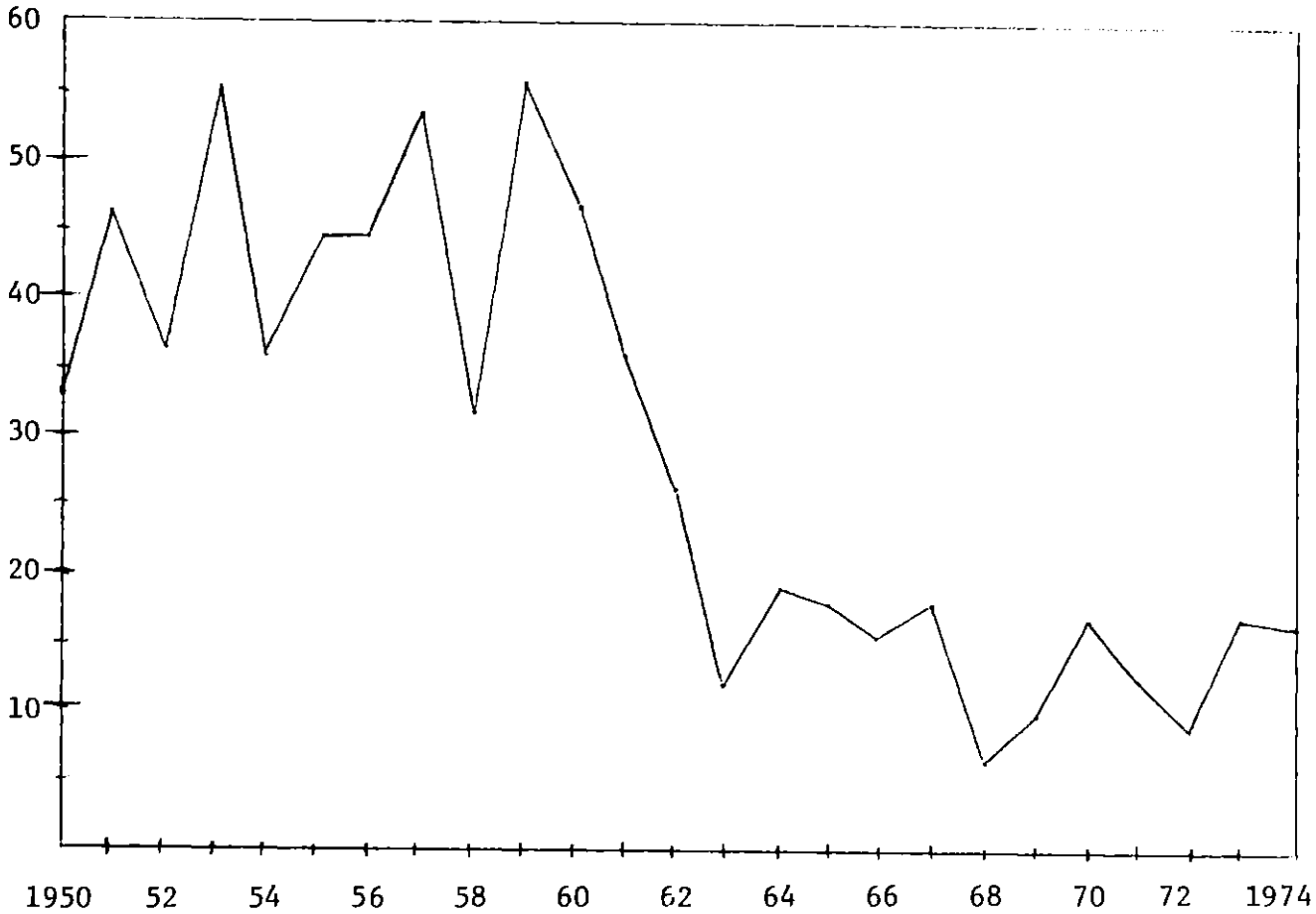
[5]The bill had two major amendments during the months before passage. First the compulsory drug licensing provision, which had been at the heart of the bill, was removed. Second a requirement that new drugs be proven effective before marketing was added. The bill was finally passed in October. See Harris, The Real Voice.

[6]The reader should note that throughout the thesis new introductions include only new chemical entities, excluding new salts and esters of previously marketed products, unless specifically stated otherwise. This is because the production technology of new chemical entities (other than salts and esters) is substantially different from that of salts and esters.

Figure 1.1
New Chemical Entities, 1950-1974



Source: H. Grabowski, see Table 1.1 above.

measure current regulatory effects on introductions. Thus the estimations generally avoid the 1960's and concentrate on the 1970's. However, the determination of the cause of this historical decline in introductions is important. Any such dramatic change in the innovative character of an industry is significant and worthy of study. Therefore, in Chapter 5, there is a reexamination of this historical fall in introductions. This reconsideration is the first attempt to examine the therapeutic class breakdown of the fall. And though the work is preliminary, the results clearly indicate that nonregulatory factors were major determinants of the fall in introductions.

Section 1.3.1. Literature Review

In this section the major elements of the literature concerning regulation and innovation in the pharmaceutical industry are reviewed. This literature review will be limited to that literature directly concerned with the effects of regulation on research in the industry.[7]

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[7]The other literature on various economic aspects of this industry is quite diverse and interesting even though it is not directly related to the issues raised in this thesis. It is worthwhile to present a brief outline of some of this important work. The literature can be conveniently divided into two subsets: the first is literature that directly deals with innovation in the industry and the second is literature concerned with other economic aspects of the industry such as profitability, pricing, and the demand side of the market.

Innovation in this industry has probably been studied more than innovation in any other industry. This is both because pharmaceutical innovations are more directly comparable to one another than other innovations and because of the availability of relatively good data for estimations. One of the better background pieces in this area is Schwartzman's, Innovation in the Pharmaceutical Industry (see the Bibliography of the thesis for more complete references).

One of the main branches in this literature on pharmaceutical literature is tests of the relation between firm and market characteristics and innovative inputs and outputs. Some of the better pieces in this area include: Comanor, "Research and Technical Change in the Pharmaceutical Industry," Grabowski, "The Determinants of Industrial Research and Development: A Case Study of the Chemical, Drug, and Petroleum Industries," and more recently, Vernon and Gusen, "Technical Change and Firm Size: The Pharmaceutical Industry." Other interesting work on innovation in the industry can be found in Schankerman, "Common Costs in Pharmaceutical Research and Development," Teeling-Smith, "Comparative International Sources of Innovation," Grabowski and Vernon, "Structural Effects of Regulation on Innovation in the Ethical Drug Industry," and Hansen, "The Pharmaceutical Development Process."

In addition to work on innovation in the industry, there is a host of other interesting work on various economic aspects of the industry. This work includes substantial branches covering pricing practices, profitability, product differentiation, and the development of the industry and its regulation.

In the pricing area see Schankerman (see above), Weston, "Pricing in the Pharmaceutical Industry," Reekie, Pricing New Pharmaceutical

(continued on following page)

In the review the major pieces of work in this area are presented and critically evaluated.

The first major piece dealing with the effects of the 1962 amendments on pharmaceutical innovation was written by M.N. Baily.[8] He estimated a productivity relationship of the form:

$$(1.3) \qquad \frac{NCE_t}{E_t} = Ae^{\alpha D+\beta P_t}u_t$$

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7 (continued from preceding page)
Products. In the profitability area the discussion has centered around expensing intangible capital and its effect on reported profit rates and on the effects of patents on profitability. For examples of the former, see Ayanian, "The Profit Rates and Economic Performance of Drug Firms," Clarkson, Intangible Capital and Rates of Return, and Grabowski and Mueller, "Industrial Research and Development, Intangible Capital Stocks, and Firm Profit Rates," among others. Two important works on patents and profitability are: Steele, "Patent Restrictions and Competition in the Ethical Drug Industry" and Costello, "The Tetracycline Conspiracy."

Some work closely related to the patents and profitability literature is work on competitive product differentiation. Among the interesting work in this area is: Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the U.S.," Reekie, "Price and Quality Competition in the U.S. Drug Industry," and Shifrin, "The Ethical Drug Industry: The Case for Compulsory Patent Licensing."

Excellent pieces on the role of regulation and the development of this market can be found in Temin, "The Evolution of the Modern Pharmaceutical Industry," and "The Origin of Compulsory Drug Prescriptions," and Mayer, "America's Health System and Medical Research: Pluses, Minuses, and Ethical Dilemmas."

Finally, there are a number of worthwhile seminar compendia which contain some of the articles cited above as well as other interesting work. These include: Link and Mitchell, ed., Impact of Public Policy on Drug Innovation and Pricing, Helms, ed., Drug Development and Marketing, and Cooper, ed., Regulation, Economics, and Pharmaceutical Innovation.

[8] Baily, "Research and Development Costs and Returns: The U.S. Pharmaceutical Industry," JPE, Jan/Feb 1972, referred to hereafter as Baily.

where:

NCE = Annual introductions of new chemical entities

$E_t = (R_{t-4} + R_{t-5} + R_{t-6})/3$

R_t = Research expenditures in year t

$$D = \begin{cases} 0 & \text{before 1962} \\ 1 & \text{1962 and after} \end{cases}$$

A = Arbitrary constant

P_t = A measure of industry research opportunities.

Baily interprets the equation as a productivity relationship. Equivalently, it is a production function in which constant returns to scale are imposed exogenously. Following Baily's interpretation, the left-hand side is the number of drugs per given level of research expenditures (in other words, the productivity of the research expenditures). He hypothesizes that this is a function of the availability of research opportunities (P_t is an inverse measure of research opportunities) and whether or not the government regulates the efficacy of new products entering the market (thus D assumes the value one in all years in which there was efficacy regulation). The hypothesized signs are α and $\beta < 0$. Baily estimated this relationship using time series data from 1954 to 1969 and obtained the following fitted equation:

$$(1.4) \qquad \ln \frac{NCE_t}{E_t} = \underset{(0.295)}{4.708} - \underset{(0.218)}{1.337D_t} - \underset{(0.0104)}{0.0385P_t}$$

$R^2 = .947 \quad \rho = -0.3 \quad D.W. = 1.98 \quad t = 1954\text{-}69.$

standard errors in parenthesis.

He interpreted the estimation results to mean that government regulation of efficacy had significantly reduced the productivity of pharmaceutical research. His calculations indicated that in the long run it would cost approximately 2.4 times as much to produce a given annual rate of introductions under a regulatory scheme as compared to a non-regulatory scheme. These results are very provocative and they have been cited frequently by critics of regulation in this industry. What do they mean?

As Baily carefully emphasizes, they should be interpreted with great care. He states, "In terms of goodness of fit and standard errors, this new product production function works well, but we have had to work rather hard to get good results, adding variables and making strong assumptions about the functional form."[9] It is appropriate to take a few pages to point out the conceptual implications of Baily's specification.

First, as noted above, the specification imposes constant returns to scale in research expenditures. This creates several problems. The structure disallows industry-wide economies or diseconomies of scale. Second, running the regression on industry-wide data requires that a marginal dollar spent on research in one firm will make the same contribution to industry R&D output as would that dollar spent in any other firm. For this to be strictly true it is necessary for the industry to be in long run equilibrium and each firm must also be in long run equilibrium. In addition there must be no intra-firm economies

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[9]See Baily, p. 77. He is very careful to point out what he sees to be problems of interpretation in his work.

of scale. These requirements are all in addition to the normal requirements of a regression equation. This should not, a priori, be taken as a more critical problem than it is in similar aggregation situations throughout economics. Most econometric relationships are based on similar equilibrium conditions. However, the restriction of the research elasticity to be unity is testable, and such a test should be done.

The next problem is that Baily's measure of the output of research (NCE_t) is the total number of new drugs introduced. This contains two distinct classes of compounds. The first class contains new single chemicals not previously marketed in any form. The second class contains new salts and esters of previously marketed products. In general, one would not expect the same production function to hold for the relatively low-cost derivative products as holds for the truly new products introduced in the course of research. Thus, regardless of how one views the therapeutic contribution of new salts and esters, one should not include them in the same regression as other NEC's.[10]

Another problem is that new products are not distinguished by therapeutic class. This introduces a question concerning the stability of the production function relationship. Fundamentally, the specification used assumes that the production function is an aggregate one. If, in fact, the production technology of new products varies across therapeutic classes, or if there are economies of scale and the true production function relationship is based on therapeutic classes, then Baily's equation will introduce specification bias into the coefficients.

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[10]The estimations in the thesis improve upon this in that the new product introduction data is exclusively NCE's excluding new salts and esters.

The final problem that needs to be pointed out is the measure of regulation. It is not clear that the dummy variable will pick up the effects of regulation. First, the law imposing the regulations was passed in 1962, but it is difficult to believe they could have had a large effect in the year (or possibly even in the two or three years following the passage). Second, regulation is not zero-one. The stringency of regulation will be directly related to the standards used to determine safety and efficacy. These standards vary substantially across the different divisions of the FDA and across time. This is because the determination of safety and efficacy is largely a matter of judgment and the judgment of different administrators varies in the determination of what is necessary for proof. In addition, the prevailing scientific standards change over time and this can indirectly affect the standards used by the FDA. Thus using only one overall measure of regulation will very imperfectly measure the effects of regulation on the introduction of new products.

As can be seen, there are a number of conceptual and econometric problems with Baily's work. However this should not be taken to mean that this work is not a significant contribution. It does imply that its results should be interpreted with caution and that, where possible, the problems should be corrected to see how the results will change.

This can be accomplished in several ways. The assumptions of the model can be relaxed and then the results examined to see if they persist. Alternatively, information from other sources can be examined to see if the assumptions of the model are satisfied. Both of these will be done below.

The next major piece that is concerned with the estimation of production function relationships is by Grabowski, Vernon, and Thomas (GVT).[11] They make a number of substantial improvements on Baily's work, though the fundamental approach to the issues is very similar.

Their most significant improvement is that they go to international data to estimate the depletion of research opportunities. In other words, one of the frequently cited criticisms of Baily's work has been that there was a drop in research opportunities in the early 1960's and that this caused the decline in the rate of introduction of new products. Thus since Baily only used a dummy variable to pick up the effects of regulation, his variable may be proxying for the fall in research opportunities rather than measuring the effects of regulation.

GVT improve this aspect of the estimation by using the productivity of research in the United Kingdom as a control for changes in the productivity of research that are induced by a depletion of research opportunities (using the assumption that research opportunities should be the same in the two countries). They show that even when the U.S. productivity figures are corrected for changes in U.K. productivity, there is still a sharp drop in productivity in 1962 that must be interpreted as being caused by regulation.

Their estimated equation was:

$$(1.5) \qquad \ln\left(\frac{NCE_t}{E_t}\right) = \underset{}{-0.49} \underset{(0.28)}{-0.85\, D_t} \underset{(0.22)}{-0.10\, T_{pre\text{-}60}} \underset{(0.58)}{-0.15\, T_{post\text{-}60}} \underset{(restr)}{}$$

$$t = 1954\text{-}74 \qquad R^2 = .92 \qquad D.W. = 1.89$$

[11] See Grabowski, Vernon, and Thomas, "Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Drug Industry," J. Law and Econ., Fall 1978, pp. 133-63, referred to hereafter as GVT.

where:

NCE_t, E_t, D_t = as above

$$T_{pre\text{-}60} = \begin{cases} 1 \text{ in } 1954 \\ \vdots \\ 7 \text{ in } 1960 \\ 7 \text{ in } 1961 \\ \vdots \\ 7 \text{ in } 1974 \end{cases}$$

$$T_{post\text{-}60} = \begin{cases} 0 \text{ before } 1961 \\ 1 \text{ in } 1961 \\ 2 \text{ in } 1962 \\ \vdots \\ 10 \text{ in } 1970 \\ \quad \vdots \end{cases}$$

Thus the variables $T_{pre\text{-}60}$ and $T_{post\text{-}60}$ are supposed to control for declining productivity. The coefficient for the post 1960 time variable was estimated using U.K. data and was restricted in equation (1.5).[12]

The second major improvement of GVT is that they relax the assumption that there was a once-and-for-all change in the stringency of regulation in 1962. In other words, a new regulatory scheme was instituted in 1962 but the stringency of regulation will vary substantially over time. In particular they argue that the stringency of regulation will be highly correlated with the average time it takes the FDA to approve a product for market. They then repeat several of their previous regressions using this delay time as their measure of regulation. The estimated effects are of approximately the same size as the other estimates. On the whole, their estimates indicate that regulation has in-

[12]The least squares estimates of the coefficient of this variable (estimated on U.S. data) is -.092. So the restriction will attribute more of the reduction in productivity to depletion than would a simple regression on U.S. data using this variable to account for declines in research opportunities.

creased the cost per drug by approximately 90-130%. So the costs have approximately doubled in response to regulation in both the Baily results and the GVT results. Finally it should be pointed out that the limitations indicated concerning Baily's work apply to the work of GVT, with one exception, their improved measurement of regulation.

This brings us to the work of Sam Peltzman. It is probably the best known work concerned with the economic effects of the 1962 amendments.[13] The focus of Peltzman's work is to measure the costs and benefits of the 1962 amendments. Most of his estimations and assumptions are not directly applicable to the questions under discussion in the thesis. However, in order to estimate the costs and benefits of the amendments, he first had to estimate the effects of regulation on the rate of new product introductions. It is these estimations that are relevant to the current discussion, and therefore attention here will be restricted to a discussion of this part of his model. For a more general critique of Peltzman's overall approach, one should consult, "An Evaluation of Consumer Protection Regulation: Comment" by T. McGuire, et al., JPE, 1975.

Peltzman's model of new drug introductions is a demand-pull model. The essential difference between his and other models is that he concentrates solely on the demand side of the market whereas other models focus on the supply side. His model assumes that all drugs are non-decaying units of therapeutic value that can be produced at a constant cost (i.e. the long run supply curve of these units is horizontal).

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[13] Sam Peltzman, "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments," JPE, Sept/Oct 1973, pp. 1049-1091, hereafter referred to as Peltzman.

Therefore the demand for these units of therapeutic value, on the part of producers of drugs, will only be a function of the size of the anticipated market.[14] Thus, rather than looking at the effect of research effort (as measured by the level of research expenditures) as the means of producing new products he attempts to measure the demand for products, and then argues that the demand feeds directly through to increase the supply of products. In other words, since the long run cost of finding new drugs is a constant, one can restrict attention to the demand curve to determine the supply of drugs and ignore the production side of the market. Thus:

$$(1.6) \qquad nce_t^* = f(X_t^*)$$

where:

nce_t^* = the number of drugs producers wish to have available in year t

X_t^* = the anticipated size of the market in year t.

He then argues that producers will estimate the size of the future market using past values of the number of prescriptions written and personal consumption expenditures on physicians' services. Mathematically:

$$(1.7) \qquad X_t^* = g(X_{t-j}, P_{t-j})$$

where:

X_{t-j} = a vector of past values of X_t

P_{t-j} = a vector of past values of personal consumption expenditures on physicians' services.

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[14] See Peltzman, p. 1052.

Peltzman then substitutes (1.7) into (1.6) to obtain:

$$(1.8) \qquad nce_t^* = h(X_{t-j}, P_{t-j}).^{15}$$

He then assumes that producers will examine the desired number of drugs and compare that with the stock available in the preceding period, NCE_{t-1}. Then producers will make up some fraction of the difference between the desired number of drugs and the number of drugs already available. So:

$$(1.9) \qquad NCE_t^* = k(nce_t^* - NCE_{t-1})$$

where:

k is a position fraction

NCE_t^* = the desired number of introductions in period t.

Substituting and solving for the reduced form of the desired level of introductions, one obtains:

$$(1.10) \qquad NCE_t^{\delta} = a + b\, X_{t-j} + c\, P_{t-j} - k\, NCE_{t-1} + u_t .$$

NCE_t^{δ}, the actual rate of introductions, can be substituted for the desired level, NCE_t^*, if one assumes that producers attain their desired level of introductions on average. He then allows for an R&D gestation period of approximately 2 years and obtains his empirical equation:

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[15] Alternatively, (1.7) could have been used in an equation to determine the level of research expenditures. The level of research expenditures could have then been used in a production function similar to Baily's. Thus Peltzman's approach is similar to a reduced form of Baily's, the primary difference being Peltzman's assumption that new drugs are "a homogeneous bit of nondepreciable therapeutic information" (Peltzman, p. 1051).

$$(1.11) \qquad NCE_t^{\delta} = a + b\, X_{t-2} + c\, P_{t-2} - k\, NCE_{t-1} + u_t \ .$$

where:

$\bar{X}_{t-2}$ = natural log of 3 year moving average of out-of-hospital prescriptions

$\bar{P}_{t-2}$ = natural log of 3 year moving average of personal consumption expenditures on physicians' services

NCE_{t-1} = Cumulative NCE's introduced since 1945.

The equation was then estimated over the 1948-1962 period to obtain the following empirical results:

$$(1.11) \qquad NCE_t^{\delta} = -2990.16 + \underset{(75.616)}{471.352}\ \bar{X}_{t-2} + \underset{(32.142)}{45.590}\ \bar{P}_{t-2}$$

$$- \underset{(0.113)}{0.672}\ N_{t-1} + u_t \qquad\qquad t = 1948\text{-}62.$$

To obtain an estimate of regulation's effect, Peltzman then extrapolated the estimated equation forward in time and compared the results to the observed rate of introductions in the post-1962 era, the difference between actual and observed introductions was attributed to regulation. The difference between this measure of regulation and Baily's is that Baily uses the post-1962 data to help estimate the nonregulatory parameters of the regression equation.

Peltzman estimates that the rate of introductions was approximately 34% of what it would have been in the absence of regulation. Baily estimates that the cost increase per drug was 240% in the post amendment period. If there was no reduction of research expenditures in

the 1960's in response to regulation (as will be shown in chapters 3 and 4 below), then Baily's results imply that the post-amendment introductions were approximately 42% of what they would have been in the absence of regulation. Thus the figures are basically comparable.

However, many of the same questions raised earlier regarding Baily's estimations apply equally to the case at hand. First, Peltzman's estimations require that there be no nonregulatory increase in the cost of producing new drugs in the relevant period. This would shift the cost curve of drugs upward in Peltzman's framework and would thereby cause a reduction in the desired level of drugs available. Thus Peltzman's omission of supply side factors is a questionable assumption. Second, his change in regulation is once-and-for-all and does not permit regulatory stringency to vary across time. Finally, his estimations treat all drugs and all regulation as homogeneous and this does not permit the necessary variation across therapeutic classes that was discussed above. Thus one has to question whether these results truly estimate the effects of regulation on new product introductions or whether some other factor has been a major determinant in the observed fall in introductions.[16]

The final piece of work to be considered is a portion of a recent book by David Schwartzman.[17] He does not use regression analysis to estimate the effects of regulation on research. Instead, he calculates the expected return to pharmaceutical research and estimates how it has

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[16]See Chapter 5 below for a more detailed discussion of these possibilities.

[17]David Schwartzman, Innovation in the Pharmaceutical Industry, JHUP, 1976, hereafter referred to as Innovation.

varied over time. The hypothesis is that factors which affect the expected return to research will affect the long run level of R&D funding. This will, in turn, affect the rate of introduction of new products over the longer run.

Schwartzman's estimates indicate that the expected pre-tax return to pharmaceutical research fell from 11.2% in the early 1960's to a current rate of approximately 3.3%.[18] These estimates are puzzling for a variety of reasons. The first puzzle is that in spite of the very low estimated expected returns that Schwartzman calculates, there have been continuing real increases in the level of R&D expenditures in the industry.

The second problem with Schwartzman's estimates is that he makes a number of strong assumptions about the expectations of managers concerning changes in demand, costs, and profit margins. This is not unreasonable, per se, except that Schwartzman never tests the sensitivity of his estimates to his assumptions.[19] It turns out that his model is very sensitive to a number of the assumptions that he makes. The Appendix shows there are a variety of reasonable assumptions under which the current expected return is in the range of 6-12%. This figure is in approximately the correct range for the cost of capital to pharma-

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[18] See Innovation, pp. 136-61. For a complete discussion of these issues, the reader should consult the appendix to this chapter. The discussion in the text relies heavily on the discussion presented there.

[19] See the Appendix to this chapter.

ceutical R&D.[20]

Finally, Schwartzman makes no real attempt to estimate the effects of regulation on the expected return to drug research. He attributes all of the fall in the expected returns to research to regulation. Some preliminary work contained in the Appendix indicates that regulation has had a significant effect on the expected return to research. However, the assumption that all of the decline in returns over the past 15 years is attributable to regulation is not confirmed.

Summarizing the literature, there have been several examinations of the direct effects of regulation on new product introductions, all of which have indicated rather large regulatory effects on introductions. However, all have relied critically on the fall in introductions that occurred in the early 1960's. On the other hand, advocates of regulation have argued that nonregulatory factors were major determinants of this fall in introductions.[21] Thus, the argument is made that regulation happened to change at a time when research opportunities were changing. GVT have made the most systematic attempt to analyze the role of declining research opportunities. Their results indicate that declining research opportunities were not a major factor in the fall in introductions, implicitly confirming the work of Baily and Peltzman.

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[20]The unweighted average Value-line β for pharmaceutical companies as a whole is 0.9. Using the Ibbotson and Sinquefeld estimates of the real average annual excess returns on the market to be 8.4% and the risk free rate estimated at .2% the cost of capital for these firms would be 7.8% after-taxes. See R. Ibbotson and R. Sinquefeld, "Stocks, Bonds, Bills and Inflation: Year-by-Year Historical Returns (1926-74)," Journal of Bus., 1976, p. 40.

[21]See Alexander Schmidt, presentation at the Writers' Seminar of the American Cancer Society.

However, there is a real issue as to whether GVT accurately measure the availability of research opportunities.

Chapter 5 attempts to further illuminate this question by disaggregating the fall in introductions and examining the therapeutic class components of the fall. However, it is worthwhile to briefly examine the GVT aggregate data to see if their measure of declining research opportunities is the conceptually correct measure. This examination is in the next subsection.

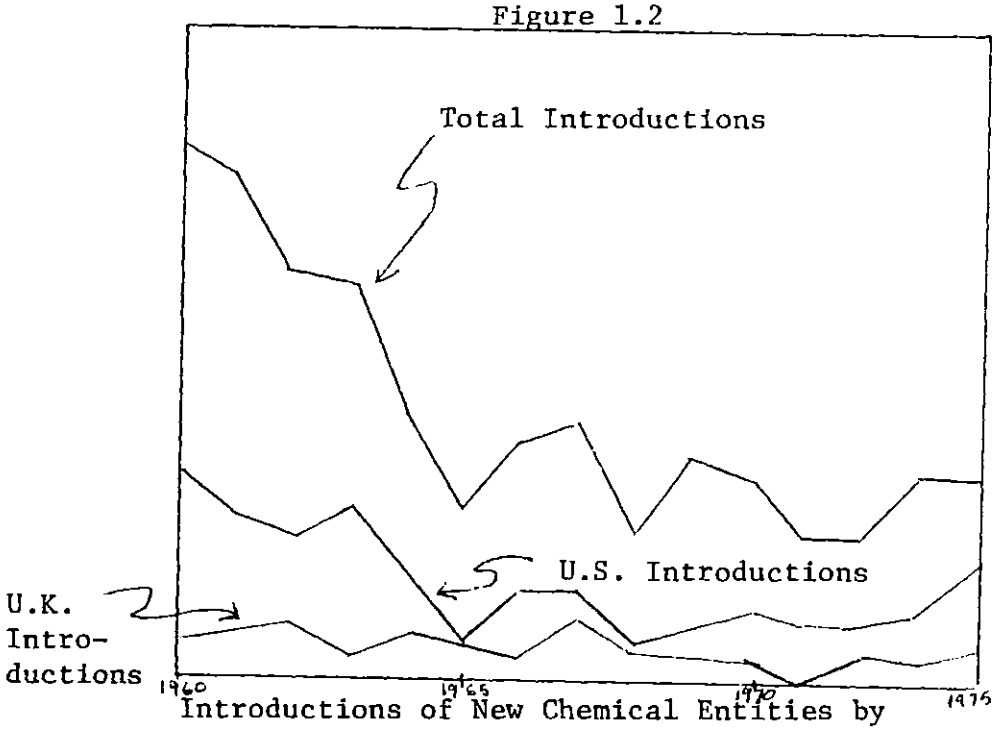
Section 1.3.2. The Depletion of Research Opportunities

Grabowski, Vernon, and Thomas claim that one can capture the effect of nonregulatory factors on U.S. new product introductions by examining introductions into the U.K. in the 1962 era. They examine how the ratio $\frac{\text{NCE}}{\text{Research}}$ changes over time in the unregulated U.K. market. They then argue that since regulations in the U.K. market did not change significantly in the 1962 period any changes in this ratio reflect the influence of nonregulatory factors.

There are three possible data series that could be examined in this regard: data for the U.K. domestic industry, data on U.S. introductions into the U.K. (and research), and the weighted average of the two. Unfortunately, which of these is the appropriate measure for the changing research opportunities of U.S. firms is open to debate and the choice makes a significant difference for the estimations. This difference can be seen in Figure 1.2 which graphs U.S. and U.K. introductions into the U.K. As can be clearly seen from the figure, domestic introductions were relatively constant in the early 1960's while the rate of

U.S. introductions fell sharply. GVT assume that the decline in U.S. introductions into the U.K. was a result of U.S. regulatory pressures due to an international spillover effect. Therefore they exclude the U.S. data from their estimations. In the pages that follow, it will be argued that U.S. regulations did not substantially affect the rate of U.S. introductions into the U.K. Therefore the GVT exclusion of U.S. data becomes a rather arbitrary exclusion that substantially affects their results.

Figure 1.2



Introductions of New Chemical Entities by U.K. firms and U.S. firms. Source: GVT.

In all fairness, the reader should note that if GVT had included the U.S. data there are a number of arguments that might be made in favor of using only the domestic U.K. data as GVT in fact did, especially since the evidence presented below is not conclusive that there were no U.S. regulatory spillover effects on international introduc-

tions by the U.S. industry. Thus the choice of either data series has a certain arbitrary element in it that substantially alters the results of the estimation.

Turning to the discussion of whether regulation had a significant effect on U.S. introductions into the U.K., there are three ways in which U.S. regulatory pressures could have caused such a drop. First, regulatory authorities could have caused a substantial reduction of research efforts in this country. Second, the authorities could have driven up research costs per project to lower the number of research projects, thus reducing foreign introductions. Third, the authorities had the power to prevent the overseas shipment of products manufactured in this country that had not been approved for marketing here. Did any of these happen?

As to the first, the answer is no. The empirical results in Chapter 4 will clearly indicate that the effects of regulation on the level of research in the 1960's were minimal. So the regulatory pressures did not influence overseas introductions through an effect on research expenditures in the 1960's.

The evidence concerning possible regulatory effects on the expenditures per project requires some background. The primary effects of regulation on expenditures per project will be to require additional tests before the product candidate can be marketed. A large fraction of the expenditures for these tests will be for additional human testing

which is primarily carried on outside the pharmaceutical company.[22] Further, the Pharmaceutical Manufacturers' Association has a long data series on the percentage of research performed outside the firm. This data is presented in Table 1.2.

Percentage of R&D Undertaken Outside the Firm

1961	1962	1963	1964	1965	1966
11.04	10.81	11.15	12.65	12.31	12.90
1967	1968	1969	1970	1971	
10.89	12.24	10.13	10.60	11.46	

It is apparent that there was some increase in expenditures in the years 1964-1966. However, the mean of this series is 11.47% and the standard deviation is .9%. Thus the 1964-1966 figures are well within normal bounds of statistical chance. So it does not appear that there was a jump in clinical research expenditures in the years following the passage of the 1962 amendments, though this evidence is not conclusive.

Finally, U.S. regulations could have caused a fall in U.K. introductions by prohibiting transshipment of unapproved products. It seems unlikely that this constraint could have had a large impact on foreign introductions. U.S. firms were, even at that time, very active on the

[22]This was discovered in the course of the interviews reported in Chapter 3. In response to the question, "Does your firm subcontract much of its research?" the nearly unanimous response was, "Only clinical research." It was further determined that most clinical research was subcontracted to outside clinicians because it is difficult for the company itself to gain access to patient populations necessary for the studies.

U.K. market,[23] which brought about the establishment of subsidiaries in that country. PMA member firms operated 57 manufacturing plants in Western Europe as opposed to only 106 plants in the U.S.[24] Thus, for the firm with a significant new product (one with a reasonable chance of commercial success) prepared for marketing, it seems unlikely that the firm could not arrange for British manufacture of its product. Together, these arguments cast doubt on the supposition that the drop in U.K. introductions (by U.S. firms) was directly or indirectly related to the U.S. regulations of that era.

This evidence leaves unexplained the drop in the rate of U.S. introductions into the U.K. However it can tentatively be concluded that something besides regulation was happening to the U.S. industry in the early 1960's. Furthermore, whatever this exogenous factor was, the changes in it are not well-reflected by a variable that measures changes in the productivity of research expenditures of British companies.

This is important because GVT, when measuring the decline in research opportunities, use the declining productivity of British domestic research as the control variable. If it is desirable to hold exogenous factors constant when estimating the effects of U.S. regulation on U.S. introductions, the above discussion indicates that it might be as appropriate to use U.S. introductions into Britain as the control rather

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[23] See GVT and George Teeling-Smith, "Comparative International Sources of Innovation," Chapter 2 in J. Cooper, ed., Regulation, Economics, and Pharmaceutical Innovation, American University, 1975.

[24] "Ethical Pharmaceutical Industry Operations and Research and Development Trends," PMA, Washington, D.C., 1967, pp. 25-26.

than the rate of British introductions. However, as Figure 1.2 clearly indicates, this would lead to significantly different results in the estimations.

The inability to hold exogenous factors constant in the estimation of regulatory effects in the early 1960's appears to be a fundamental problem with these pure time-series estimations from the early 1960's. It is clear that this was an era of flux in the industry, which makes it difficult to separate out the effects of regulatory and other factors using a single time-series data set. This suggests that a clearer picture might be obtained if the data could be disaggregated for more information. A strong possibility in this regard is to break down the data into individual therapeutic classes. This would give a more detailed picture of the decline in introductions and could lead to a deeper understanding of the factors affecting new product introductions. This approach is the one followed in this thesis. This is done in two ways.

First, data from individual therapeutic classes is used to estimate the effects of regulation on new product introductions in the 1970's. Second, the therapeutic class breakdown of the fall in introductions of the early 1960's is analyzed. This second procedure will clearly indicate that significant nonregulatory factors were involved in the decline in introductions of the early 1960's.

Section 1.4. Summary

In summary, there was a major fall in the rate of new product introductions in the pharmaceutical industry in the early 1960's. This happened concurrently with a qualitative change in government standards

for the marketing of new products in this industry. These events have generated a significant literature which analyzes some of the effects of regulation on innovation in this industry in the 1960's.

There are several major gaps in our understanding of the effects of these regulations on innovation in the industry which will be filled by this thesis. The first gap is that previous work has concentrated entirely on the historical fall in introductions of 1962. Therefore, the available estimations may or may not be a reliable indicator of current regulatory effects. This is overcome with current estimates of the effects of regulation on introductions.

Also, concerning a closely related issue, it appears from the above discussion that there may have been nonregulatory factors involved in the 1960's decline in introductions. This possibility is also explored in more detail later in the thesis. Further, previous work has not examined possible regulatory effects on research spending. These effects of regulation are also considered in the course of the thesis. That analysis will indicate that regulation has had a substantial effect on research expenditures in the industry. Throughout the thesis there has been an attempt to clarify and extend previous work on the effects of regulation on innovation as well as to contribute original information to our understanding of regulation and its impact.

The reader will find the first clarification and extension in the Appendix to this Chapter. In it Schwartzman's estimates of the expected return to pharmaceutical research are examined. In the first part of the Appendix, a number of Schwartzman's assumptions are relaxed to see how sensitive his estimated expected return is to minor changes in as-

sumed parameter values. In the second part of the Appendix, the effects of regulation on the expected return are estimated.

Appendix to Chapter One.

Several years ago David Schwartzman estimated the expected return to pharmaceutical research and development. This estimate has been published in several places and has received substantial attention in the literature.[1] Schwartzman estimates the expected return to be 3.3%, which he then goes on to say is much too low to be sustained in the long run. He interprets this to mean that the future will bring declining investment in pharmaceutical R&D which should be avoided as a matter of public policy. These estimates are reconsidered in this appendix. The focus will be on two issues.

First, Schwartzman claims that his estimate of the expected return is an upper bound. It will be shown that this is not the case. In other words, when a number of Schwartzman's assumptions are relaxed (either independently or together) the expected return is substantially greater than 3.3%. Second, according to Schwartzman's calculations, the expected return has fallen from 11.2% in the early 1960's to the current rate. He assumes all of this fall in expected return can be attributed to regulation. In the second part of this appendix there is an explicit attempt to estimate the effect of regulation on the expected return to pharmaceutical R&D.

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[1]See David Schwartzman, Innovation in the Pharmaceutical Industry, JHUP, 1976, Schwartzman, The Expected Return from Pharmaceutical Research, AEI, 1975, and Schwartzman, "Pharmaceutical R&D Expenditures and Rates of Return," in Drug Development and Marketing, R. Helms, ed., AEI, 1975, pp. 63-80. For references to Schwartzman's estimates see

Section A.1. The Expected Return to Pharmaceutical R&D Under Alternative Assumptions

Schwartzman's estimate of the expected return depends on several estimations and assumptions which he made in the course of his study. He estimates that it costs $24.4 million (1972 dollars) to produce a new drug and that the development time is approximately ten years.[2] He further estimates that the sales of a new drug will be $11.0 million per year for fifteen years (with a 2 year build-up period at the beginning and a 2 year decline at the end) and that the profit margin will be 15.4% of sales.[3] Using these assumptions, he sets up a discounting equation:

$$\text{(A.1)} \qquad \sum_{i=1}^{10} C_i(1+r)^i = \sum_{j=1}^{15} \frac{Y_j}{(1+r)^j}$$

He then solves this equation for the interal rate of return, which exists, is unique, and is positive in this formulation (it is positive if $\sum_j Y_j < \sum_i C_i$). It also follows that the cost of capital for this project, call it r^*, will be less than the unique internal rate of return if and only if the present discounted value of the project (using r^* as the discount rate) is positive. Thus it is important to determine the internal rate of return, or the "expected return" as Schwartzman calls it, and compare it to the cost of capital for pharmaceutical projects. The solution to (A.1), under Schwartzman's assumptions, yields an internal rate of return of 3.3%.

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[2] See Innovation, pp. 67-71.

[3] See Innovation, pp. 140-44.

Schwartzman claims that his return figure is an upper bound for the true expected return. He bases this claim on the fact that his estimate of the expected development time is on the low end of the possible values.[4] Thus if this time were placed closer to its probable value, the overall return would fall. On the other hand, he argues that the only assumptions that would lower the rate of return are the assumptions that pharmaceutical markets will not continue to grow in the future as they have in the past and the assumption that the gross margin on sales is 15.4%.[5] He then suggests that the assumption concerning development time is stronger than the assumptions concerning gross margins and market growth. This naturally suggests a test of the sensitivity of the estimated return to the various assumptions, which was not carried out. These tests are carried out here.

The tests will be of assumptions which Schwartzman himself indicated were sources of possible error. Additional possibilities are taken from his book. The one place where supplemental information is used is in the area of development cost. He estimates that it costs $24.4 million to produce a new drug but indicates that this might be in error. The author has independently estimated these costs and the estimated figure is $21.6 million (See Chapter 2). In addition, Hansen has made similar estimates using a completely different methodology and obtains an esti-

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[4]See Innovation, pp. 65-69, 139-43.

[5]See Innovation, pp. 144, 158. In all fairness to Schwartzman, he did test the sensitivity of his model to the gross margin assumption. However, this was the only such test carried out and it was not tested simultaneously with a relaxation of the other assumptions as is done below.

mate of $21.0 million.[6] Thus Schwartzman's estimate of the cost is taken as the relevant estimate.

Turning to Schwartzman's other assumptions, he indicates that the domestic sales of drugs grew at an annual rate of 7.9% from 1960-72 and he claims that foreign demand grew at an even faster pace.[7] He then assumes that demand will not continue to grow in the future. He also indicates that the gross profit margin on sales could be as high as 20%. Finally he indicates that product development time could be as long as fifteen years and product life could be as long as 20 years.[8] The tables on the following page report the expected return under these alternative assumptions.

As can be easily seen, the expected return is much more sensitive to the assumptions concerning profit margins, market growth, and product life than to the assumption that product development time is ten years as opposed to fifteen. In addition, little reason has been offered to make one believe that pharmaceutical markets will not continue their historical growth rate. Therefore, when one considers the very high growth rates of the international market, the estimated return with a 7% market growth rate and a fifteen year development period (with a 15.4% gross margin and a fifteen year product life) is probably close to the lower bound on the expected return which Schwartzman sought. This estimate of 5.9% is considerably larger than Schwartzman's esti-

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[6]See Hansen, "The Pharmaceutical Development Process," Mimeo, University of Rochester, 1978.

[7]See Innovation, p. 158.

[8]See Innovation, pp. 65-69, 143-49.

Table A.1. The Expected Return to Pharmaceutical R&D Under Alternative Assumptions

15 year Product Life

20 year Product Life

Part A: No Growth In Demand

DT \ GM	15.4%	20.0%
10	3.3	5.1
15	2.9	4.5

DT \ GM	15.4%	20%
10	5.1	7.5
15	4.5	6.1

Part B: Demand Growth = 7%

DT \ GM	15.4%	20.0%
10	7.1	9.9
15	5.9	8.3

DT \ GM	15.4%	20.0%
10	9.4	12.2
15	7.9	10.3

Part C: Demand Growth = 10%

DT \ GM	15.4%	20.0%
10	8.7	12.3
15	7.2	10.5

DT \ GM	15.4%	20.0%
10	11.2	14.8
15	8.4	12.8

DT = Development Time
GM = Gross Margin

mate. And it is easy to see that there are a number of situations in which the expected return would be much larger than this figure.

Limiting consideration to the case with 15 year product lives, the estimates indicate that the true expected return to pharmaceutical R&D is in the range of 5.9% to 12.3%. These numbers would be in approximately the right range for the cost of capital to this industry.[9]

Section A.2. The Effect of Regulation on the Expected Return

This brings us to the second task of the Appendix, estimating the effect of regulation on the expected return. Schwartzman attributes the decline of the expected return from 11.2% in the early 1960's to 3.3% in the early 1970's to the effects of regulation. This is an assumption on his part since he does not attempt to directly estimate regulatory effects. In this section the effects of regulation on the expected return will be estimated directly. This will include a direct estimate using all of Schwartzman's assumptions and an estimate using some of the alternative assumptions presented above.

Turning to the first, it is necessary to estimate the effects of regulation on new product development times and on the cost of development. The estimates to be presented in Chapter 2 of this thesis indicate that regulation has approximately doubled the cost of a new drug.[10] These estimates are very comparable to previous estimates of these regulatory effects (Chapter 2 contains explicit comparisons with other work).

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[9]See the text of Chapter 1, footnote 20, where it indicates that the cost of capital in this industry is approximately 8%.

[10]See Chapter 2.

Thus without regulation, using Schwartzman's cost estimates as the baseline, the cost per drug would be $12.2 million.

It is difficult to directly estimate the effects of regulation on new product development times. However, a reasonable approximation can be made. Over the period 1970-76 average regulatory delays in obtaining new drug approval were approximately two years. However, there are also increases in development time in addition to direct NDA approval times. If we take these delays to be one year (the estimates were derived using both one and two years of additional delay and were relatively insensitive to this assumption) then development time in the absence of regulation would be seven years. The expected return with a seven year development time and a $12.2 million development cost is 8.8%.[11] Thus one would conclude that under Schwartzman's original model the reduction in the expected return to 3.3% could not be entirely attributed to regulation.[12]

The final exercise is to estimate the effects of regulation on the expected returns under the alternative assumptions presented above. Taking the same cost estimates but allowing for a 7% market rate of growth gives an ex-regulation expected return of 13.1%. Thus regulation, under this scenario, caused the expected return to fall by 6.2%.

In conclusion, it is worth pointing out that most of Schwartzman's discussion of the effects of regulation on the expected return results from concern over the level of pharmaceutical research expenditures. Thus Schwartzman argues that regulation has driven down the expected

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[11] If development time is shortened to six years, the expected return rises to 9.2%. This would be the unregulated expected return if regulation is responsible for a full 40% of development time.

return and that this will cause a decline in the long run level of pharmaceutical R&D. However, it is possible to directly estimate the effects of regulation on the level of research expenditures in the industry. This has been done and comprises Chapter 4 of this thesis.

Chapter 2. The Direct Effect of Regulation on New Product Introductions

In this chapter estimations are reported of the first attempt to measure the direct (production function) effects of regulation on new product introductions in the 1970's. These estimates are carried out on disaggregated therapeutic class data from the 1968 to 1976 period. The results will indicate a large and significant effect of regulation that persists over a variety of specifications. To carry out the estimations required the development and application of an improved, therapeutic class, measure of regulation that represents a significant improvement over previous measures.

The basic equation to be estimated is:

$$(2.1) \qquad NCE_i = f(Res_i, Reg_i)$$

where:

NCE_i = annual introductions of New Chemical Entities in therapeutic class i,

Res_i = a distributed lag of past value of research expenditure in class i, and

Reg_i = a distributed lag of past values of regulatory stringency in class i.

Thus new product introductions, in a specific therapeutic class, are a function of lagged research expenditures and regulation in that particular class. This disaggregated specification is a clear improvement over previous work because pharmaceutical companies carry out research on specific projects in specific areas in order to market products in

those areas.[1] Thus, research expenditures in specific classes usually lead to new products in the desired area. Therefore, to obtain the overall rate of introductions as a function of research and regulation, these individual class outcomes must be aggregated from the underlying disaggregated structure. As a result, much greater statistical precision can be attained by specifying the production function equation in terms of the individual therapeutic classes.[2] Thus the estimations in this chapter are based on the disaggregated data.

Before turning to the actual estimations it is necessary to discuss the correct way to measure the stringency of government regulation that individual products will face when they are marketed, since this will be central to the estimations. After this discussion, some preliminary estimations dealing with econometric issues are reported. These are followed by the final estimations and interpretation of results.

Section 2.1. The Measurement of Regulation

To correctly estimate the effects of regulation on new product introductions it is necessary for the stringency of government regulation to be correctly measured.[3] The proposed measure represents a significant im-

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[1]The reader should also consult Chapter 3 which clearly describes companies attempts to select projects in specific areas.

[2]See Malinvaud, Statistical Methods of Econometrics, pp. 130-7, 216-21.

[3]It is important for the reader to note that there is a detailed discussion of the measurement of regulation for use in a research expenditures equation in Chapter 4. That discussion is complementary to this one and not a substitute. Thus certain areas are given a more complete treatment in that discussion, including: the discussion of econometric issues (especially the discussion of measurement error and missing observations on the within-class variable), the discussion of causes of regulatory delay (continued on following page)

provement over previous measures. This is because previous authors have failed to take proper account of the variation of regulation across therapeutic classes and across time, as will be discussed below. However, before reviewing previous measures and proposing the new one, it is necessary to briefly review what a good measure of regulation should measure in the present context.

The goal is to model the effect of regulation on the expected level of research expenditures necessary for a given rate of new product introductions.[4] There are two primary regulatory effects in this regard. First, there is an increased level of spending for tests, regardless of the effect of regulation on the probability of obtaining a new drug at the end of the testing period. Second, there is a reduced probability of obtaining a new product, holding the level of spending constant. Therefore, when comparing alternative measures ot regulation, the correlation of the measure with these two factors is the relevant criterion.

To date, there have been two different measures of regulatory stringency. First, Baily used a dummy variable that assumed the value zero before 1962 and the value one thereafter.[5] Next GVT used the overall average delay that new products faced in gaining approval.[6] They

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3 (continued from preceding page)
at the FDA, and the discussion of the correct demarkation of therapeutic classes. There are also some tabulated values of the regulatory delay variable for specific therapeutic classes.

[4]Alternatively, this can be viewed as the expected decrease in the number of new drugs at a given level of research expenditures.

[5]Baily, see also Section 1.3. of Chapter 1.

[6]See GVT.

also used Baily's dummy variable and obtained qualitatively similar results.

The motivation of the dummy variable comes from the assumption that there was a once-and-for-all change in the stringency of the new drug approval process in 1962. The dummy also implicitly assumes that the stringency faced by all drugs will be the same, regardless of the therapeutic class into which the product will be introduced. GVT improve upon this by using the average delay that a product faces in gaining approval by the FDA. The use of this variable amounts to a relaxation of the assumption that the change in regulation was strictly once-and-for-all. They implicitly recognize the importance of the standards and activities of the regulatory authorities in determining the impact of the efficacy requirements. However, they maintain the second assumption and so continue to assume that the stringency of regulation faced by individual drugs will be invariant with respect to the therapeutic class into which the drug will be introduced.

It is worthwhile to examine this latter assumption. Wardell and Lasagna have done a detailed study on the availability of various therapies in the U.S. as compared to their availability in Britain.[7] They demonstrate quite conclusively that the relative availability of therapy varies substantially across therapeutic classes and across time. They attribute the differences in availability of therapies to differences in regulation. This hypothesis will be tested below.

The finding of differences in availability across classes and time would be a surprising result if one views the FDA as a monolithic

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[7]Wardell and Lasagna, AEI, 1975.

agency. However, this is not true since the Bureau of Drugs is divided into six therapeutic divisions.[8] Each of these is headed by a division chief who has a high degree of latitude in setting divisional standards of safety and efficacy. These, in turn, determine how difficult it is to obtain approval for a new product. In addition there are differences in how willing different divisions are to work with the companies to speed the entire testing and approval process. These differences are important in determining regulatory stringency.

In addition to these factors there is substantial variability in the technology of proving efficacy in different classes. These technological variables revolve around the ease or difficulty of objectively establishing efficacy. For instance, to objectively prove the effectiveness of an antibiotic is relatively straightforward. It is only necessary to demonstrate that the product kills the bacterium.

On the other hand the appropriate standards for proving the efficacy of a drug for heart disease is very much open to question. To truly establish efficacy, it is first necessary to establish the effect of a drug on a factor known to be correlated with cardiovascular ailments (e.g. the effect of a drug on blood lipids which are known to be correlated with hardening of the arteries). It is then necessary to establish the effects of the drug on the incidence of the disease itself. This can be extremely difficult, expecially since many of these disease mechanisms are only imperfectly understood. Thus it is hardly a coincidence that cardiovascular drugs have been subjected to the greatest

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[8]These divisions correspond quite closely to the therapeutic classes used here and in Chapter 4.

delays in approval for marketing and that the issues of efficacy are much more difficult to resolve in this area.[9]

Thus, there are good theoretical reasons to believe that stringency of regulation varies across therapeutic classes. Therefore, any correct measure of regulation that varies across therapeutic classes will dominate its aggregated counterpart. Fortunately the same dominance holds on statistical grounds as well. The greater the variation in a right-hand side regression variable, the greater the statistical precision with which one can measure its effects.[10] So it should be concluded that a measure of therapeutic class delay is better than an overall measure of the delay faced by all products.

However, there remains the question of whether or not regulatory delay really measures what is meant by the stringency of regulation. There should be a strong inverse correlation between the average delay faced by a new product and the probability that the product will eventually be approved, ceteris paribus.[11] There should also be a significant correlation between approval times and the number of tests which regulators will impose on the efficacy testing process. If for no other reason, this should happen as a result of the time required to review the test results.

At the same time, as discussed in Chapter 4, there may be measurement error in this variable due to firms varying responses to changes

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[9]See Wardell and Lasagna, pp. 55-78, for a discussion of the delays in marketing in various classes of compounds.

[10]See Malinvaud, Statistical Method of Econometrics, pp. 216-21.

[11]See Chapter 4 for a more detailed discussion of this issue.

in regulatory stringency, though this effect should be small. Finally, regardless of potential problems with the proposed measure, it should be remembered that the proposed variable dominates previous measures of regulation. This dominance holds on both theoretical and statistical grounds.

Section 2.2. Preliminary Estimations

The arguments presented in the previous section and in Chapter 1 indicate two primary problems with earlier empirical work on the effects of regulation on the rate of new product introductions. The first problem centers around the difficulties in interpreting the result of the pure time series estimations of introduction rates in the early 1960's time period. The second involves the measurement of regulation and the use of therapeutic class specifications. This section and the next present new estimates of the effect of regulation on the rate of new product introduction that overcomes both of these problems.

A therapeutic class specification was estimated over the 1968-76 time period. The choice of this time period was related to data availability and the desire to avoid the controversial data of the early 1960's.

This starting date has several advantages and disadvantages. The primary disadvantage is that it will limit the number of observations and thereby reduce the precision of the econometric estimates. On the positive side, it completely avoids the controversial 1962 period. This circumvents both the possible changes in production possibilities in that era and short-run adjustments to the new regulatory requirements.

More importantly, these estimations are the first that analyze regulatory effects on introductions in the 1970's.

The use of cross-sectional estimations has the distinct advantages listed in the previous section, and some others. It will permit us to test some of the specification assumptions of previous work. It is also a disaggregated approach to estimation, which is statistically superior to aggregate estimation when disaggregation is valid, as it is here.

The basic model is the general version of Baily's production function model. The generalization is in the form of removing Baily's imposed constant returns to scale:

$$(2.2) \qquad NCE_{k,t} = \alpha + \sum_{i=1}^{n} \beta_i Reg_{k,t-i} + \sum_{j=1}^{m} \beta_{j+n} Res_{k,t-j} + e_{k,t} .$$

where:

$NCE_{k,t}$ = New products introduced into k^{th} class in t^{th} year

$Reg_{k,t-i}$ = Average regulatory delay in k^{th} class in i^{th} lagged period

$Res_{k,t-j}$ = Research expenditures in the k^{th} class in j^{th} lagged period

$e_{k,t}$ = Random error term.

Data on new product introduction was obtained from the University of Rochester's Center for the Study of Drug Development and Paul de Haen, Incorporated. Data on average regulatory delay was obtained from the FDA through the University of Rochester. Both of these data series are available from before 1962. Data on research expenditures, by therapeutic class, are available from the Pharmaceutical Manufacturers'

Association. It is this data that constrains the time period over which the equations can be estimated. The data were collected from 1965 to 1968 and 1971 to the present. They are not available for 1969 and 1970. This constraint on availability will create several estimation problems.

Theoretically, Equation (2.2) should be estimated with a 3 to 5 year distributed lag on past values of research expenditures and a somewhat longer lag structure on past values of regulation.[12] Both lag structures could potentially begin with the first lagged value and extend backward. However, if there is a fully-specified lag structure, and no procedure is used to impute values for the missing observations for the research variable, there will only be six observations available for estimation. Two methods can be used to overcome this problem. First, one can use the information from the available research data to impute values for the missing observations for 1969 and 1970. Alternatively, the lag structure can be truncated and estimation carried out using only the original data set. The latter procedure will almost certainly cause biases in the estimation procedure as there is definitely a time series correlation in the research variable. This will mean a regressor is correlated with a left-out variable and will cause the usual biases. The first procedure, however, results in statistical tests of questionable validity.[13]

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[12]See Baily and GVT for a discussion of the lag structure of research expenditures. Their results are similar to noneconometric discussions in the literature. See Clymer for an example of noneconometric work in this area.

[13]See Maddala, Econometrics, pp. 201-7, for a discussion of estimation techniques when there are missing observations.

It was decided that a combination of the two approaches would be best. First, values for the research expenditures variable in 1969 and 1970 were imputed. Then a nested test was run to determine the lag structure of the research expenditure variable. The tests indicated that only the fifth lagged value of the research expenditures variable and the fifth and sixth lagged values of the regulation variable belonged in the regression specification. However, as is obvious from Table 2.1., this result is somewhat arbitrary. Any of the individual research variables serve as a good measure of the effects of research expenditures in the equation. This result is not surprising since, even when the gap in the data is closed, there are only seven time-series observations in the individual therapeutic classes.[14] Thus it is not possible, given the data available, to estimate the lag structure of research expenditures in the equation because most of the movement in this variable is between the cross-section units.[15]

The other important result from Table 2.1 is that the estimated effects of regulation are an important determinant of the flow of new chemical entities onto the market. Also the coefficients of the regulation variable seem to be relatively insensitive to changes in the

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[14]This can be lengthened by 2 years if the lag structure of past research is truncated at 3 years. This will be discussed below. However, in the present context, such a truncation defeats the purpose of distinguishing the separate effects of the past values of research.

[15]Since the tests indicated that the fifth lagged value of research is the appropriate measure of research, it is the one used in subsequent estimations.

Table 2.1

Ordinary Least Squares Regressions of
New Product Introductions on Research and Regulation

	Dependent Variable	Independent Variables								F	R^2
		Const.	Reg_{-5}	Reg_{-6}	Res_{-3}	Res_{-4}	Res_{-5}	Res_i	R^*_{-4}		
(1)	NCE	2.43	-.049	-.061	.038	-.060	.060	.038		7.02	.49
		(0.77)	(.022)	(.023)	(.027)	(.040)	(.028)	(.007)			
(2)	NCE	2.47	-.048	-.058		-.018	.056	.038		8.08	.47
		(.78)	(.022)	(.023)		(.027)	(.028)	(.007)			
(3)	NCE	2.42	-.048	-.058			.038	.038		10.76	.46
		(.78)	(.022)	(.023)			(.006)	(.006)			
(4)	NCE	2.30	-.047	-.059	.034			.034		9.42	.43
		(.80)	(.023)	(.024)	(.006)			(.006)			
(5)	NCE	2.35	-.046	-.055		.034		.034		8.70	.41
		(.81)	(.023)	(.024)		(.007)		(.007)			
(6)	NCE	2.35	-.048	-.059				.036	.036	10.02	.44
		(.78)	(.023)	(.024)				(.007)	(.007)		
(7)	NCE	0.23					.025	.025		16.00	.27
		(.53)					(.006)	(.006)			

t=1970-1976

Definitions:

All variables as above except:

$$R^*_{-4} = (Res_{-3} + Res_{-4} + Res_{-5})/3,$$

Res_i = Sum of all research variables included in equation.

Correlation Matrix

	Res_{-3}	Res_{-4}	Res_{-5}
Res_{-3}	1.00	0.98	0.96
Res_{-4}		1.00	0.98
Res_{-5}			1.00

specification of the research variable.[16] The sum of the two regulation variables varies between -.106 and -.110 which is a variation of approximately one standard error of the sum of the coefficients.

Finally, it is worth noting that if no measure of regulation is included in the equations reported in the preceding table (see the last equation for an example of this specification), the estimated coefficient of research is implausible (see Section 2.4. below). This confirms the basic notion that such an equation is misspecified.

Thus it must be concluded that research and regulation are both important determinants of the flow of new products onto the market. However, the estimations were carried out with imputed values for some observations of the right-hand side variable. To avoid this problem, one can note that only the fifth lagged value of the research variable is necessary for a complete specification of the equation. This will permit reestimation without including any of the missing data.[17]

The remaining econometric problems involve pooling and the fact that a number of the cross-sectional time-series units had no new products introduced. The former was handled with a standard pooling test which indicated that pooling is valid. The latter problem introduces a general truncation problem since the dependent variable is bounded

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[16]This remains true so long as at least one of the lagged values of research is used. It is not true if the research variable is omitted.

[17]This means that the estimations can be carried out over the period 1970-73, 1976 without using any missing data.

from below at zero.[18] Therefore, a Tobit estimation procedure was used for all of the regressions that appear in the rest of the paper.

Section 2.3. Final Estimations

The lag structure of the regulation variable was reestimated on the shorter data set and the pooling tests were repeated. The tests indicated that only the sixth lagged value of regulation was significant. In spite of the fact that the fifth lagged value of regulation was no longer significant, the overall estimated effect of regulation was approximately the same due to an increase in the size of the sixth lagged coefficient. In general, the Tobit procedures indicated that the least squares estimated constant was biased upward and the other coefficients were biased toward zero. In addition, the least squares standard error of the regression was biased toward zero, as expected.

The final estimation of the basic equation was:

$$(2.3) \qquad NCE_{k,t} = \underset{(1.137)}{1.549} + \underset{(.011)}{0.046}\ Res_{t-t} - \underset{(.045)}{.122}\ Reg_{t-6} + e_{k,t}$$

t = 1970-73, 1976
standard errors in parenthesis.

These results indicate that there is a strong effect of regulation on the flow of new chemical entities onto the market. However, before exploring their implications in depth, it is useful to examine the sensitivity of this estimate, due to the small number of time-series

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[18] See Tobin, "Estimation of Relationships for Limited Dependent Variables," EMA, 1958, McFadden, "Quantal Choice Analysis: A Survey," Annals of Economic and Social Measurement, 1976, and Maddala, 1977, pp. 162-71, for treatments of these issues.

observations. A valid question to ask is whether the results will persist over a longer time period. There are two ways to obtain more time-series observations for the estimation. The first is to use the imputed values for research expenditures for the years 1969 and 1970. This will permit the use of the 1974 and 1975 introduction data and will add twelve observations to the sample. This was done and appears as Equation (1) in Table 2.2.

The second valid way to obtain more observations is to use the third lagged value of research expenditures as the measure of research effort. Given the results in Table 2.1. this variable is a good measure of research effort, even though it is not the "best" such measure in the absence of data restrictions. Furthermore, those results indicated that the use of the third lagged value of research did not (apparently) lead to a bias in the regulation coefficient. Thus, by using this variable the data can be expanded to include the introduction data from 1968 and 1969 which will provide a check on the stability of Equation (2.3).

As can be seen by comparing the regressions in Table 2.1. with Equation (2.3), the results are quite insensitive to the changes in the sample. The difference in the estimated coefficients of both the research and regulation variables are well within the bounds of statistical chance. The estimates in the table do indicate a somewhat smaller effect of regulation than in Equation (2.3) and the reader should keep this in mind in the next section. However, it remains that Equation (2.3) is the theoretically superior estimation and so it will be used to examine the implications of the estimates.

Table 2.2.

Tobit Regressions of New Chemical Entities on Research and Regulation*

Dependent Variable	Independent Variables				Period
	Constant	Res_{t-5}	Res_{t-3}	Reg_{t-6}	
(1) NCE	1.83 (0.87)	.043 (.009)		-.113 (.033)	1970-76 42 obs.
(2) NCE	0.72 (.70)		.042 (.007)	-.093 (.028)	1968-76 54 obs.

*Both equations use imputed values for research. Equation (2) includes 1968 and 1969 because the third lagged value of research is used.

Section 2.4. Interpretation

The most important result of the econometric estimation has been the effect of regulation on the rate of new product introductions. The estimated effects of regulation are quite large and highly significant. Equation (2.3) indicates that with regulation at its observed values in the sample, the average rate of new product introductions was 2.07 per class, per year. If delays had been at their pre-1962 levels during this time period (about 7 months) and there had been a concomitant decrease in the other aspects of regulation to their pre-1962 levels, the best estimates indicate that there would have been an average of 4.35 new products per year per class, with no change in research expendi-

tures.[19] So the rate of introduction fell approximately 52% from what it would otherwise have been (i.e. the cost per drug rose by about 100%). This estimate is quite large, however it is not out of line with what others have found. GVT estimate the cost per drug increased approximately 86% as a result of regulation. Similar results were found by Baily and Peltzman.[20]

These empirical results are quite striking and are more so when they are examined in detail. To begin, they are time-series cross-section estimations where the measure of most controversy (the regulation variable) has very little systematic movement.[21] The data set and techniques are very different from those others have used and yet the model seems to give plausible and accurate results according to a wide range of criteria.

One good check on the reliability of these equations is to examine the implied cost per drug and compare it with previous noneconometric estimates. The best existing estimate of the cost per drug is by Hansen. He estimated the cost of a new drug using company data on the level and timing of their research expenditures on specific development projects.[22]

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[19] In addition the regulation variable exhibited a great deal of movement in the period under consideration. It ranged between 8 months and 53 months, the mean was 25.7 months and the std. deviation was 10.9 months. This indicates that the estimated effects of regulation will be relevant for a wide range of values of the delay variable and these extrapolations are valid.

[20] See Chapter 1, above.

[21] See below, Section 2.5.

[22] See Ron Hansen, "The Pharmaceutical Development Process," University of Rochester Mimeo, 1978.

Hansen estimated profiles of drug development spending, the probabilities of product candidates passing the various phases of the testing program, and the cost of each phase. Using this micro-micro approach, the (undiscounted) cost per drug was estimated to be $21.0m (1972 dollars).[23] Equation (2.3) indicates that the cost per drug is $21.7m. These figures are strikingly close even though they were estimated using very different techniques. This represents strong confirmation of the reliability of the basic equation. This is further confirmed when the regulation variable is not included in the estimated equation.[24] In that specification the estimated cost per drug is $39.0m which is much higher than other existing estimates.

These results are also quite similar, for a wide range of criteria, to previous estimations on aggregate data from the 1954-1970 period. In comparing the estimates it should be kept in mind that the data and techniques are very different and so the results are independent.

First, it is useful to compare the estimated change in the ratio of new drugs introduced to research expenditures for a change in regulation, the magnitude, $\frac{\partial(\frac{NCE}{Res})}{\partial\ Reg}$. At the mean of their sample, the GVT estimates indicate this number to .0008.[25] The estimates above, when combined with the estimates of the previous chapter, indicate this number is .0005, which is quite close.

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[23] All dollar figures are in 1972 dollars.

[24] See Section 2.2. above.

[25] $\frac{\partial(\frac{Y}{X})}{\partial Reg} = \frac{\partial \ln \frac{Y}{X}}{\partial \ln\ Reg} \frac{Y}{Reg \cdot X}$, where Y = NCE and X = Res.

Also the GVT estimates indicate the elasticity of research productivity with respect to regulation is -.46.[26] The estimated elasticity of the current work (at sample means) is -.39. These are quite close.[27]

Finally, one can calculate the implied elasticity of the rate of introductions. This will indicate whether there are industry-wide economies or diseconomies to research in individual classes. This estimate is 1.5 which indicates that the equations of Baily and GVT are misspecified because of the aggregate formulation and their imposition of constant returns to scale.

Thus by a large range of criteria, the estimated cost of a new drug, the estimated effects of regulation, the stability of the effect of regulation over a variety of specifications, and the implied elasticities, the results of the model are believable and stable.

Section 2.5. Problems of Interpretation and Social Welfare

In this section problems of possible specification error and social welfare are examined. Fundamentally, the latter question centers around whether there is a left-out regressor that is correlated with the regulation variable. The primary possibility in this regard is that the regulation variable could be correlated with a variable that would

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[26] $\frac{\partial(\frac{Y}{X})}{\partial Reg} = \frac{\frac{\partial Y}{\partial Reg} \cdot X - \frac{\partial X}{\partial Reg} \cdot Y}{X^2} \cdot \frac{\partial Y}{\partial Reg}$ was estimated above. $\frac{\partial X}{\partial Reg}$ is estimated in Chapter 4.

[27] The closeness between current estimates and previous estimates should not be taken as direct confirmation of those results. The role of research depletion in declining introductions in the early 1960's is still a real issue which will be explored more deeply in Chapter 5.

measure the inherent ease (or difficulty) of obtaining a new product from a given level of research spending. It has commonly been alleged that this correlation is what caused the fall in introductions in the early 1960's.[28] It is important to note that this correlation of regulation with the research opportunity variable is supposedly a spurious correlation. In other words, it so happened that in the early 1960's regulatory stringency increased at the same time that research opportunities were falling. Alternatively, there is not an underlying structural equation that is supposed to cause a correlation between regulation and research opportunities. Given this, it must be determined if there is a spurious correlation that would be causing the results in the estimated equations presented above.

It is difficult to give a final answer to such a possibility but it does not appear to be the case. One might expect to find a spurious correlation if the measures of regulation in the individual classes moved together, or if there was systematic movement in them over time.[29]

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[28]See Henry Grabowski and John Vernon, "Structural Effects of Regulation on Innovation in the Ethical Drug Industry," in Essays on Industrial Organization in Honor of Joe S. Bain, pp. 181-205, and GVT, 1978, for discussions of these issues. See also Section 5.3. below.

[29]In Section 5.3. a strong case is made that declining research opportunities in particular therapeutic classes were a major factor in the decline in introductions of the early 1960's. However, differentials in research opportunities across classes are not responsible for the effects of regulation measured above. To see this, dummy variables were introduced into the regressions for each therapeutic class to allow for different research opportunities. In that estimation, the coefficient in Equation (2.3) was -.16 with a standard error of .05. However, the dummies were insignificant and since they were not clearly required by theory, they were excluded in the regressions reported above.

There is no obvious time trend in the regulation variable. If average delay is regressed on a constant and a time trend, the trend is positive but only half the size of its standard error (the coefficient was .5). This result remains for several versions of the time trend, including the log and exponential forms. It also remains if dummy variables are used for each class in conjunction with the time trend. Furthermore, in a regression with delay on the left-hand side and dummies and a time trend on the right-hand side, the R^2 is less than .10. This does not show that there is no correlation between the regulation variable and a left-out variable. However, the movement of the within class variable should be contrasted with the relatively smooth behavior of the overall regulation variable during the early 1960's. Using the GVT data for the overall average regulatory delay as the left-hand side variable in a regression with only a constant and a time trend, the R^2 is .92!

In addition, it is worthwhile to investigate the cross-sectional correlation of the regulation variable. This is presented in Table 2.3. As can be seen, there are no strict patterns to the correlation matrix. In some cases the correlation is high (as between A & D), in others low (as between C & F), some positive and some are negative. Thus it is difficult to argue that there is a simple explanation of the results presented above because the regulation variable is <u>spuriously</u> correlated with a left-out regressor.

Table 2.3.

Correlation of Within-Class Regulation Variables

	Classes					
Classes	A	B	C	D	E	F
A	1.00	.83	.30	.96	-.42	.92
B		1.00	.24	.70	-.44	.75
C			1.00	.20	-.78	-.06
D				1.00	-.42	.95
E					1.00	-.21
F						1.00

Source: author.

The final issue of importance is social welfare. The evidence presented above shows that there has been a large reduction in the rate of introduction of new products in the face of more stringent regulation. Put differently, there has been an increase in the cost per product due to the increased testing requirements and the lowered probability of obtaining a new drug. It is important to keep in mind that these findings do not indicate that there has been a drop in social welfare due to the regulations.

In fact, the explicit purpose of regulation such as this is to reduce the flow of products onto the market (or increase the cost per product), through reducing introductions of ineffective products. In other words, the conceptual basis of regulation is the unregulated market

results in an insufficient level of testing for new products entering the market place. Thus if there is a large drop in introductions as regulation stiffens, it only indicates that the trade-off between greater confidence in the efficacy of products and the number of products produced is steep. Such has been the finding of the above estimations and it should not be construed to mean we are worse off with stiff regulation of product quality and a relatively low rate of introductions.

Section 2.6. Summary and Conclusions

In summary, this chapter has presented the first estimations of the direct effects of pharmaceutical regulation on new product introductions in the 1970's. These results indicate that regulation has had a very large effect on the rate of these introductions. The estimated coefficients indicate that regulation has lowered the rate of introductions by slightly more than 50%, holding the level of research constant. In other words, the cost per drug has approximately doubled.

In addition, the results indicate that a much clearer picture of regulatory effects emerges from estimations on data from individual therapeutic classes. In fact, the disaggregated data are what made the estimations possible since six observations would have been very insufficient. Now attention is turned to the effects of regulation on research expenditures. These effects are analyzed in the following two chapters. Then in Chapter 5 the estimates presented above will be combined with those in Chapter 4 to estimate the overall (direct and indirect) effect of regulation on introductions.

Chapter 3. The Pharmaceutical Research and Development Decision Process

Section 3.1. Introduction

In this chapter there is a detailed examination of the R&D decision making processes used in pharmaceutical firms. The primary motivation behind the chapter is the determination of how pharmaceutical firms change the level and allocation of research expenditures in response to changes in the stringency of regulation. However, to accomplish this, it is also necessary to examine general pharmaceutical R&D decision making in some detail. This leads to a detailed description of the actual way in which a highly research intensive industry goes about R&D project selection, which is of great importance in its own right.

This is important because, in spite of the many wide-ranging studies of R&D, there is still only a vague notion of how R&D and R&D decision-making are actually carried out in major corporations.[1] This is especially troublesome since an area as complex as the R&D decision is precisely a case in which a Herbert Simon style bounded rationality constraint would most be expected to apply. In the face of the infinitely complex issues surrounding project selection, an important question is how do firms decide which research projects to pursue. Do firms consider all relevant information in project selection or do they limit themselves to a particular subset? If it is a subset of relevant information, what determines

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[1] See Mansfield, et al., Research and Innovation in the Modern Corporation, Norton, 1971, pp. 47-63, for an example of the existing economic work on R&D decision making. See Kamien and Schwartz, "Market Structure and Innovation: A Survey," JEL, March 1975.

the limits and components of the subset? This chapter offers a case study of R&D decision making for a particular industry: the pharmaceutical industry.

The chapter presents the actual way in which the pharmaceutical industry makes its research decisions and the way it has made these decisions in two very different environments. It thus contributes to a much better understanding of the black box of the R&D intensive firm and of its internal workings. This understanding will in turn broaden our understanding of this very important aspect of our economic growth.

The behavioral information presented herein was developed from interviews with high level executives in twelve major R&D intensive pharmaceutical companies. These twelve firms include eight of the largest fifteen American manufacturers and four of the largest five world-wide manufacturers. From these interviews a concise picture was developed of how pharmaceutical companies make their R&D decisions and how this decision making process has changed over time. The most surprising, and possibly the most important, finding of the interviews was the overall similarity of responses to questions in different firms. This is particularly unusual because the interviews were conducted around open ended questions. This lends confidence to the information as a good description of the way in which a "representative" pharmaceutical company makes its research decisions.

As indicated above, in addition to questions of R&D in general, this chapter sheds light on some important issues that are of special interest in the pharmaceutical industry. In particular, the evidence in this chapter indicates that pharmaceutical research and development decision

makers had a very limited information set in the 1960's. They did not consider the impact of regulation on the profitability of research projects and did not consider this factor in making their project selection decisions. This result implies that goverrment regulation had no effect on the allocation research resources in this industry in the 1960's, which will be confirmed econometrically in Chapter 4 below. This turns out to be the case. However, for reasons that are not altogether clear, the information set with respect to which R&D decisions were made expanded dramatically between the 1960's and the 1970's and regulation entered the information set. With the consideration of regulation, there developed an inverse relationship between research and the stringency of regulation of new drug products.

One of the more interesting aspects of the interviews is that nearly all companies reported a basic change in R&D decision-making between the late 1960's and 1970's. Throughout the paper differences in the decision making between these two periods are emphasized. A major issue is why this change occurred. However, this question deserves individual attention and is not treated here. In the thesis the discussion is limited to the actual changes that have occurred between the mid-1960's and the present.

A major finding of the chapter is that in spite of the many changes in the R&D resource allocation process, the control of R&D resources still rests largely in the hands of the scientists actually doing the research. However there have been substantial pressures within all firms to involve non-scientific disciplines in the R&D resource allocation decision. This has resulted in those disciplines now having a strong voice in certain

decisions, especially those where the scientific criteria are not clear cut. When the scientific criteria are clear cut, they dominate the decision process. Therefore to properly understand the allocation of resources in the firm we must understand the decision making process that these scientists use and the implications of that system.

One of the changes brought about by changes in the R&D environment has been a change in the basic budgetary process within the firm. During the 1960's the R&D budget was often set, implicitly or explicitly, as a fixed percentage of the company's sales. This is no longer the case. Research projects are now forced to "justify" their existence and the resources they require during budget proceedings in a type of zero-based budgeting.

In addition, the pressures mentioned above to involve other disciplines besides the scientific ones in the R&D resource allocation decision have resulted in a more quantitative approach to the allocation decision. The nature of the information available for the quantitative approach has also lead to quantitative factors having much more weight for short term projects than for long term projects.

Finally, an independent conclusion is that as firms research in an area and find that a competitor has brought out a product that is similar to one that they were trying to develop in their own research, there is a strong tendency for companies to stop the research they were doing. It is not correct to attribute all, or even most, of this response to regulatory pressures against me-too products.

The chapter begins with a discussion of the path that a drug follows as it travels from its first conceptualization in the head of the scien-

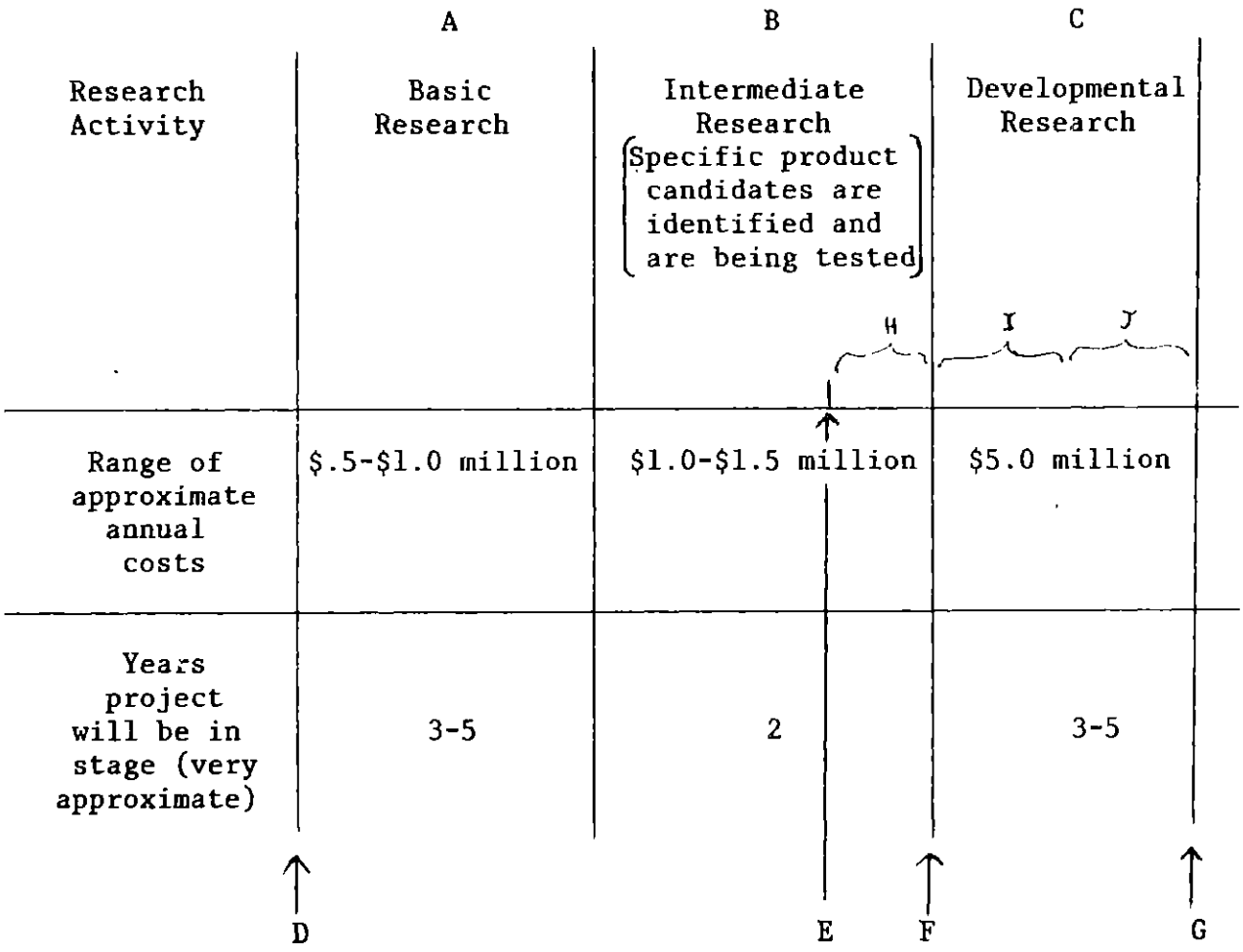
tist to final marketing. This is found in Section 2. Then each of the areas indicated above will be covered in some detail. Throughout, the reader should keep in mind that the chapter is a largely descriptive piece and that economic analysis of the reasons these firms make decisions as they do and the implications of these decision processes for public policy analysis will form the basis for my continuing research in this area. The econometric tests of this model are presented in Chapter 4.

Section 3.2. The Stages of Pharmaceutical Research

So that the reader may have a framework for reference in later discussions, here is a brief description of the overall process of pharmaceutical research and development. The major decision points in the process are identified and briefly described, as well as the kind of research that occurs between decisions.

A diagram of the process appears on the next page. The key decisions and different types of research are labeled with capital letters and there is a key at the bottom of the page. The description that follows is chronological from the time when the scientist first has the idea until the product is marketed. A much more detailed discussion of certain parts of this process will be presented later in the chapter as they connect with particular hypotheses and conclusions.

The most important research decision of the pharmaceutical company is the initial decision to enter a new area of research, point D on Diagram 3.1. It is important because basic research is necessary to generate the leads for the other research. After the decision is made to enter into an area of basic research, the personnel will either be transferred from



Key

A = Basic Research
B = Intermediate Research
C = Development Research
D = Initial Research Decision
E = IND Filing
F = Major clinical studies begin
G = Market Introduction

H = Phase I human tests
I = Phase II human tests
J = Phase III human tests

Diagram 3.1

existing projects within the company or hired from outside sources, with the former being the much more usual case.

Once the necessary personnel and facilities are available, basic research begins. During the usual three to five years of this basic research phase large numbers of drug candidates are tested using screening devices the company has developed for finding pharmacological action in a particular class of drugs. The vast majority of all chemical compounds screened will fail the test and which will end tests on that particular compound. The screening procedure is a low-cost method of separating compounds that warrant more careful testing from toxic substances and from substances that have no observable pharmacological action.

The quality of screens varies significantly from company to company and within a company from area to area. For instance it is well-known that Hoffman-LaRoche has been very successful in developing Central Nervous System (CNS) drugs. Part of the reason for this success is the relative quality of the Roche screens for CNS drugs. This means that the screens are relatively good at eliminating drugs that are unlikely to pass later stages of the testing procedure. Since the later testing procedures are more costly, this holds down overall research costs. Good screens eliminate few, if any, drugs that would pass the later stages of the testing, since the one drug incorrectly eliminated might have been the one big "winner" from the research project.

After the screening phase is completed the successful drugs are retested using biological models. The goal of the modeling process is the same as that of screening, but there is more accuracy, specialization, and a higher cost. As drugs enter this stage, project expenditures will

increase substantially. Occasionally, if radical new information has evolved since the initial research decision, this cost increase will be accompanied by detailed project review but that is unusual.

After the modeling phase of animal testing the drug is ready for testing in humans. Either just prior to first testing in man or just afterwards, the next major decision is reached. This decision is whether or not the project's potential products are of sufficient quality to warrant continuation. If there is a careful reevaluation prior to the first human tests then there will not be a detailed review after initial human testing. However in some firms this major decision is made after the initial human testing. At this decision point many factors are carefully recalculated for the first time since the initial research decision.

At this time the expected sales of the product are recalculated. There is also a serious attempt to consider the manufacturing cost of the product and some tentative estimates of price and output will be sought. These calculations will be discussed in more detail below.

However let me now point out that at the initial stages of the research process there is an attempt to examine the market of the product, the likelihood of success, and the project's cost. At this point the company will want to reevaluate these factors, because after this point in the research process, the project will begin to represent a substantial drain on the company's resources, approximately $5 million per year that the drug is in the Phase II and Phase III studies (which I will define in a moment). Therefore if there is any information that might help the company to identify unprofitable projects, the pre-IND stage is the appropriate time to discover and use it.

To begin human testing the company must file an Investigational New Drug application (IND) with the Food and Drug Administration (FDA). After filing the IND the company begins Phase I human toxicology studies. These are small scale tests on a limited number of human subjects primarily to determine human toxicity. These short-term tests usually last only a few weeks, but they signify a critical point for the drug research, since the company is fairly certain the drug will have some (possibly toxic) pharmacological activity. So if it is determined that the drug is not toxic, a major hurdle in the discovery and development process will be passed.

If all goes well in Phase I clinical studies, the drug will be introduced into fairly wide ranging populations to determine human efficacy. These tests can run for several years and represent tremendous sums of money. If the drug is found to be efficacious, the company will begin Phase III clinical studies to test for unusual side-effects of the drug. If these are successful, the company will file a New Drug Application (NDA) with the FDA. The FDA then reviews the application and will approve the drug if it feels safety and efficacy have been proven. At times the FDA will ask for additional tests. And, occasionally, the FDA will simply turn down an NDA.

Concurrent to Phase II and III clinical studies, the company will try to insure that it can manufacture the drug at a reasonable cost. This is usually not a significant problem, but if it is there will be round-the-clock efforts to discover ways to manufacture the drug more cheaply.

The most important control the pharmaceutical company exercises over resource allocation is the basic decision to begin research in an area. The second most important form of control is periodic project review.

Every project that a company has will be reviewed at least annually. These project reviews are intended to weed out unproductive projects and to funnel additional resources into projects when major breakthroughs occur.

Operationally, most projects are seeking drugs with multiple claims. The claims are that the drug will stop symptoms X, Y, and Z and have low side effects. As research progresses the number of claims usually falls. Sometimes so many claims are dropped that the project is no longer worth pursuing. Project review is intended to guarantee that such projects are dropped quickly. In addition breakthroughs can expand claims and in such cases project review can funnel additional resources to the project.

At the earliest stages of research, project review will be annual since new information develops slowly and resource expenditures are relatively small. In the later fast-moving stages of research the review process is more frequent.

This completes the basic framework of pharmaceutical research. In subsequent sections certain aspects will be described in more detail as needed. Now attention is turned to the changes in the basic structure of the R&D decision process that has occurred over the past fifteen years.

Section 3.3. Changes in the R&D Decision Process

In comparing pharmaceutical R&D in the 1960's and 1970's one finds significant differences in decision making. One of the most important areas of change has been in the area of project selection and review. In other words changes in the R&D resource control exercised both by top corporate management and other disciplines within the corporation. The

first subsection deals with changes in the basic decision of whether or not to engage in an area of research. The second examines project review at various stages in the research cycle. Next changes in the decision to enter human testing are discussed. Throughout, the emphasis is on changes in the decision process that have occurred in the last decade and a half.

Before beginning, a definition and reminder are necessary. First, a research project is the basic unit of ongoing research. Research projects vary in size from one or two people working on them to dozens of people. In a large pharmaceutical company there will be anywhere from 10 to 25 projects in progress at a point in time.

The reminder is of the importance of the basic decision to formally enter research in a given area. The reader should note that the basic research decision determines the course of future research but does not necessarily refer only to decisions concerning "basic research" (perhaps primary research decision is more descriptive). However all decisions and review proceedings will receive some discussion because it is necessary for a clear understanding of how a change in the company's internal or external environment can affect the direction and size of research in this industry. This is particularly true of government regulation.

Section 3.3.1. The Basic Research Decision

The basic research decision is largely driven by the scientific expertise and intuition of the members of the research community within

the pharmaceutical company.[2] During the 1960's the scientist had nearly complete control over the distribution of resources among areas of research. With the 1970's came a lessening of the scientists' power, but it is still the most significant factor in research decision making. This is true in particular as regards the basic decision to enter a new area of research.

The process is initiated when a member (if the company, as is often the case, is organized around chemist-biologist teams it will be a pair of members) of the scientific community within the company gets an idea about a possibly fruitful avenue for future research. These ideas are generated from a variety of sources but come primarily from the professional literature, seminars, and from professional interaction on the staff. The scientist is given significant latitude in this quest for research ideas and, according to R&D executives, he is driven to satisfy "medical need."[3]

After the idea is conceived, it will be informally discussed around the laboratory. This will give the scientist a good indication of the idea's validity and indicate if it is worth pursuing. There is a signifi-

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[2]In this case the discussion centers around a basic research project but the decision process described would also be appropriate for a new developmental project, a product acquisition, etc.

[3]"Medical need" is a composite of various factors about the disease states of possible interest to the scientist and the state of pharmacology in the area. R&D executives, when asked how they would characterize medical need in the scientist's mind, always emphasized the disease incidence in a given area. Some said this was the only factor while others referred to other factors as well. All maintained that the scientist "at the bench" never looked up the number of people suffering from a given disease indication. Instead they stated that he has a superb informal grasp of the number of people suffering from a given indication in the same way that many macroeconomists may seldom, if ever, actually look up the unemployment rate or the rate of inflation but at a given time have a pretty good grasp of the approximate size of both.

cant a priori information available, even at a very early stage, about the basic validity and value of the insight. There may be uncertainty about which of a class of compounds will lead to therapeutic improvement, but there can be reasonable certainty that one of the class will result in significant improvement.

Then at some point the person who has the basic idea goes to the head of his research unit and suggests the idea be pursued in a formal project. This is the primary source of all new research projects undertaken by pharmaceutical companies.

There are also other sources of projects that will be considered at this stage, these include: the management of the company, the marketing department, and possibly the clinical staff (which does not ordinarily get heavily involved in basic research). However these sources are much less usual than proposals from the basic research staff. Also if this staff believes new products are unlikely to emerge from others' project proposals, the projects will not be taken.

At this stage, potential projects will be considered at an annual meeting explicitly called for this purpose. Today, projects are evaluated in terms of a number of factors supplied by various disciplines within the company. These include: the research chemist's and biologist's opinion about the technical feasibility, the clinician's opinion about the clinical feasibility and his rough estimates of the probable clinical cost of the project, estimates of the overall cost that such a project is likely to bear before it produces a new drug, the likelihood that the FDA will approve a drug of the type that will be produced (given the evidence that the clinician thinks he can produce), the marketing department's conception

of the drugs' potential sales and marketability and whether the existing marketing force will be able to handle the product without extensive retraining or expansion, whether the project can be carried out with existing research facilities and personnel without placing undue strains on the resources of the system, and the project's synergism with existing research and product lines of the company.

This sophisticated decision making system is a development of the last ten years. However, before details of this extremely complex system are presented, there will be an account of the much simpler system of the 1960's.

In the 1960's three primary criteria dominated the decision process. They included the research chemist's and biologist's opinion about the scientific feasibility of finding a drug with the attributes indicated in the area in which the project would be looking, the clinician's opinion about clinical difficulties, and the project's synergism with other activities of the company. All three considerations received some weight though the first and last dominated the process.

The initial stages of new product discovery were basically as described above, with the scientist initially having an interesting research possibility and approaching R&D management. The primary difference with the system in the 1960's and current procedure is one of degree. In the 1960's the scientist was the only possible source of new projects and scientific opinion was virtually autocratic whereas today there could be other disciplines involved at the beginning. If the scientific criteria were good, there was often some attempt to discuss the project with other disciplines in the company, but the scientists made all final selection

decisions due to the absence of a formal system for handling inputs from other groups. However even in this autocratic system, there was usually input from the clinician and an attempt to consider synergism.

The clinician would indicate the clinical feasibility of the proposed project even though there was no formal attempt to estimate expected costs, number of patients, or some of the other important clinical variables. This was, in some sense, a rational approach to these decisions because few companies had encountered areas of research where clinical costs could drive research expenditures to extreme levels.

The final two characteristics considered in the 1960's decision making were the project's synergism with existing projects and the likelihood that the firm's existing marketing team could adequately market the product. Both of these factors were informally considered by the R&D management while reviewing the project. Synergism with existing projects was relatively easy for the R&D managers to evaluate, since they were well aware of possible interproject linkages.

Companies considered, and still consider, whether a potential product would be in the area of their "franchise". This term, as used by several companies, implies a special relationship between the detailmen of the company in question and the doctors who will prescribe heavily from a particular class of drug. This relationship develops for several reasons. First detailmen spend more time developing a strong relationship with doctors that can, and frequently do, prescribe their company's drugs. Second, since doctors specialize, a company's reputation as a manufacturer of quality pharmaceuticals is more likely to be known within areas where

it shares market leadership. Therefore the doctors should be more receptive to the visits of the detailmen from that company.

Finally, there are significant economies of scale in presenting greater numbers of products to the same doctor, and if a new market is entered, which implies that there may be an entirely new set of doctors to visit, it may not be possible for the existing detailing force to adequately cover the new market. In this case it may be necessary to hire a complementary detailing force to cover the new doctors which entails a large fixed cost. In fact this recently happened to one major U.S. manufacturer.

Thus there are several marketing incentives for a company to produce additional products in areas where it already has products. The incentives to carry out research in areas where the company possesses expertise have already been discussed. Together these factors indicate that a company should specialize in research and that is in fact what is observed. The incentives have not disappeared since the 1960's and neither has this aspect of pharmaceutical R&D and market shares.

The process of basic research project selection has changed drastically in the last ten to fifteen years in most pharmaceutical companies. To summarize the changes, in the 1960's companies left control of the R&D resources almost exclusively in the hands of the R&D scientists but, as time passed, the companies took a much stronger interdisciplinary approach to allocating the R&D budget between research areas. With this change there has developed a formalized system to insure that all disciplines' inputs are considered in the project selection process. As a general rule, this has resulted in the decreasing in importance of the opinion of

the basic research people, the chemist and biologist, and the overall increase in importance of many other factors. The point should not be oversold; R&D management and scientists still exercise significant control over the allocation of R&D resources, but the opinions of other professionals within the company are now used more frequently.

To summarize, all of the information described below will be developed for all potential projects. The scientific information will actually be used for all project selection decisions. The information developed by the other disciplines will only be used if the scientific criteria are not clear cut, which will often be the case.

The chemist's and biologist's opinion, together with the judgment of the clinician, are still the most important decision criteria. This input amounts to two statements. The head of the biology unit states whether or not he believes the proposed project (i.e. the synthesis of a certain class of compounds for investigation of the possible pharmacological effects of a particular type, or to cure a particular symptom of a disease) has a reasonable chance of biological success. The head of the chemistry section makes a similar statement about the technical feasibility of producing small amounts of the compounds for laboratory use and economically producing large amounts for commercial use. The chemist also indicates, where possible, the possible dosage forms since solely injectable dosages place significant constraints on the economic market. Essentially the same information was presented by the initial proponents of the project, but the information has been verified by the heads of chemistry and biology.

If the information contained in this part of the report is highly favorable, the project will be undertaken. If it is ambiguous then other factors become important in determining whether or not the project is taken. If the information indicates the project does not have a reasonable chance of technical success, the project will not be pursued. The only factor that could discourage a project with a high probability of chemical and biological success is the opinion of the clinician about the technical feasibility of scientifically and statistically determining the presence of the desired effect.

The clinician's opinion can be divided into two separate parts. The first part concerns the feasibility of scientifically demonstrating the presence of the effect that the biologist thinks will be present. Some examples can best illustrate the difficulties that can be involved in this area.

All are aware of pain in the presence of injury, a headache, or that associated with certain diseases. Imagine that a biologist thinks the administration of a certain compound will significantly reduce the pain associated with headache or that associated with lower backache. How is this effect measured and how is a control group set up?

A second example provides an even clearer picture of this type of problem. It is a well-known fact that as people age there is a strong tendency for many men and women to lose their memory and some of their mental faculties (senility). It has been suggested by a research biologist that a particular class of compounds could significantly retard this process. The chemist thinks that the synthesis of the proposed compounds will be relatively easy. However measurement is a major obstacle since

people lose their mental faculties in different ways and at different rates. Some people lose their ability to remember recent events but retain a firm grasp on events that happened in childhood. For others it is the opposite. Some people lose their memory gradually over a period of fifteen to twenty years and others lose theirs essentially overnight. What is the proper control in such a situation? The attempt at statistical rigor can essentially eliminate such a research project because it is impossible to set up an accurate experiment with enough people involved to have any hope of good statistical evidence. This problem can plague a research project and, therefore, before the project is undertaken, the clinician is called upon to give his opinion about the expected difficulties.

This is related to the other area where the clinician's opinion is required. He is also required to estimate the number of people that will be needed for the clinical experiments, the length of time that the experiments will have to run, and the type of long-term tests that will be required. These factors largely determine project costs during the years it will represent a substantial drain on the company's resources.

In the past fifteen years these considerations have become more important for several reasons. The most important is the dramatic increase in the costs of clinical testing. Clinical testing can easily cost a company $5.0 million per year, or more. If the chances of success are low or if this stage of the testing process is expected to last 15 to 20 years, there is little chance that the company will find the project to be an acceptable economic investment. So, as costs have increased, companies have put more effort into research planning.

During project selection overall project cost is also estimated. This cost will be influenced by several factors. First is the perceived difficulty of developing acceptable ways of determining if the hypothesized pharmacological activity is present in animals. This is important because it is impossible to test every product candidate in human beings due to the cost and morality of doing such experiments.

In some areas screening is relatively easy. For instance, if a particular bacterium lives in certain animals and causes disease in human beings, then if a drug kills the bacterium in the animal, it is likely that it will also kill the bacterium in people.

In other areas, such as arthritis or depression, it can be very difficult to develop adequate screening procedures using animal models.[4] Thus, the expected cost of developing a drug in such an area will be significantly higher.

Another element of this decision is the quality of the company's existing screens in the area. For instance, Roche has very good screens for Central Nervous System drugs. Because developing screens is a large fixed cost Roche would view the expected development cost of a new CNS remedy as much less than would a company that had never worked in the area before. The information supplied by the clinician and the difficulty of testing the potential products in laboratory animals are then pooled to estimate overall product development costs.

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[4]This discussion is related to the depletion of research opportunities discussed above. One point that is often made concerning research opportunity depletion is that pharmaceutical research is now more concerned with finding products to treat debilitating diseases closely linked to the aging process. Since these diseases are difficult to model in animals it drives up research costs.

In addition, there are other economic inputs into the decision process, through the marketing department.

A product description is given to the marketing department, and these experts are asked to estimate the product's sales potential. These estimates are generated for a variety of product characteristics. Characteristics vary in terms of indications the product can treat, side effects, and whether or not the product will be available in oral or injectable form. An important thing to remember about this estimate is that it is based on limited information. It amounts to an estimate of what a particular pharmaceutical market will look like in five to ten years time, and has very wide confidence bounds. However, it is usually an important means of indicating whether the marketing department feels the potential product can generate significant sales even if its characteristics are very attractive. As such, it is an important signaling device to discourage selection of projects with a low economic return. It is also an important device for indicating the areas and claims upon which the research project should concentrate, since the various sales estimates can be a good means of indicating the relative economic importance of various claims.

There are two other situations in which this consideration can be important. The first is for potential projects with short expected development times. This will usually be for new indications for existing products. In this case the marketing input about expected sales is much more reliable because the shorter time frame significantly increases the reliability of information concerning market characteristics.

Another consideration that enters the basic research decision making process is the likelihood of Food and Drug Administration approval of the product. This estimation is usually rough, because of uncertainty about the eventual product and the nature of future regulation (when the drug will be submitted). This is not to say that regulation will have little impact.

In certain cases regulation, the testing requirements, and likelihood of approval have had a significant observable effect on the R&D activity in a given therapeutic area. For instance, research on new β-blockers has been drastically affected by the stringency of regulation and the probability of FDA approval. Another obvious area is oral contraceptives. Few companies have ongoing research in this area because of FDA testing requirements. In other areas, the effect is less obvious but most executives indicated that regulation will usually have some influence.

As the R&D executives consider the potential project, another consideration is whether existing facilities and personnel can handle the project. This may be a problem because of research capacity bottlenecks. For instance if the project calls for extensive toxicology testing and the existing testing facilities are already under severe strain, the project may be postponed. Sometimes an alternative is for the company to subcontract some of this research but many companies have an aversion to this which will detract from the project's chances of acceptance.

Existing resources may also be inadequate because the company does not currently carry out the type of research proposed. In such a case it might be necessary for the company to hire additional researchers. Gener-

ally, companies consider research hiring to be a major company commitment both in terms of hiring transactions costs and because most companies are strongly averse to firing research personnel. To proceed with such a project usually requires the explicit approval of high-level corporate executives outside of the R&D area. Thus, the company will carefully scrutinize projects requiring new hiring.

The final consideration in new project selection in the 1970's is the project's synergism with other company projects and products. These considerations were discussed above, in reference to the decision making process of the 1960's, and are qualitatively the same.

In conclusion it must be reemphasized that the most important consideration is still the scientific one. If the scientific and technical side looks favorable, i.e. if the scientists feel there is a real medical need and the cost and likelihood of approval are reasonable, the project will be taken. The other considerations (besides the issue of whether the project can be handled in existing facilities) become important only in cases where the scientific and technical picture is muddied. Then close scrutiny will be given to all of the considerations listed above.

Section 3.3.2. Changes in the Process of Basic Research and Early Development

The changes between the 1960's and 1970's in the process of basic research and early development can be characterized by company attempts to gain greater control over resource expenditures. For the sake of brevity the discussion will be limited to a description of resource allocation

decisions during this stage of research.[5]

There are two potential resource allocation decisions once the basic research project is under way. One is to increase the level of funding to the project and the other is to terminate the project. There is little evidence that the former decision has changed much in the relevant past. When a significant lead is uncovered there has always been a substantial shift of manpower into that area of research. However, the process for weeding out unproductive projects has undergone major revisions through a more formal project review process.

All companies now use a formal system of project review that guarantees each project will have at least an annual review, though some are reviewed more frequently. In general, a project just getting started will be reviewed annually and then, as leads develop and more company resources are committed, the frequency of review increases. As specific candidates are identified and animal toxicology studies are begun, annual review will give way to quarterly. Subsequently, review may change to monthly and a high-ranking interdisciplinary committee will be set up to monitor the project. In the last stages before filing the NDA, review may be weekly or bi-weekly. This system is designed to insure that all segments within the company get adequate input especially later in the process when large resources are being expended. However, such a system has not always been used. In the 1960's there was less frequency and interdisciplinary involvement in project review.

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[5]For a more detailed description of the kind of research taking place at this stage see Innovation, pp. 31-38, 43-47.

Another change has been the increasing use of hurdles for continued project funding. The specific form of the hurdle depends on the type of project involved. Generally the scientists must prove that some potential products possess certain characteristics by specified dates. If the project fails it may not be funded for the following year. This system is designed to weed out scientists' "pet" projects. This gives an objective reason, well in advance of the imposition of the standard, for the discontinuation of the project. This system can also give R&D managers, who may be caught up in a particular project, more perspective on a project's actual progress.

Thus companies are trying to cut losses on unproductive projects by identifying them as early as possible. However, there is a definite "art" in the process described. It is important to cut losses on poor investments, but it is also important to guarantee that projects are not cut too early, because one successful project can pay for many failures. Therefore the R&D manager's experience in being able to recognize the unfruitful project is very important. This is perhaps the reason there exists such inter-firm diversity on the issue of hurdles for the project to clear.

Section 3.3.3. Changes in the Research Decisions Surrounding the Drug's Introduction into Man

Let us now turn our attention to changes in decision processes that occur much later in the R&D path of the new product. When a potential new product is introduced into man there is a substantial jump in the project's research expenditures. This can be seen on Diagram 2.1 at the start

of the chapter. Annual project expenditures jump from about $1.5m to about $5.0m shortly after the first human tests because of high human testing costs. This jump means that to begin human testing is a major decision.

The decision can occur either just prior to the beginning of human tests or just afterwards. At this point the company tries to determine if the product generated by the research project is of sufficient quality to warrant the investment of the resources (i.e. will it generate sufficient positive cash flows (sales net of costs)) necessary to market the product. In most companies there is a good understanding of sunk cost and the calculations are made with respect to unexpended resources. In some companies this calculation of the return expected for the unexpended resources is formally calculated, in others the estimates are informal. A nearly universal characteristic of this decision is that it is more quantitative than the basic research decision because of the greater reliability of the quantitative techniques at this stage.

In many cases there is a bias on the part of the scientists to go forward with a project at this point if the technical criteria look favorable. However there has been less sympathy given to this position over time.

In the past fifteen years there have been several significant changes in the decision making process at this point. The basic emphasis, as above, has been in the direction of a more careful and interdisciplinary approach to the decision to enter human testing. This change has resulted largely from the realization that other disciplines within the company, besides the R&D scientists, can make valuable inputs into this decision.

Once again, however, the R&D scientists' considered opinion is still the most valuable information source. In looking at this stage of the decision process it is useful to examine current decision making and then contrast that with the process existing in the 1960's.

In most companies the decision variables are basically the same as used for the preliminary research decision but the information about those variables has changed significantly. Also, the weights of various factors in this decision are remarkably similar to their weights in the initial research decision.

In estimating expected returns the company will try to estimate the manufacturing cost of the drug. This will often be the first attempt to estimate these costs because it is the first stage at which an accurate description of the actual drug product is available. Since it is costly to estimate manufacturing costs the company only desires to expend these resources on drugs it feels are likely to be manufactured at some point. Also if the estimated costs are too high, the company can often develop cheaper manufacturing processes.

Expected sales are also reestimated at this point. This is the same variable referred to in the discussion of the preliminary research decision. But the accuracy of the estimates has increased substantially because at this stage of the research project there are one or two specific candidates (usually one) with known characteristics. Similarly the sales predictions are for markets two or three years in the future as opposed to five to ten years for the initial decision. These combine to make the resulting estimates much more accurate.

In addition the clinician reevaluates the number of patients necessary for the clinical tests, the length of time that each testing stage will require, the specific information that will have to be developed to prove efficacy for the compound, the likelihood that such information can be developed, and overall and yearly expenditure estimates for the project. At this stage the clinician will have precise information about the product and should be able to accurately answer these questions.

Another factor reconsidered at this point is the Food and Drug Administration's stance on products of the type produced and its stance on the kind of information that will be produced by the clinician. If the clinician feels a particular test is essential for a valid proof of efficacy, and the FDA takes a dim view of that test, this could have a strong negative impact on the decision to proceed. Basically, if the company feels it is unlikely that the FDA will approve a drug of this type, given the existing state of technology in the efficacy proving area, then it is unlikely that the company will go ahead with the particular drug.

It should be emphasized that this information will be similar to information sought at the preliminary research stage, but the prospect that the current regulatory stance in the FDA will be the prevailing stance at the time that the company files its NDA is much higher than at the early stages of research. In other words, when the company started the research project, it knew that it would be at least five years before the project would generate an NDA. Thus there was some variability in the expected regulatory environment the drug will actually face. At the later stages of the research project there is less time for the FDA to change. This could cause project abandonment at this stage. Also occasionally a

project generates a product very different from that initially expected, in which case there would be a need to evaluate regulatory possibilities in terms of the product that has actually appeared.

All of these factors are important, to some extent, in the decision at this stage. However, they will seldom influence decisions unless radically unfavorable information comes to light in one of these areas. The project will seldom be carried forward on the strength of the information developed in these areas.

The primary positive driving force of projects at this stage are scientific factors. When one considers the type of information that has been developed since the initial research decision was made, the reasons for this are obvious. It rests on the fact that most information developed in the course of research is information about the scientific feasibility of the basic idea that was submitted before research was begun. In other words, the most important new information that has become available since the research project was begun is that, in fact, a chemical exists with such and such characteristics that is apparently successful at treating indication X. The belief that the drug is successful rests on the drug passing tests A, B, and C which the research scientists believe have a high correlation with successful treatment of X. On the whole, if the decision makers believe that there is a favorable outlook from the scientific point of view, then the project will probably be carried forward. If they feel that the scientific outlook is unfavorable, the project will not be carried forward.

In summary, this is a stage for one last check to make sure the product warrants the large-scale expenditures necessary to prove efficacy.

All relevant information about the product is brought together for a final evaluation. Any sufficiently negative factor can cause a product to be dropped but it is usually scientific confidence in the product that will be the motive power of wanting to carry the project forward.

In the 1960's the decision to enter the human testing stage was less important than it is today. The combination of lower expenses and lesser control of the research establishment by general corporate management resulted in very little nonscientific input into this decision. This is not to say that other information was not developed at this stage, but it was not used in the decision making process. An example will best illustrate this point.

When a drug comes up for human testing, the drug is expected to have the beneficial properties being sought. The most important unknown is whether the drug has some unknown faults in addition to its beneficial characteristics. Once this issue is settled, there will be the need to prove the drug is effective but this can usually be done. Therefore, if Phase I tests show no adverse reactions, it is often only a matter of time before the drug will be proven effective. This means that corporate management will take a great deal of interest in drugs that successfully pass Phase I studies because the drug will probably have a significant impact on the corporation as a whole if it should go on the market (especially on the corporate profit and cash-flow pictures).

As a result the corporate management desires to have detailed information about drugs that pass Phase I tests. This information consists of the drug's expected manufacturing cost, price, expected sales under different prices, the estimated length of time for the drug to reach the

market, and the development costs that are likely to be incurred between the end of Phase I and marketing.

In the 1960's this information was used exclusively as a method of improving corporate planning. With the advent of the 1970's this information has come into use as a means of making better decisions about which drugs should be taken on for further testing and which ones should be stopped.

Section 3.4. Other Changes in the Research Process

There have been a number of other changes in the decision making process since the 1960's. These changes have been separated from the others for a better presentation.

Section 3.4.1. Changes in the Budgetary Process

One important area of change has been in the method used to determine the size of the research and development budget. The basic approach used by most companies has undergone a radical revision much in keeping with the other changes already mentioned.

In the 1960's the usual system was to give the research division 5% to 10% of pharmaceutical sales as its budget (in some companies this was an explicit rule-of-thumb and in others it was more implicit). After the research division received its budget, it was divided among existing and newly formed projects in the manner described above, with the research scientists determining the final allocation with little input from other disciplines within the company.

Today the budgeting process resembles a zero-based approach. The individual project managers decide how much money their project will need for the upcoming year. These are then added together, with some attempt to use statistical averaging to get closer to an expected value for expenditures. For instance, there may be three projects that are entering a certain phase of animal toxicology studies that is expected to last six months, and, on average, only one third of the projects that enter this stage will pass it. It may be the case that the next testing phase, following the one the projects are ready to enter, is very expensive. Since one, two, or possibly all three, of the projects can reasonably be expected to fail the first test, the combined budgets will include an allocation for each project for the first stage, but only an allocation large enough to fund one or two of the projects for the second test.

After the R&D managers add up the expenditures for the individual projects they have a total budget which they submit to the executive committee of the corporation. The executive committee then reviews the budgetary request. Usually the request budget is too high and the R&D division is asked to trim it. This process then iterates to convergence.

From the viewpoint of resource allocation within the company, the current budgetary procedures are far superior to those used in the 1960's. The funds allocated in this manner permit the R&D managers to review the projected use of funds before the total amount of the budget is set. They, implicitly or explicitly, have to arrive at a ranking of projects and the value of those projects to the company. And they must justify, project by project, the total size of the budget.

Furthermore, the corporate executives have a chance to review the projects before they allocate the R&D budget. The beneficial aspect of this is that the executive committee can increase the size of the budget if the research projects appear, as a group, to be better than that encountered in previous years, and vice versa for poor projects. This process also has the advantage that the research managers can fight against the budget trimming if the group of projects appears to be very good to them. The executive committee can use this as a signaling device. The harder the R&D people fight for more money then, ceteris paribus, the greater the probable value of the currently available projects.

Section 3.4.2. Quantitative versus Intuitive Approaches and Short Term Projects

There are a significant number of short term projects undertaken by pharmaceutical R&D establishments. These projects are often to obtain approval for the use of a drug for new indications. For instance, Ciba-Geigy is currently seeking approval for one of its drugs, used in the treatment of gout, for administration to heart attack victims to prevent the recurrence of heart attack. Such projects will usually be of shorter duration than the original project to gain approval for the drug because of the safety and toxicology data that has already been generated about the product. In this case the reliability of quantitative date for use in project selection, is much higher. For instance, marketing data instead of predicting what a market will look like in ten years is examining a market for next year or the year after. The product profile can be established with far greater certainty, since the claims sought are very spe-

cific. These mean also that doctor surveys about the need for the new indication will be a much more reliable indicator of potential sales. Manufacturing data and cost figures are not estimates, but the actual costs the company has encountered in manufacturing the product. Finally, the stiffness of regulation can be known with certainty since the company can actually contact the FDA and ask what kind of data would be necessary to gain approval of the product for the new indication.

Combined, these factors mean that the approach to deciding whether the project should be undertaken can be a very reliable application of the Present Discounted Value formulation. There will be little uncertainty in the variables and the rate-of-return can be calculated very accurately. This indicates that the quantitative approach should be relied on much more heavily for projects of this type and projects of shorter life in general.

Section 3.4.3. The Importance of Market "Franchise" and Competitors' Behavior

One interesting aspect of the current decision making process concerning the allocation of research dollars is the ways in which pharmaceutical companies respond to the behavior of competitors. In general, companies try to engage in research that is within areas of their "franchise". In other words they prefer to bring out drugs in areas where they already have an established sales force and in areas where their company has an established reputation.

The reader should also remember the already described desire to be the first to market a product for a given indication. Several inter-

viewers reported that if virtually identical products are brought out as little as three to six months apart, the product that first appears will get a large majority of the market, and maintain this share indefinitely. Therefore if a competitor markets a product in a given area, that is the same as a product of another company, there is little point in the second company continuing research. In fact the response on the part of companies is often to drop the product under development since there are few medical or economic reasons to pursue it. This effect may have been mistakenly interpreted by some as a drive to establish comparative efficacy by the FDA.[6] Several members of the industry indicated that comparative efficacy is not currently practiced by the FDA and these facts could offer a plausible explanation of why it is so often discussed.

Another effect that this drive to be the first produces is a strong incentive to be aware of the type of products that your competitors are bringing out and what their timetables are. Over time information networks develop among people who are working in the same field (this does not refer to any form of industrial espionage). The firms already established in a given field will be a part of this information network. This creates the incentive to stay in fields where the company as a whole is aware of the state of the art. This is further incentive for the market shares in individual therapeutic areas to be concentrated in the hands of relatively few companies.

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[6]Comparative efficacy is a standard of efficacy more stringent than ordinary efficacy. Under comparative efficacy a drug would have to be proven superior to already existing medications (in order to be approved) rather than simply effective as a treatment. The current law requires ordinary efficacy.

These effects combine to indicate that we should see companies specializing in given areas of research (not even mentioning any possible economies of scale for research in a therapeutic area).

Section 3.5. Summary and Conclusions

In this chapter there has been presented a careful description of the pharmaceutical R&D decision process. Two very different descriptions were presented, one for the 1960's and the other for the 1970's. In the 1960's the research scientists had nearly complete control of the decision making apparatus. Their decision criteria were medical need and scientific feasibility and they did not consider the stringency of government regulation in their decisions. This implies that regulation should not have affected the level or allocation of research in the 1960's.

This description also revealed a movement away from a fixed research budget, with the right to allocate the budget among different projects left almost exclusively in scientific hands, to a zero-based budgeting approach where all professional disciplines within the companies are asked to contribute to the allocation decision. This has resulted in a large voice still belonging to the scientists, but with other disciplines having a much more active role. It has lead to a pharmaceutical research establishment that closely resembles in many respects the neoclassical paradigm of the way a research establishment should make decisions in a major corporation.

The current approach is also much more quantitative. This is an externality of the more interdisciplinary approach to the decisions. When one discipline is alone making the decision, it is not important that the

variables under consideration be comparable to variables that another discipline might use. What is important is that the people making the decision be able to compare the variables. As more disciplines are involved there is the need to translate the informal intuition to quantitative and formal information that can be examined by other disciplines. This leads to a quantification of the variables under consideration. There still exists significant variation in approaches to quantification, with some companies more quantitative than others, but all companies are much more quantitative than in the 1960's.

In addition to the above changes in the degree of quantification, we have seen that companies have a greater tendency to rely on quantitative data when considering short term projects. This is consistent with what should be expected from theory as the quantitative information has much greater relative reliability for short term projects as opposed to long term projects.

As a side issue we have seen some of the reasons why firms tend to be concentrated in different therapeutic classes in both research and marketed products. There may also be other reasons for this like possible economies of scale to research in given areas and the fact that one significant new product will capture a large share of an existing market. Over time additional new products will be brought out that will lower the market share of the product and other firms will have sales highly concentrated in that particular class, but at a point in time there will be high concentration.

The need to be aware of competitors' behavior was also shown implying that the firm will tend to concentrate on areas where it is well informed about the state of the art.

As will be shown in Chapter 4, these differences in decision making processes have lead to significant differences in the way these organizations respond to new information. In particular, in the 1960's these research organizations did not change the allocation of research resources in response to changes in regulation. However in the 1970's, when regulation was explicitly considered, there was a negative effect of regulation on research expenditures. Let us now turn to an econometric estimation of the system described above.

Chapter 4. The Impact of Regulation on Research Expenditure

Section 4.1. Introduction

In this chapter the analysis developed in the previous chapter is molded into a formal econometric model of the R&D expenditure decision. Section 4.2 summarizes the interview information of chapter 2 into formal theoretical models of R&D expenditure in the 1960's and the 1970's. Section 4.3 then develops the statistical models and hypotheses that are tested in the succeeding sections. Before proceeding a note on methodology is in order.

The approach presented here recognizes that there are costs involved with organizational decision making. Consequently, particular decision processes will be used by an organization at a point in time and these processes will not necessarily take into account all possible factors that have a marginal effect on profits.[1] They do not take these factors into account because the fixed cost of changing the organizational decision making process to take account of the factor outweigh the potential benefits of improved decisions. Thus, before one should expect an organization to respond to a change in a factor, even if the factor will affect profits, the decision making process of the organization must be examined. If the firm does not consider a factor, either im-

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[1] A large portion of the behavioral theory of the firm literature deals with these kinds of issues. For example, see Cyert and March, A Behavioral Theory of the Firm, Prentice-Hall, 1963, Simon, "Theories of Decisionmaking in Economics and Behavioral Science," AER, 1959, Joskow, "Firm Decisionmaking Processes and Oligopoly Theory," AER, 1975, and Spence, "The Economics of Internal Organization: An Introduction," Bell Journal, 1975.

plicitly or explicitly, then no response should be expected. Therefore, in the pages that follow the decision making process described in the last chapter is reviewed and summarized in order to bring out the factors that are considered explicitly and implicitly in making the R&D expenditure decisions.

Section 4.2. A Model of the Pharmaceutical Research Organization's Project Selection Process

In this section, the aim is to develop a predictive model of how the pharmaceutical research organization will respond to new information, particularly changes in regulatory stringency. In order to develop this model it is necessary to determine the range of factors considered by the firm when the research decision is made, which is here called the information set. The information set consists of two factors, the variables and factors explicitly developed as relevant to the decision at hand and the knowledge possessed by the decision makers themselves through training and experience. Thus an item could be expected to affect a decision either because it is explicitly developed and thereby influences the decision or because those making the decision implicitly take it into account, due to their wide-ranging experience in dealing with such considerations. The organization cannot respond to information that is not in the information set.

In this section the decision making process is examined in detail. The first subsection deals with an overall framework of the procedure while the following two subsections develop this construction into models appropriate for the two different periods that are identified in the first subsection.

Section 4.2.1. The Basic Research Decision Reviewed

The unit of research in a pharmaceutical company is the research "project". At a given time a major company will have 10 to 25 projects under way. The initial motivation of research projects comes primarily from the scientific community of the pharmaceutical company. Though there are exceptions, they are uncommon.

The scientist who has the idea will eventually go either to the research director in his primary area of interest or to the company's over-all research director (depending on the size of the research organization and its internal structure). After some discussion, the project will be put into a formal proposal. This proposal forms the primary information base that is used in determining whether or not this project should be pursued as a formal research project of the company.

The proposal will be evaluated at an annual meeting where all current and proposed projects are scrutinized to determine whether or not they should be pursued. For some existing projects, approval is automatic; for all new and some existing projects the approval process is very detailed and stringent. This meeting also serves as a secondary source of information since those in attendance often contribute important additional information to that available directly from the written project proposal. Thus the information available in the proposal and that available from the participants in the meeting determines the information set available at project selection time.

In the 1960's the formal proposal was a fairly simple document. The primary subjects of interest were the scientific and technical feasibility of the proposal and the "medical need" for such innova-

tion.[2] In the 1960's the attendance at the annual meeting was almost exclusively limited to members of the scientific community. In fact, some companies in the 1960's did not hold these meetings at all. The head of the R&D section of the company would make project selection decisions, often without consulting other scientists on his staff and usually without consulting other disciplines within the company. In all companies the final decisions were left entirely in the hands of scientists. Their motivation was to encourage products that had a high probability of technical success and that were likely to generate projects with a significant medical need. Their information set only included these factors.

Today the situation is very different. The range of disciplines that have input in the formal project proposal has been expanded significantly to include clinicians, marketing people, chemists, biologists, and regulatory affairs personnel. The information developed before a decision is made to take a project includes wide-ranging estimates of the preliminary costs of investigation and the likelihood of success, estimates of the number of people, time and cost to be incurred in clinical (human) studies, the difficulties expected in the regulatory review and approval phase, and the product's expected sales and/or market share once it is introduced. Also the annual review meeting is now a formal part of nearly all companies' decision making processes. In

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[2]Medical need is generally thought of, by the scientists in pharmaceutical companies, as the number of untreated patients in a given area and their degree of suffering. It is related to economic value though the relationship is implicit. Technical feasibility is the probability of developing a new drug from the project (see Chapter 3, note 3).

other words, in this decision making environment, any factor that should significantly affect the expected profitability of a project will probably be taken into account.

However, the primary factor is still the scientific one. If the scientists feel that there is a clear-cut medical need and the technical probability of success is in the right range, then it is likely that that project will be pursued. The interdisciplinary information will be used when the scientific criteria fail to distinguish clearly between projects.

Thus, there have existed two different methods of project selection at different times. In addition, there are significant differences that currently exist among firms. Though all firms have moved from a simple system of relatively complete scientific domination in the 1960's to a more interdisciplinary approach today, some firms rely more heavily on nonscientific information than do others.

The important point to note is that all firms have expanded the information bases used in project selection. In the 1960's the scientists had very limited information. They only took into account medical need and technical feasibility. For current purposes, the most important factor they did not consider was information concerning the stringency of government regulation. Thus, it is to be expected that if the effect of regulation on research expenditure is estimated in the 1960's, none will be found. Further, if the effect is reestimated over the 1970's the effect will be significant and negative.

In the next two subsections formal theoretical models of the decision processes for the 1960's and 1970's are presented. The purpose

is to lend precision to the arguments that have been discussed in this subsection.

Section 4.2.2. The Model of the 1960's

According to the description given, the primary criteria in 1960's project selection were medical need and technological feasibility. According to the scientist-managers (and others) interviewed, no other information was actively developed to improve decisions. Further, since none of the participants in the decision would be expected implicitly to take account of other factors (e.g. regulation) the interviewees claimed that the selection decision was made solely on the basis of the data described above.

Given this description, there is the following functional relationship:[3]

(4.1) $Res = f(TF, MN)$

where:

TF = State of technological feasibility (i.e. the probability of success)

MN = Medical need

Res = Research expenditures

and:

$f_1 > 0, f_2 > 0$.

[3]All variables are in terms of therapeutic classes with the subscripts suppressed.

A priori $f_1 > 0$ (where $f_1 = \frac{\partial f}{\partial TF}$) because as the state of science improves (i.e. it becomes easier to develop new products) additional resources will be drawn into research.

The second element of the research decision of the 1960's was "medical need". As pointed out above, medical need is determined by the number and degree of suffering of patients with a given disease. Therefore, one should anticipate a relationship between this criterion and the product's potential economic return.

These factors, which are important in determining scientific interest in an area, should be fairly closely related to a product's expected sales. The relationship is less than perfect in that the expected sales of a product are also related to how long and how frequently a drug will have to be administered and whether the product can be self-administered (e.g. a tablet or capsule form). Nonetheless expected sales should be closely related to medical need.

The close relationship between the decision criteria of the scientists, medical need and scientific feasibility, and the economic profitability of the research project, which is largely determined by sales and probability of success, should be noted. It may be one of the primary reasons why firms could profitably permit the scientists their high degree of latitude in project selection in the 1960's.

Section 4.2.3. The Model of the 1970's

In the transition between the 1960's and the 1970's, the primary change in firms' approach to this aspect of R&D was the realization that profitability could be improved by using a wider diversity of informa-

tion in the project selection decision.[4] For the purposes of this study, the most important additional factor that firms considered in their decision making was the potential impact of regulation on the profitability of individual projects. However, there were a number of fundamental changes in the decision process.

The description presented in Section 4.2.1. indicates that in the 1970's firms calculate the expected sales of potential products, carefully consider the probable cost of development, estimate the probability of success, and consider the stringency of regulation in their project selection decisions. This results in the following functional relationship:

(4.2) $Res = g(ES, C, p, Reg)$

where:

Res = Research expenditures by therapeutic class

ES = Expected sales of potential products

C = Expected development cost

p = Probability of obtaining a new drug which the company would wish to market (this variable does not include regulatory effects on the probability of success)

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[4]At this point it is not clear if the realization that more information could improve project selection enough to offset the increased decision costs (costs from information development and the increased use of the decision makers time) was a realization of a fact that had been true for a long time. There may have been a change in either the nature of research or other factors (including, possibly, regulation) in the mid to late 1960's so as to make profitable, the previously unprofitable, additional information gathering activities. This issue is of great importance to understand why firms use the decision processes but it is unimportant for the purposes of this discussion. The only relevant fact is that the change occurred.

Reg = Expected stringency of regulation when the potential product is submitted for approval

and:

$$g_1 > 0,\ g_2 \overset{?}{\gtrless} 0,\ g_3 > 0,\ g_4 < 0\ .$$

$g_1 > 0$ because as the expected sales of a potential product increase it is ceteris paribus, more likely that the project will be taken. Thus an increase in expected sales should drive up research expenditures.

g_2 has an ambiguous sign. As the expected costs of research increase there will be an increase in research for all projects taken. However if one examines the expected return of a given project, it will fall. At the margin this implies that certain projects will not be taken that would have been taken with lower research costs. This creates an ambiguity in the sign of this variable.

$g_3 > 0$ because as the probability of technical success increases, the marginal return to all affected projects should increase. This implies that more projects will be taken and will drive up research expenditures.

$g_4 < 0$. This results derives mainly from the interviews at pharmaceutical companies. Theoretically regulation could either increase or decrease research expenditures. It would increase them by causing more tests to be run on each project. An increase is also possible because the regulatory authorities certify the efficacy claims that companies make for their products. This should cause doctors to place more reliance in the claims and could increase sales.

However there are other stronger effects. The primary one is that regulation substantially lowers the probability that a drug will ever

reach the market. This is a combination of those products actually rejected and those that are abandoned before NDA approval.[5] In addition, expected sales are lowered because they are delayed while the FDA considers the application for approval. Finally, the number of claims that a company can make for an approved product is limited to those which it can demonstrate to the regulators' satisfaction. This limits companies' set of choice in advertising decisions and, ceteris paribus, will lower sales. From theory alone the net effect of regulation is ambiguous but the consensus of those interviewed is that regulation will reduce research expenditures.

Section 4.3. The Empirical System and Hypotheses

In this section the theoretical models of the preceding section are developed into their empirical counterparts. Due to the lack of data some of the theoretical variables will not appear in this section. They were included in the previous section to give a fuller treatment of the decision process and to indicate to the reader how the full system appears. The errors introduced by the exclusion of variables will be discussed in Section 4.4.

Section 4.3.1. The Basic Empirical System

The stringency of government regulation can affect the level of research expenditures in two ways. First it affects the amount of money spent on a given project and second it affects the number of projects

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[5] See Chapter 3 above.

taken. Unfortunately, there is only one measure of regulation which will prevent the separation of these two effects. Thus the empirical system will measure the net of these effects. Mathematically:

$$(4.3) \qquad \frac{\partial Res}{\partial Reg} = \beta_{12} < 0$$

where β_{12} will be a parameter of the regression model presented below.

The expected sales of a potential product will affect research expenditures by increasing the number of research projects that will be taken. Formally:

$$(4.4) \qquad \frac{\partial Res}{\partial ES} = \beta_{11} > 0 \ .$$

By combining (3.3) and (3.4), and by taking the usual linear approximation, a linear econometric model of the level of R&D expenditures is obtained:

$$(4.5) \qquad Res = \alpha + \beta_{11} ES + \beta_{12} Reg + \varepsilon$$

where the prior expectations of the signs of the coefficients are: $\beta_{11} < 0$, $\beta_{12} > 0$.

Section 4.3.2. The 1960's Empirical System and Hypotheses

According to the model of the 1960's resource allocation process, presented in Section 4.2., firms responded to new information only as it pertained to medical need and scientific feasibility. Since medical need is closely related to the expected sales of a product, an empirical model of the determination of resource allocation in the 1960's can be described as a special case of the model presented for the 1970's. In

particular, the theoretical model of the 1960's indicates that firms did not respond to government regulation in their project selection processes. Therefore, in an empirical model of the 1960's, this variable should have a zero value. However in special circumstances regulatory constraints, in the form of additional tests required for approval of some drugs, were placed on the research process. So there may have been some change in the dollars spent, per project, as a result of regulatory pressures. However, this parameter should be small in the empirical estimation. If present, it should be positive. In addition, the size of firms' responses to changes in expected sales may have been different in the 1960's. In that era scientists were analyzing medical need, not expected sales. This could mean the scientists placed a different implicit weight on this factor than it now has.

Therefore, if the empirical equation of the 1970's is reproduced one can observe the hypothesized equation of the 1960's by imposing the hypothesized restrictions on that equation. Thus:

$$(4.6) \qquad Res = \alpha + \beta_{21}ES + \beta_{22}Reg + \varepsilon \ .$$

The hypotheses are:

$\beta_{21} > 0$, β_{22} should be equal to zero or small and positive.

Finally, there has been another class of hypotheses generated by the theoretical section of the paper which can be motivated by a brief review. The model of the 1960's predicts that firms did not respond to changes in regulatory stringency but did respond to changes in medical need. The model of the 1970's indicates there were explicitly different

responses to regulation between the two periods. In addition the model of the 1970's indicates there may have been implicitly different responses to expected sales between the two periods.

These observations indicate an additional pair of hypotheses:

(A) $\beta_{21} \neq \beta_{11}$

(B) $\beta_{22} > \beta_{12}$.

These hypotheses, and their tests, are perhaps the most important of the chapter. This importance rests both on the theoretical value of the hypothesis and the information about the validity of the econometric model that can be gained by the test.

Theoretically these hypotheses test whether the behavioral information generated in the interviews (i.e. the reported differences in decision making) are of sufficient importance to generate empirical differences in behavior. This in turn will indicate if the change in decision making between the two periods is an important factor that must be treated in an accurate policy analysis or merely a second-order effect.

These tests are also important for the econometric results of the chapter. If the model is able to test such a relatively sophisticated hypothesis, it will indicate that the basic model and data are reasonably good. This is especially true since the identifiable biases in the model bias the regulation coefficients toward each other. But that is to anticipate and will be examined more carefully in Section 4.5. Now attention is turned to measurement.

Section 4.4. Measurement and Biases

The quality of the empirical results will depend on how well the theoretical variables of Sections 4.2. and 4.3. are measured by their empirical counterparts. In this section, careful attention has been paid to these issues.

However, the correct resolution of a number of the measurement issues leads to discussions that are not of general interest. Therefore the discussion in the text of the paper will be limited to a motivation of the variables and a description of the problems introduced by their shortcomings. A more detailed treatment has been placed in the Appendix to this chapter where the reader can verify the results cited in the text.

Section 4.4.1. The Regulation Variable

As has been shown above, government regulation of new drug introductions can potentially have a significant impact on pharmaceutical research expenditures.[6] This effect comes from several sources. First it can directly affect the level of research expenditures by forcing

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[6]It is important for the reader to note that the discussion of the measure of regulation presented here is complementary to that of Chapter 2 and not a substitute. To reduce overlap between the discussions, certain issues were treated more completely in one place or the other. Thus, in certain areas, the discussion is more complete in Chapter 2, including: previous measures of regulation are discussed more completely there and the current measure is placed in the perspective of previous efforts, there is a better motivation of the need for a therapeutic class measure of regulation as opposed to previous aggregate measures, and there is a statistical analysis of the cross-section time-series movements in the proposed measure of regulation. There is also a more complete discussion of possible correlation between regulation variables and left-out regressors in the Literature Review and in Chapter 5.

companies to perform additional tests on each project they pursue. This effect is positive. A second and larger effect, according to the firms interviewed, occurs because regulation lowers the profitability of the individual research project. This results in fewer projects being undertaken and thereby lowers the level of research expenditures.

However, the latter effect depends on the firms taking this change in profitability into account in their research decisions.[7] Further, firms' reactions in this sphere will be based on how they expect the regulatory authorities to deal with their products when they are presented for approval. Thus changes in regulation that do not affect these expectations should not have an effect on the level of research expenditures through this mechanism.

These factors indicate two criteria for an accurate measure of the impact of regulation on research expenditures. The measure should be highly correlated with the additional tests. The measure should also accurately reflect the information that firms have available to them regarding the stringency of regulation that new products will face several years hence when they are submitted for approval.

These problems can be approached by scrutinizing the information firms have in their possession when they make their research decisions. Even when companies try to be well-informed about the stringency of regulation in an area, their access to information is limited. Even over a long period of time a single firm will make only a few submissions to the Food and Drug Administration. So this source constitutes a very small sample of limited value.

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[7] See Chapter 3 above.

A second possible information source is a company's informal dealings with the regulators at the FDA. Regulators' attitudes about particular products and their attitude in general can be very illuminating. Some individuals, and even whole divisions, of the Bureau of Drugs are known as difficult to work with (and vice versa).[8] In certain cases regulators will indicate the need of a particular test to establish efficacy conclusively. The company can later use this information in project selection decisions, especially if it is an expensive and time-consuming test (e.g. certain tests required for new birth control pills).

A hypothetical source of information could be the submissions and success rates of other companies. However, information on submissions is protected as a trade secret while an application is under review, though some is released when the new drug application becomes inactive. This happens either when the company abandons further research on the product or when the NDA is finally approved. Most companies realize the value of the information contained in an NDA to their competitors. So even when they do not intend to continue to seek approval for a product they maintain the NDA as an "active" one to protect the information contained in it. This leaves approved drugs as the primary source of information about regulatory stringency. Once a new drug is approved, the dates of submission and approval of its NDA become public knowledge. This information is one of the primary indicators of the stringency of regulation available to the companies.

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[8]This is based upon interview information.

The attempt to model the effects of regulation on research expenditures should closely parallel this primary source of information. This can be accomplished by measuring the average delay that a drug faces in different therapeutic classes at different times. This is the measure of regulation used in this paper. It should perform well because it closely reflects the information companies have available when they are forming their expectations about the stringency of regulation a potential product would face.

Before discussion the other characteristics of this variable it is worthwhile to take some time to sketch the causes of delay for an individual drug submitted to the agency. Much of the available information is anecdotal, but it is useful to develop an intuitive understanding of the regulatory agency's activities.

These are three primary causes for delay once a product is submitted for approval. The first is additional testing required by the agency. The second is review time, the time it takes for the agency to evaluate the information contained in the application. Finally there is some delay from bureaucratic uncertainty.

During the course of review of an application, the FDA occasionally concludes that additional tests are required to prove efficacy. The company must perform these tests if it desires approval of the product. This causes delay while the tests are being run.

Probably the most important aspect of delay is pure review time. Delay so classified is time required to evaluate and arrive at a decision based on the information contained in the application. This source of delay is primarily a function of the complexity of the medical issues

involved. Such complexity drives up both the time required to evaluate the material in the application (since more material should be included in complex situations) and the time to arrive at a decision after the material has been assimilated.

Another cause of delay is bureaucratic uncertainty over goals. This results in confusion of whether or not to approve products. It is difficult to tell how much of the delay results from this. Though it is expected that such delay can be important in isolated examples, in general it should not be a significant cause.

This implies that the two primary factors in delay are additional testing and review time. A few examples will further illuminate how delay seems to work. It is best to draw these examples from the extremes of the regulatory area since these more readily illustrate differences.

One extreme is the general class of antiinfectives. The general purpose of antiinfectives is to kill a specific (or class of) organism(s) inside the body. The evaluation of effectiveness is usually straightforward. Either the drug kills the organism or it does not. If it does, the administration period for the product is usually short term. This eliminates the need for evaluation of the product in a long-term setting. In other words, the tests and the costs and benefits of administration are relatively clear-cut.

This can be contrasted with the case of cardiovasculars. These products are very difficult to evaluate. Current thought indicates there is a high correlation between blood lipids and heart disease. However there is no widely accepted theoretical basis for these correlations and the general disease mechanism is imperfectly understood.

In addition, the drugs to treat cardiovascular disease often require long term administration with significant uncertainty about side effects. According to one interviewee, the FDA's position on several cardiovascular drugs is that a company must prove the product's effectiveness in treating a given symptom and show the relation between the symptom and the disease. The evaluations of cardiovascular drugs are very long and drawn out with few new drugs approved. It is also more likely in such cases for additional tests to be required before a product is approved. In general, the more uncertainty about a product's effectiveness, the longer the waiting time and the greater the possibility of additional required tests.

In general this approach views the FDA as seriously attempting to perform the function of evaluating new drugs' effectiveness. Such a position may overstate the agency's benevolence to the consumer, but it is a reasonable approximation for the purposes of this thesis.

However, there is still the problem of correlation with the technology variable. Does this variable represent substantial improvement in this area? In the absence of a good measure of technology it is difficult to be certain if the correlation is less or more. Based on the information available, it appears that this regulation variable represents substantial improvement in this regard but the information is so limited that a final conclusion cannot be reached.

Available information indicates that throughout the pharmaceutical industry there was a fall in research opportunities in the early 1960's.[9]

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[9]See GVT, pp. 134-9, for a good discussion of this. See also the Appendix to Chapter 5 and Section 5.3.

If this is true, and since this is the one main discernible movement in technology, then the within class variable is a substantial improvement. The time series movement of this variable is very substantial compared to that of the aggregate average. For instance, the aggregate average delay moved steadily upward from 1962 through 1967. In four of the six therapeutic classes over which the estimation will be done there was a fall of at least five months between successive years before 1965. In one class there is a steady and systematic drop from 1962 through 1965. This can best be seen by comparing the overall delay with two "representative" therapeutic class delay schedules:[10]

Table 4.1

	1962	1963	1964	1965	1966	1967	1968	1969
Overall average	17	18	22	25	31	36	31	44
Dermatologicals	17	18	38	11	16	21	16	32
Antiinfectives	24	19	14	13	31	38	25	38
	1970	1971	1972	1973	1974	1975	1976	
Overall average	29	19	17	29	21	26	23	
Dermatologicals	18	16	10	22	11	35	27	
Antiinfectives	23	20	18	10	13	35	15	

Source: author

It is easy to see that there is much greater movement in the within-class measures. Further they do not show the systematic upward trend throughout the early 1960's.

[10]All delays are in months. The source of the delay data is the FDA through the University of Rochester's Center for the Study of Drug Development.

Therefore a tentative conclusion would be that the within-class variable should be less correlated with technology than the aggregate variable. Further, given the significant time-series movements and the generally accepted knowledge of research opportunity is that it fell in the early 1960's, there is no reason to believe that the within-class variable should be correlated with technology. However, the lack of positive knowledge of a correlation does not say that it is not there, merely that it does not exist a priori.

In spite of the fact that the proposed variable appears to have some reasonably good properties and seems to correct several of the flaws of previous attempts in this area, there remain some problems with the proposed approach.

The first problem is that the objective of this variable is to measure the overall stringency of regulation by measuring the delay that actually occurs when particular drugs are put before the FDA. However, if a company expects to encounter stringent regulation, presumably it will carry out additional tests before the drug is submitted. Thus companies have an input into how long it will take before an application is approved and the degree of their impact will depend on the alternatives open to them in terms of additional tests they can perform before submitting an application. This situation is formally analogous to a market situation.

If we take that analogy, it is similar to trying to estimate a supply curve by observing movements in prices and quantities when it is known that the supply curve itself has a random element that causes it

to shift at times.[11] The only formally correct solution to such a problem is an instrumental variables approach. However, in this case, there are no valid instruments available. Fortunately, there are characteristics of the variable that should mitigate the effect of these problems on the econometric work. First, there is a consensus that "most" of the movement in the delay variable is a reflection of the changes in the Food and Drug Administration's stringency of regulation. Referring to the market analogy, this is the same as "most" of the movement taking place in the demand curve when the objective is to estimate a supply curve. Second, and much more important, the companies regard the delay variable as a good indicator of the stringency of regulation. Thus they use it to form their expectations about how difficult it will be to get drugs approved in the future. The fact that companies regard it as a good measure and use it to form their expectations means that the variable should perform well for the purposes intended here. However, the companies also use their dealings with the FDA to modify the expectations of the stringency of regulation. This is equivalent to introducing a random measurement error in this variable which will bias the estimated coefficient toward zero.[12]

There remain two important issues in the development of the regulation variable. First, it turns out to be important for the estimation of

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[11]It is necessary to note that this problem introduces a measurement error problem in the right-hand side variable but not a simultaneous equations problem. The delays in approval and time required to adjust research budgets remove the simultaneity.

[12]See Levi, "Errors in the Variables Bias in the Presence of Correctly Measured Variables," EMA, 1973. Hereafter referred to as Levi. It will also bias the other coefficients of the regression. This problem is given a more complete treatment in the empirical section.

the econometric model to obtain a correct demarcation of therapeutic classes. Second, when the correct therapeutic class specification is used, in some years, in some classes, no new products were approved by the FDA. This creates a problem in measuring the regulation variable in those cells in the cross-section time-series model.

Since for current purposes it is only important that these issues be correctly resolved, and since their resolution is fairly involved, the text of the paper will only contain a discussion of the final procedures used and the biases these problems introduce into the final estimations. A complete discussion of these issues can be found in the Appendix to this chapter.

If an incorrect therapeutic classification is used it will induce measurement error in the regulation variable. Therefore, this issue was discussed in some detail with the executives during the interviews. Nearly all felt that a broad therapeutic classification was the appropriate one for the purposes of this research.

Given the broad therapeutic classification system there is still a problem in that during some years no new products appeared in some of the classes. There are several reasonable alternatives to dealing with this issue. The basic problem is that if no new drug appears in a given year the average delay cannot be derived. This problem was solved by carefully examining the information that companies have available to them in such situations. The information they have includes the past history of regulation in the particular therapeutic class at issue, the fact that no new drug was approved in the class (which would probably be interpreted, ceteris paribus, as more stringent regulation), and that the

overall stringency of regulation has changed since the last time period. The importance of the first two is obvious; the last is important because the firm is temporarily prevented from distinguishing changes in stringency in the class being examined from changes in overall stringency. All three pieces of information have some a priori relevance to the firms' attempts to determine stringency in the class at issue. So it is an empirical problem to determine exactly which sources of information the firms used and how they used them. The empirical tests to determine the "best" (empirical) specification of the regulation variable are contained in the Appendix. The final measure used was developed by taking the last value of the within class delay (call this the delay for period t-1), deriving the first difference for the overall average delay (between periods t and t-1), then adding the first difference of the overall average to the within class value of t-1 to obtain the value for period t. The motivation is that companies supplemented their knowledge of how stringent regulation was in t-1 with knowledge of how overall regulation had changed, since between t and t-1 the only new information they have about the class in question is that no new drug appeared and how average stringency changed.

Section 4.4.2. Expected Sales

In measuring this variable the primary effort is to model companies' formation of expectations about the future expected sales of a new product. One of the primary factors firms use in estimating the possible sales of a new product is the size of the existing market (which the product will enter). This in part reflects the feeling that few new

products will enter a completely new market because there exist some form of drug medication for a very wide range of illnesses. It also reflects the fact that in those cases where there is the solid chance to develop a product that is truly unique, the decision to proceed will almost certainly depend on scientific criteria and not on the opinion of the marketers about the potential market. Finally the size of the existing market is used because it is difficult to develop a superior alternative to this crude measure.

For all of these reasons companies tend to rely heavily on the size of the existing market and try to estimate the market share that a product will obtain. This procedure can lead to errors, especially when a product is introduced into an existing market but the nature and scope of the market change after the product has been introduced (a la Valium). However, total market size is a primary part of the companies' estimates of expected sales and, therefore, it is what will be used to estimate expected sales in the empirical section.

Section 4.4.3. Possible Biases

There are a number of possible biases in the proposed equation. The first of these centers around the regulation variable used. It captures a subset of the information that companies have available regarding the stringency of regulation. The full set includes the companies' own dealings with the FDA and information from possible sources in other firms. This creates a measurement error problem in the variable. This effect is increased by the absence of new drugs in some classes in some

years. This measurement error will or will not be serious depending on how well the variable captures the companies' information set.

The other primary source of bias is introduced due to the exclusion of the technology variable. The bias introduced from this exclusion is unknown and does not have an a priori sign. As argued above, the expected size of this bias is small because there is no reason to believe that the technology factor is correlated with any of the right-hand side variables of the regression but its true effect is unknown. However, even though movements in technology should not be correlated with the other right-hand side variables, technology may shift over time and across classes. Thus there is a liberal use of dummy variables in the equations estimated below to eliminate biases introduced by shifts in the technology variable.

Section 4.5. Estimation and Interpretation

The sample used in estimation covers six different therapeutic classes for the years 1965-1968 and 1971-1976.[13] The years 1969 and 1970 are omitted because data were not collected in those years on the left-hand side variable. This coincides with major changes in the firms' resource allocation process during those years. Thus they would have been unusable in the tests to be performed.

The first tests performed were pooling and lag structure tests. The pooling tests were run on the cross-sectional units. The equations

[13]The six therapeutic classes are CNS, Cardiovascular, Neoplasms, Anti-infectives, Respiratory, and Dermatologicals. The classes for Digestive and Vitamins were not used due to a lack of sufficient products marketed for reliable estimates of the regulation variable.

included the current value of the sales variable and the first three lagged values of the regulation variable (the need for lagged values will be explained in a moment). These tests indicated that pooling was valid if a separate dummy variable was included for each therapeutic class.[14] The need for these dummies was attributed to the left-out technology variable, which had different values in different classes.[15]

The next specification issue was the length of the lag structure. Since pharmaceutical companies face significant adjustment costs in changing the level of research expenditures in an area, exogenous variables should have a lagged effect on the level of research.[16]

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[14]The initial pooling test was run with only one constant term in the pooled regression to test if there were any differences in the basic equations. Pooling was rejected at the 5% level. Given this hypothesis was tested that there were differences in the intercept terms but not in the slope coefficients. Thus a dummy variable was included for each therapeutic class. Using a Chow test the derived F-statistic was 1.44 which compares with a critical value (F(20,40)) of 1.84. Thus pooling is not rejected.

[15]As discussed earlier, the inherent ease of getting a new product (called technology in this paper) is not measured explicitly in the model and therefore appears in the error term. This has different values and leads to the different intercept terms.

It also induces serial correlation in the regressions which results in most of the D.W. statistics being around 1. However, the gaps in the data and the fact that ρ should be different for different therapeutic classes indicate that a correction for serial correlation would not be wise. This serial correlation will not induce biases in the estimation.

[16]These adjustment costs are of several kinds. First there are significant start-up and shut-down costs for research projects. These are related to hiring scientists and acquiring the physical facilities to carry out the testing. Second, companies perceive a significant commitment to the scientist when he is hired, partly because most companies feel that if they lay off scientists, their ability to attract top quality scientists in the future will be impaired. Therefore most companies are very averse to laying off scientists and rely on attrition to lower staff size.

The estimation of the lag structure was performed using a nested test for the length of the lag.[17] The initial lag structure included the first five lagged values of the regulation variable and the current and first lagged value of the sales variable.[18] Using the nested test to eliminate variables that were insignificant the fourth and fifth lagged values of the regulation variable were eliminated and the lagged value of the sales variable was also eliminated.[19] This resulted in a final specification of:

$$(4.7) \quad Res_{i,t} = \alpha_i + \beta_1 S_{i,t} + \beta_2 Reg_{i,t-1} + \beta_3 Reg_{i,t-2} + \beta_4 Reg_{i,t-3} + \varepsilon_{i,t}$$

where:

$Res_{i,t}$ = Research expenditures in the $i^{\underline{th}}$ class, in $t^{\underline{th}}$ period

α_i = Dummy variable = 1 for $i^{\underline{th}}$ therapeutic class, 0 otherwise

$S_{i,t}$ = Sales in $i^{\underline{th}}$ class, in $t^{\underline{th}}$ period

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[17] See Hausman "Specification Tests in Econometrics", EMA, 1978.

[18] Because there were insufficient degrees of freedom to perform the pooling tests with the full range of possible lagged variables in the specification, that test will have a bias toward acceptance of pooling. However, it was the best test that could be done under the circumstances.

[19] To perform the nested test, an initial specification was used that was much broader (i.e. had a longer lag) than the a priori final specification. If the last lagged value of a variable was not statistically significant, it is eliminated and the regression is repeated. The progressive shortening of the lag structure by only one lagged value per iteration preserves the independence of the tests.

The fact that the lag structures of the two variables is different should not be surprising because the sales variable follows a relatively smooth trend while the regulation variable has significant time-series movement.

$Reg_{i,t-j}$ = The $j^{\underline{th}}$ lagged value of regulation in $i^{\underline{th}}$ class, in $t^{\underline{th}}$ period

$\varepsilon_{i,t}$ = Random error.

One of the primary results from the theoretical section above is that there were two very different decision making processes used to make R&D resource allocation decisions in the two different periods, the 1960's and the 1970's. This result will be the first tested in this section.

The proposition is that in the 1960's the scientists made the research decisions of the pharmaceutical companies. Since they did not have access to or develop information concerning the stringency of regulation, the hypothesis is that they did not respond to changes in that stringency. However, this hypothesis is difficult to properly test. If an equation is merely estimated over the 1960's there is a problem of interpretation of the results. Since the explanation of these problems will proceed more easily if there is a concrete example from which to proceed, the basic equation that was derived above was estimated over the 1960's. The estimated results were:

$$(4.8) \quad Res_{i,t} = \alpha_i + \underset{(.028)}{.076}\, S_{i,t} + \underset{(.175)}{.209}\, Reg_{i,t-1} + \underset{(.176)}{.053}\, Reg_{i,t-2} + \underset{(.162)}{.011}\, Reg_{i,t-3} + \varepsilon_{i,t}$$

Mean of dependent variable: \$48.6 m

Standard error of regression: \$6.3 m

t = 1965-1968 $\quad R^2 = .94$

Standard errors in parenthesis.

To test the null hypothesis that regulation had no effect, a t-statistic can be constructed for the estimated values of the three regulation variables. The sum of those three coefficients is .27 while the standard error of the sum is .32.[20] The hypothesis is that regulation had no effect on research expenditures. Since the estimated sum is not statistically different from zero (at even the 10% level), the hypothesis is not rejected.[21] However, this leaves a substantial problem of interpretation. While the estimated values are close to zero and their standard errors are large, this only indicates that the probability of a type II error (the probability of not rejecting H_o when false) is relatively small. However the power of the test cannot be calculated in general.[22] Thus failure to reject a null hypothesis is statistically (usually) much less strong than being able to reject a null hypothesis.[23] These problems are made worse in this case because there is a

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[20]The appropriate hypothesis to be tested in this situation is that the sum of the coefficients is zero. The standard error of the sum is calculated using the variances and covariances of the individual coefficients. The reader should note that there is a mathematically equivalent F-test but that it is not the test to restrict the coefficients simultaneously to zero.

[21]To increase the statistical power of testing for no regulatory effects, since there are only a limited number of degrees of freedom, the test was repeated using a nested test and you cannot reject the hypothesis that all of the coefficients are zero.

[22]One minus the probability of a type II error is the power of the test, which will be a function of the significance level and the coefficients under the alternative hypothesis. In the case presented here, the power of the test will be .68 if $\alpha = .05$ and .52 if $\alpha = .01$ (both assume that the alternative hypothesis is that the sum of the regulation coefficients is the observed value of .29). See Mood, Graybill, and Boes, Introduction to the Theory of Statistics, pp. 406-412, and Cohen, Statistical Power Analysis for the Social Sciences, Chapter 2.

[23]This problem can be summarized by noting that classical hypothesis testing concentrates on type I error rather than type II error.

measurement error of unknown dimensions in the regulation variable. Finally, there is the problem of the left-out technology variable. The correlation with that variable may be biasing the coefficient and thereby causing the "no effect" result.

Fortunately there is another test which avoids these problems. There is not only the hypothesis that there was no effect in the 1960's, but also the hypothesis that the effects in the 1960's were different from the effects of the 1970's. But first examine the following equations:

$$(4.9) \quad Res_{i,t} = \alpha_i + \beta_{11}S_{i,t} + \beta_{12}Reg_{i,t-1} + \beta_{13}Reg_{i,t-2} + \beta_{14}Reg_{i,t-3} + \varepsilon_{i,t}$$
$$t = 1965\text{-}1968$$

$$(4.10) \quad Res_{i,t} = \alpha_i + \beta_{21}S_{i,t} + \beta_{22}Reg_{i,t-1} + \beta_{23}Reg_{i,t-2} + \beta_{24}Reg_{i,t-3} + \varepsilon_{i,t}$$
$$t = 1971\text{-}1976$$

Now, another of the results of the theoretical section was that the effect of external factors on the R&D resource allocation system should be different. This result comes from scientists' lack of attention to regulatory stringency (according to the interviews conducted) during the 1960's. Further, the resource allocation process of the 1970's explicitly took this factor into account. Thus there are two null hypotheses that should be tested. They are:

$$(4.5.1) \quad \beta_{11} = \beta_{21}$$

and

$$(4.5.2) \quad \beta_{12} + \beta_{12} + \beta_{14} = \beta_{22} + \beta_{23} + \beta_{23} \cdot$$

A preliminary test can be run to guard against possible errors introduced by the technology variable.[24] The regressions (4.9) and (4.10) were run separately and then in pooled form. The hypothesis that they had the same coefficients was rejected at the 5% level. However, this does not directly test (4.5.1) and (4.5.2) because there may have been a shift in the omitted variable, technology, between the 1960's and 1970's. Therefore the regressions were reestimated with a separate set of dummy variables. The pooled specification would then have two sets of dummy variables for each therapeutic class, one for the 1970's and one for the 1960's. When that regression was performed several of the additional dummy variables were significantly different between the two time periods, indicating that there probably had been a shift in the technology variable between the two time periods. To specifically test the hypotheses in (4.5.1) and (4.5.2) the following specification was used:[25]

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[24]This entire approach permits the problem to be translated into a test of a null hypothesis where the theory predicts the hypothesis will be rejected. This will yield confidence intervals and yield estimates of the probability the conclusions are wrong.

[25]This format has the convenient property that the hypotheses can be tested directly from the coefficients in the regression. To test that sales had a different effect in the 1965-1968 period than the effect it had in the 1971-1976 period it is only necessary to examine the coefficient, γ_{11}. It if is statistically significantly different from zero, then the hypothesis that the effects are the same is rejected with the usual confidence bounds. To test (3.5.2) the sum of the coefficients, $\gamma_{12} + \gamma_{13} + \gamma_{14}$ is examined using an F-test. If the sum of these is significant (i.e. the hypothesis that the sum is zero is rejected) then (3.5.2) is rejected.

$$(4.11)\quad Res_{i,t} = \alpha_{i,1} + \alpha_{i,2} + \beta_{21}S_{i,t} + \gamma_{11}\bar{S}_{i,t} + \beta_{22}Reg_{i,t-1} + \beta_{23}Reg_{i,t-2} + \beta_{24}Reg_{i,t-3} + \gamma_{12}\overline{Reg}_{i,t-1} + \gamma_{13}\overline{Reg}_{i,t-2} + \gamma_{14}\overline{Reg}_{i,t-3} + \varepsilon_{i,t}.$$

where:

$\alpha_{i,1}$ = 1 in $i^{\underline{th}}$ therapeutic class; zero otherwise

$\alpha_{i,2}$ = 1 in $i^{\underline{th}}$ therapeutic class from 1965-1968; zero otherwise

$S_{i,t}$ = Sales in $i^{\underline{th}}$ class in $t^{\underline{th}}$ period

$Reg_{i,t}$ = Regulation in $i^{\underline{th}}$ class, $t^{\underline{th}}$ period

$\bar{S}_{i,t}$ = Sales in $i^{\underline{th}}$ class in $t^{\underline{th}}$ period from 1965-1968; zero otherwise.

$\overline{Reg}_{i,t}$ = Regulation in $i^{\underline{th}}$ class in $t^{\underline{th}}$ period from 1965-1968; zero otherwise

Note: γ_{12} is an unbiased estimator of $(\beta_{22}-\beta_{12})$, as γ_{22} for $\beta_{23}-\beta_{13}$, etc.

The estimated regression was:[26]

$$(4.12)\quad R_{i,t} = \alpha_{i,1} + \alpha_{i,2} + \underset{(.019)}{.083}\, S_{i,t} - \underset{(.069)}{.007}\, \bar{S}_{i,t} - \underset{(.239)}{.211}\, Reg_{i,t-1} - \underset{(.222)}{.686}\, Reg_{i,t-2} - \underset{(.226)}{.868}\, Reg_{i,t-3} + \underset{(.279)}{.420}\, \overline{Reg}_{i,t-1} + \underset{(.473)}{.739}\, \overline{Reg}_{i,t-2} + \underset{(.444)}{.879}\, \overline{Reg}_{i,t-3} + \varepsilon_{i,t}$$

[26]The reader should note that this regression constrains both periods to have the same lag structure. This could cause a problem if it were the case that there were only differences in lag structure. However the separate estimations show that this is not the source of differences, but that they are more fundamental.

Mean of dependent variable: $83.8 m

Std. error of regression: $14.8 m

F-statistic: 46.6 $R^2 = .96$

Examining these results, the hypothesis that expected sales had the same effect in the two periods cannot be rejected. This would indicate that the scientists, when examining medical need in the 1960's, were implicitly taking account of the economic value of research in much the same way that is explicitly done today when the economic value is carefully measured in terms of expected sales.

However, the hypothesis that regulation had the same effect in the 1960's as in the 1970's is rejected. The sum of these three coefficients is 2.04 and their standard error is .92.

This test has several advantages over the preceding one. First it clearly shows that the two decision-making processes did not respond to changes in regulatory stringency in the same way. Further, this test has a well-defined statistical interpretation. It indicates that with a 95% confidence level the hypothesis that the effects were the same is rejected.

Moreover, these results indicate that the estimated zero effect of regulation in the 1960's should not be attributed to the measurement error in the regulation variable. If serious measurement error problems were introduced into the equation then this would bias the hypothesis that the two sets of regulation variables had the same effect toward

acceptance (nonrejection).[27] Since the data and the variables are accurate enough to test this relatively sophisticated hypothesis, it is difficult to believe that the finding of a small positive effect in the 1960's equation is a result of these problems.

Finally, and most important of all, these findings support another of the basic hypotheses of the paper. Since firms did not take regulation into account in their decision-making process in the 1960's, it did not have an effect on the level of research expenditures in that period. This result strongly supports the basic approach to research that has been followed in this study. It indicates that it is not enough to show that a variable should have an effect on profitability for it to be taken into account in the firm's resource allocation decision. Additional factors must also be examined before this conclusion can be reached. These factors are centered around the company's internal organization and the way in which the organization handles information. If the decision-making process is not well-equipped to process information regarding the variable in question, then the fixed cost of changing the organizational structure to be able to take account of information and the fixed cost of developing the information may well outweigh the

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[27] Levi has shown that the sign of the inconsistency in the presence of measurement error can be estimated by the signs of Plim $(\frac{1}{T} X'X)^{-1}$ Plim $\bar{\beta}$ where X is the matrix of observed right hand side variables and $\bar{\beta}$ includes only the estimated coefficients of the variables with measurement error. Therefore if the signs of the inconsistency are the signs of $\bar{\psi}$ then $\hat{\psi} = (\frac{1}{T} X'X)\bar{\beta}$, is a consistent estimate of $\bar{\psi}$. Using such an estimate it appears that all regulation coefficients are biased toward zero.

gains that can be obtained from the superior resource allocation decisions that are made.

Section 4.6. The Effect of Regulation on Research Expenditures in the 1970's

The empirical results in the previous section clearly establish that the 1960's and 1970's research expenditure equations are not generated from the same model. Therefore we must estimate the equations separately to obtain unbiased estimates of the effect in the different periods. In particular, the length of the lag must be reestimated on the basis of new information that the equations are different.

Therefore the nested test on the lag in the 1970's equation was repeated. The results indicated that the second, third, fourth, and fifth lagged values of the regulation variable belonged in the final specification.[28] The final estimation was:

$$(4.13)\quad Res_{i,t} = \alpha_i + \underset{(.020)}{.051}\, S_{i,t} - \underset{(.210)}{.604}\, Reg_{i,t-2} - \underset{(.220)}{.932}\, Reg_{i,t-3} - \underset{(.266)}{.932}\, Reg_{i,t-4} - \underset{(.276)}{.529}\, Reg_{i,t-5} + \varepsilon_{i,t}$$

Mean of Dependent Variable: \$107 m

Standard Error of the Regression: \$14.19 m

F-statistic = 63.45 $\quad R^2 = 96$

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[28] The nested test procedure was slightly different than the standard one. It was not known, a priori, how long it would take firms to begin reacting to changes in regulation and therefore the first lagged coefficient was not constrained to be nonzero. It was treated as any other coefficient on the end of a lag. Thus when it was not significant it was dropped. In this case, where both the beginning and end of a lag is unknown and both the first and last lagged values were insignificant, the one with the lowest t-statistic was dropped.

The interpretation of this equation is quite interesting. It states that if there is a one month increase in the average delay that a new drug faces, there will be no drop in research expenditures the following year. However, the year after that, research expenditures will drop by approximately six hundred thousand dollars, from what it otherwise would have been. The next year research will drop by over nine hundred thousand, and so forth. There are several interesting thought experiments that can be performed with these numbers to give an indication of the magnitude of the variables involved. First take the year 1976. Average research expenditures in each of the six therapeutic classes under consideration was $178 m. Now suppose that in 1974 the average delay for a drug appearing in one of these classes had been 21 months instead of the actual value of 22 months with accompanying changes in the other aspects of regulation that are correlated with the delay in approval. If this had happened, the regression parameters indicate that there would have been an increase in research expenditures of approximately $3.00 m with a standard error of $.46 m. This represents about 1.7% of the research expenditures in each therapeutic class! The standard error in percentage terms is approximately .3%. One can also calculate the increase in research if the average delay were decreased by one month in all of the five preceding years.

It is also interesting to estimate the percentage drop in research expenditures in 1976 that resulted from regulation. This can be done by reducing the observed values for the second, third, fourth, and fifth lagged regulation variables to 7 months (the average delay before 1962) and multiplying this difference times their corresponding parameter es-

timates and then comparing them with average expenditures in the six therapeutic classes. The standard error of this estimate can be derived in a similar straightforward manner using the variances and covariances of the parameter estimates. The average research expenditures in these six classes in 1976 was $173 m. The estimated mean effect of regulation in lowering the expenditures was $37 m with a standard error of $7.1 m. In percentage terms this mean effect is 32.6% while the standard error is approximately 4.1%.[29]

However a strong word of caution is in order in the interpretation of these results. The estimated regression model was assumed to be linear. This creates significant problems of interpretation when the values of the right-hand side variable are extrapolated beyond the sample. In that region, if the linearity assumption is not strictly true, the estimated standard errors of the coefficients may be only a rought guide to the true variability of the estimates. In estimating the change in research that would have occurred if regulation were set at 7 months such an extrapolation was done and these results should therefore be viewed with caution.

In spite of these qualifications, the estimated effect is quite large and highly significant. It indicates that regulation has had a very significant impact on research expenditures in this industry during the 1970's.

However, a very important qualification to note is that there are no social welfare consequences to these estimates. It may well be that

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[29]See Johnston, Econometric Methods, pp. 153-5 for the methodology used in obtaining these predictions and their standard errors.

society is better off with the lower level of research expenditures in this area. If the lower level of expenditures results in only effective drugs being marketed, it may be socially preferable to make this trade-off. The important point is that before an intelligent choice can be made about the stringency of regulation in this area, there must be a sound understanding of the tradeoffs involved. The results presented here should help to illuminate one aspect of these tradeoffs.

Section 4.7. Summary and Conclusions

There have been a number of important factors illuminated by the results presented in this paper. These include both results concerning the impact of government regulation of pharmaceuticals on research in that industry and on the proper way to proceed in trying to evaluate such an issue.

The econometric results presented herein indicate that government regulation did not have a significant effect on the research expenditure patterns in the industry in the 1960's. The result rests on the fact that the R&D decision makers did not develop or use information regarding the stringency of regulation in that era. The apparent reason for this lack of attention is that the cost to the scientists who made the decisions, in terms of time, was not perceived to be worth the benefit of increased precision in project selection.

This result has important implications for public policy in this area. It demonstrates that regulation had little effect on research expenditures in this era. This means that if the large fall in the rate of introduction of new drugs is attributed to regulation, the only inter-

pretation is that it must have been the result of the government preventing the marketing of ineffective drugs.[30] The only other possible way in which regulation could have been the primary factor was if it drove up research costs in this period. However this is not plausible both because most literature indicates that the largest past escalation in costs came later in the 1960's and because the positive effect of regulation on research expenditures in a therapeutic class, as estimated in the 1960's equation, was very small.

The second important result in this area is that in the 1970's there was a significant change in the research decision process from that which prevailed in the 1960's. This new process had the capacity to handle information regarding regulatory stringency and as a result, firms responded very strongly to changes in regulatory climate during this era. The effect of even small changes in the stringency of regulation on the level of research is apparently quite large. The size of these effects indicates that there is a large trade-off of research expenditures for the increased certainty that new products are effective. This trade-off needs to be carefully considered in future public policy decisions in this area.

However there is a second class of results that are perhaps more important. These results presented here show that significant insights can be gained, in studying public policy problems, by looking inside firms and seeing how they actually process information in the face of very complex problems. These insights can also lead to specific, em-

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[30]The effects of regulation on new product introductions is considered explicitly in Chapter 2.

pirically testable, hypotheses that will illuminate the complex public policy problems under examination.

In the particular example under study there was no reason to believe that pharmaceutical companies would not have responded to changes in regulation during the 1960's, until the decision making process of these firms was carefully examined. However the interviews made it clear that they did not respond and the investigation of this finding has lead to a significant improvement in our understanding of these issues.

There remains a significant question relevant to the issues at hand that has received only passing mention in the preceding discussions. Why did the decision making processes change between the 1960's and the 1970's? There are several plausible explanations that are consistent with the available evidence.

The first possibility is that the expected profitability of research fell so much in the late 1960's that companies had to search for ways to improve profits. One way that they came up with was to change the decision process. This seemed to be the prevailing story in pharmaceutical companies during the interviews. The fall in profits was attributed to changes in both regulation and research opportunities. This has some appealing points, but it is not consistent with the profit maximizing approach followed here because it indicates that the changes would have been profitable all along but were not made for reasons that are unclear. In this area the inclination of the author is not to rely totally on the information given by the companies. The reason is that he feels that the reliability of the companies' descriptions of what they actually do is probably more reliable than why they do it.

Another possibility is that the nature of research changed between the two periods. The decision making process exclusively using scientific opinion has a comparative advantage over the interdisciplinary approach in several situations. If the kind of research changed to include less of this kind of research it may have made it worthwhile to change the entire decision process (assuming that all projects have to be evaluated in basically the same way).

There is a final possibility. Given the size of the effects of regulation on research in the 1970's, it must be inferred that regulation has had a large effect on research profits. Further it may be that in the absence of regulation the scientific approach is superior to the other. If this is true, it may have taken the companies some time to discover that their research organizations could make more net profits if regulation were considered in the decision making process. When they did discover this, in the late 1960's, they changed the entire decision process so this one factor could be taken into account.

Unfortunately, the evidence presented here does not distinguish between these possibilities.

Appendix to Chapter 4

This appendix deals with the correct measurement of regulation. The conceptual issues surrounding the regulation variable were dealt with in the main body of the paper. The basic approach is to measure regulation in different therapeutic classes by the average delay faced by drugs in those classes. There remain two technical issues. First, it is important for the correct estimation of the empirical model to use a correct demarcation of therapeutic classes. Second, when the correct therapeutic class divisions are used, in some classes, in some years, no new products were approved. Either of these, if not correctly resolved, will induce measurement error in the regulation variable and cause biases (and inconsistencies) in the estimated coefficients of the regression.

Turning to the first, the empirical equations derived in the paper are assumed linear. They determine the level of research expenditures as a function of expected sales and regulation. The underlying hypothesis of using therapeutic classes is that firms, in forming expectations about sales and regulation, are more sophisticated than to lump all projects into the general area of pharmaceutical research. The author was told that firms are aware and take account of differences in the stringency of regulation and expected sales in different therapeutic classes. This implies that aggregating across therapeutic classes will reduce the efficiency of the econometric estimation (this is the usual aggregation problem). However in this case the problem is worsened because the average delay variable will depend on the therapeutic classification. In the particular situation at hand, aggregation leads not

only to inefficiencies but to inconsistencies in the estimation. Therefore it is necessary to exercise care in the classification. Further, an incorrect therapeutic classification scheme (e.g. one that is too broad) will lead to the same biases and inconsistencies.

In order to avoid this problem, pharmaceutical executives were questioned about which of several therapeutic classifications they used in forming expectations about regulatory stringency. They indicated that a broad classification should be used.

The primary reason is that regulation will have its primary influence at a relatively early stage of drug research. Firms will let regulatory expectations discourage them from research in certain areas but only rarely will a known product at an advanced stage be discarded due to expected regulatory stringency. In addition due to the serendipitous nature of drug discovery, only the broad general area of a drug may be known at a very early stage of research.

Given the broad classification used, there remains another problem. In some years no new products appeared in certain therapeutic classes. This poses a difficulty in measuring the average delay. This must be resolved by examining the information available to the firm in that situation.

The firm is aware that regulation in the therapeutic class in question is different from other therapeutic classes because it has observations on previous values of regulation. The firm is also aware that a special event happened in that no new drugs were approved. This could result from few new drugs being submitted or it could result from very stringent regulation (or both). A priori it is not clear which is more

accurate. Finally the firm also has information about how overall stringency has changed since the last observation of delay in the class under consideration.

There are two ways the firm could form expectations about stringency in this situation. One will be called static expectations and the other will be called complete information expectations.

Under the static expectations approach the firm responds to the lack of new information in a particular class by assuming that stringency is unchanged. So the firm extrapolates the last observed value of regulation forward as the best estimate of the current value. This approach implies that regulation of different drugs is so different that information about how overall stringency has changed will not improve predictions of regulation in the class in question.

Another possible reaction by the firm would be to use the information about how overall stringency has changed to supplement the existing information about past stringency in the class under discussion. Thus the firm could sum the last observed value of within class regulation and the first difference of over-all regulation. The interpretation of this approach would be that though there are differences between classes in stringency, stringency has a tendency to move in the same direction in all classes. This is called the complete information expectations mechanism.

In both cases there is additional information the firms can use. This is the fact that no new drug appeared in the class and year in question.

Both mechanisms represent plausible ways in which firms could form their expectations in the absence of a new drug. Thus the choice between them must be made on empirical grounds.

A preliminary set of regressions was run as a test for pooling of the cross sectional units. This test was performed separately with each of the regulation variables. Due to a lack of degrees of freedom this test could not be run using a full lag specification, so a modified lag structure using just the first three lagged variables was used. The results indicated that pooling was valid if a dummy variable were included for each therapeutic class.

The most direct test between the two variables is to include them in the same regression and see which yields significant coefficients. This was done but the results indicated that the extremely high collinearity between the two variables thwarted attempts to distinguish between them.

However there is an alternative procedure which removes the collinearity. The procedure is to use the static expectations variable and other variable which has the value zero when a new product appears and the value of the first difference of overall regulation when no new product appears.[1] This will directly test for a response to the additional information provided by the change in overall regulation in those years in which no new drug was approved. A very broad lag specification was used. The results of the estimation were:

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[1]I would like to thank Franklin Fisher for suggesting this test.

$$Res_{i,t} = \alpha_i \underset{(.239)}{-.601}\ Reg_{i,t-1} \underset{(.234)}{-.284}\ Reg_{i,t-2} \underset{(.238)}{-.169}\ Reg_{i,t-3}$$

$$\underset{(.285)}{-.125}\ Reg_{i,t-4} \underset{(.618)}{-.188}\ FD\ Reg_{t-1} \underset{(.526)}{-.588}\ FD\ Reg_{t-2}$$

$$\underset{(.539)}{-1.59}\ FD\ Reg_{t-3} \underset{(.536)}{-1.10}\ FD\ Reg_{t-4} \underset{(.014)}{+.147}\ S_{i,t} + \varepsilon_{i,t}$$

Std. error of regression = 18.8 Mean of dependent variable = 88.8

$F(14,39) = 34.7$ $R^2 = .93$

where:

$$FD\ Reg_{t-j} = \begin{cases} 0 \text{ if a new drug comes out in a class in a given year} \\ \text{The first difference of overall regulatory delay between period t-j and t-j-1, otherwise} \end{cases}$$

$Reg_{i,t-j}$ = The $j^{\underline{th}}$ lagged value of average delay in class i

$S_{i,t}$ = Sales in the $i^{\underline{th}}$ class

$Res_{i,t}$ = Research in the i^{th} class.

These results clearly indicate that firms respond to the information contained in the movement in the overall variable when a product does not appear in a particular class. The third and fourth lagged values of this variable are significant by themselves. The sum of the coefficients on this variable is 3.5 and the standard error is 1.3 which is significant at the 5% level.

Therefore, it was concluded that this information should be included as part of the measure of regulation.

Chapter 5. Overall Effects, the 1960's Reconsidered, Summary and Conclusions

Section 5.1. Introduction

In this chapter the estimations and analyses of the previous chapters are combined to form estimates which indicate that new product introductions have been greatly reduced by regulation. In fact, the estimates suggest that introductions would rise to approximately their 1950's levels if regulatory stringency were lowered to its pre-1962 levels.

After these estimates are presented, attention is turned to the fall in introductions of the early 1960's. This fall is broken down into its individual therapeutic class components to see if this will shed further light on the underlying factors causing the fall. The results will clearly indicate that nonregulatory factors were very important, and these factors are discussed. The summary and conclusions follow this discussion.

Section 5.2. The Overall Effects of Regulation on New Product Introductions

In order to estimate the overall fall in introductions, the direct effect of regulation on introductions (estimated in Chapter 2) must be combined with the estimates of the indirect effect (from Chapter 4). Returning to the simple model presented at the start of the thesis we have:

(5.1) $NCE = f(Reg,Res)$

and

(5.2) $\quad Res = g(Reg, \bar{X})$.

We desire:

(5.3) $$\frac{dNCE}{dReg} = \frac{\partial f}{\partial Reg} + \frac{\partial f}{\partial Res} \frac{\partial g}{\partial Reg}$$

The estimates from Chapter 2 and 4 show that:

$$\frac{\partial f}{\partial Reg} = -.122, \quad \frac{\partial f}{\partial Res} = .043, \text{ and } \frac{\partial g}{\partial Reg} = -3.0 ,$$

where all derivatives are calculated in terms of the long run effect (i.e. the distributed lags are summed for an overall effect).

Therefore:

$$\frac{dNCE}{dReg} = -.122 - (.043)\ (3.0) = -.251 .$$

So if the average delay time is reduced by four months in a given therapeutic class (with a concomitant decrease in the other aspects of regulation that are correlated with the average delay time), in the <u>long run</u> there would be one additional product per year, introduced into that therapeutic class. Considering that the average delay time for the two estimations was in the range of 22 to 25 months, and that there were only two products introduced per year, per class, this number is quite large. If regulatory delay were reduced to the pre-1962 average of seven months, the estimates indicate that there would be an increase in the rate of introductions by 200% over its current rate. This is the first estimate of the total reduction in introductions resulting from regulation in the 1970's.

Several additional points should be noted regarding these estimates besides their large quantitative magnitude. First, they demonstrate that regulation is currently a very significant factor affecting the flow of products onto the market. Thus, the estimated trade-offs should be considered by regulators in their decisions to set the safety and efficacy requirements at particular levels.

Also, the estimates indicate that the indirect effects of regulation on research has had as large an impact on introductions as the direct effect. This is noteworthy since previous authors have not examined this aspect of regulation.

Finally, the econometric estimations underlying the estimated effects represent a signifcant improvement over previous attempts to measure regulatory effects. This improvement is the result of using disaggregated data. This suggests that the disaggregated data may also be helpful in examining the historical fall in introductions of the 1962 era, to which we now turn.

Section 5.3. The 1960's Fall Disaggregated

As stated in Chapter 1, there was a large drop in the rate of new product introductions into the U.S. market in the early 1960's. And, as argued throughout the thesis, new product introductions are a function of research, regulation, and the availability of research opportunities. In this section there is an attempt to determine the role played by various factors in the drop in introductions of the early 1960's. The reader should note that these are only tentative explorations because of the

paucity of the available information. However the available data will be examined and tentative conclusions reached.

All econometric procedures in this area are plagued by the absence of a good measure of research opportunities. While this exercise is no exception, one way to approach the problem is to extrapolate the production function equation of Chapter 2 backward in time to the mid-1950's. Since the equation will measure changes in the variables besides research opportunities, differences between the equation's predicted values and the observed introduction rates can then be attributed to changes in the availability of research opportunities. This will be especially enlightening if there are large and systematic differences between the predictions and the realizations since there are not long runs of residuals in the post-1965 era (the OLS D.W. statistic is 1.92 for the basic estimated equation over the estimation period).

However, the proposed extrapolation immediately presents several problems. First, for the estimated equations to be valid over the entire period, the firms and regulators would have had to move immediately to a new long-run response pattern to the efficacy requirements when they were passed in 1962. Chapter 4 indicated that this is very unlikely since it took firms until the late 1960's to move to a new equilibrium response function in allocating research expenditures. Thus the equations might not perform very well in the four to six years following 1962.

An attempt was made to overcome this problem by reestimating the equation (using the research data described below) including observations from the early 1960's. In these estimations a shorter lag structure was used for the regulation variable in the early time period. However these

additional regulation variables (i.e. the additional lagged values) were not significant in the estimations and this procedure was abandoned. However this procedure only indicates that the measure of regulation used does not pick up effects in the years immediately following 1962. It may be that there were regulatory effects, but that another variable is required to measure them. Thus, if there are systematic negative residuals following 1962, these might reasonably be attributed to short run adjustments to regulation.

The other problem in the extrapolations is that research expenditure data, by therapeutic class, is not available prior to 1965. To overcome this problem, it was assumed that the percentage of research expenditures allocated to each therapeutic class was stable over time. Thus, the percentage of total research expenditures allocated to each therapeutic class was estimated from available data. This was then extrapolated backward in time and multiplied by the observed overall industry research expenditures for which data is available back to 1951. These values were then used in the extrapolations of the equations.

However, as noted in Chapter 4, research expenditures vary over time since this variability is the driving force behind those estimations. Fortunately, the only major determinant of research expenditures, in the 1950's and 1960's, that would not be expected to follow a relatively smooth trend is research opportunities. Thus, if research opportunities changed systematically among the different classes between the 1950's and mid-1960-s, the proposed research expenditure variable will probably not reflect true research expenditures. However, the residuals of the fitted equations will be attributed to changes in research opportunities. Thus,

for current purposes, it makes little difference if research opportunities changed introductions by acting directly on introductions or through the research expenditure variable.

Despite the above arguments, it should sitll be emphasized that the above procedures are definitely subject to error. Therefore, the results of the extrapolations should (and will) only be used for a rough qualitative examination of the factors affecting new product introductions in the relevant time periods. Even these qualitative examinations should be viewed with caution.

The extrapolations were carried out and the equation's predicted values were plotted against the observed values. These graphs form the Appendix to this chapter. In examining the residuals, first notice that the equation predicts much better starting in approximately 1962 than it does in the preceding time period. Thus, in spite of the fact that the measured effect of regulation from the 1962 amendments is zero (since only the sixth lagged value of regulation is used), the equation does much better for the post-1962 era. Based upon previous work in the area (see Chapter 1) one would have expected large negative residuals in the 1962-1967 period since the equation's measured effect of regulation is at the pre-1962 level for that entire period. This indicates that the low introduction rates of the early 1960's can be explained quite well without relying on regulatory effects of the 1962 amendments.[1]

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[1]The reader should note that the estimated equation demonstrates a large regulatory effect for the 1970's. And, repeating the earlier textual argument, it has been indicated that the measure of regulation used did not pick up regulatory effects, even with a shorter lag structure for the variables in the early 1960's. Since the proposed measure of regulation
(continued on following page)

The next thing to notice about the residuals of the estimations is that there are runs of positive residuals in several classes in the pre-1962 era. The most striking of these is the Central Nervous System (CNS) class. This area is of particular interest since thalidomide, the drug whose side-effects were a very signficiant factor in the passage of the 1962 amendments, was a CNS product. It is also important because a large percentage of the decline in introductions that occurred in the early 1960's can be attributed to this single class of products.

However, the econometric procedures used in the extrapolations are somewhat suspect. However, to avoid these problems and get a clear picture of the role of this class in the overall decline in introductions, one can compare actual introduction rates in the 1954-1961 period with those of the 1962-1969 period. There was a decline of 55% in the overall average introduction rate between the two periods. However, CNS introductions fell by 74% between the two periods (from 13.6 per year in the early period to 3.5 per year in the latter), whereas introductions in the other five classes fell only 37%. It can therefore be concluded that the fall in introductions in this area in the 1962 era was qualitatively different from the fall in the rest of the industry.

There are several possible explanations for the CNS decline. First, there may have been an exhaustion of CNS research opportunities. This possibility is strengthened because Hoffman-LaRoche introduced Librium and Valium in the early 1960's. There is little doubt, given the strength

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1 (continued from preceding page)
may simply be inadequate, one would expect unmeasured regulatory effects to appear in systematic negative residuals in that period. Since these do not appear, it must be presumed that regulation was not having an effect.

of these two products' sales over time, that they offered a substantial improvement over their predecessors. Therefore, it might be concluded that these products were so much better that they preempted the potential for improvement in the area and thus reduced research opportunities. However, this leaves unexplained why others did not circumvent the Librium and Valium patents as happened with the broad-spectrum antibiotics.[2]

This leads to the second possibility. It is possible that the thalidomide incident made physicians more cautious in their approach to new CNS products. Previous authors have suggested that thalidomide changed society's willingness to try new drugs (for example see GVT, pp. 138-9). However, the possibility that it differentially affected CNS products has not been explored. Along this line, it is interesting to note the drop in introductions of tranquilizer and tranquilizer-like products in the post amendment period. Twenty eight new major and minor tranquilizers were introduced from 1954 to 1961, while only ten were introduced from 1962-1969. Eleven hypnotic sedatives were introduced in the early period as opposed to only one in the later.

Whether exhaustion of CNS research opportunities or increased company and/or physician caution caused this decline is not clear. However, it is clear that the decline in CNS introductions was qualitatively different from the decline in other areas.

Several conclusions can be drawn from this examination of the decline in new product introductions. First, the rate of introductions fell in

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[2]See Costello, "The Tetracycline Conspiracy," Antitrust Law and Econ. Rev., 1968 and Steele, "Patent Restrictions and Price Competition in the Ethical Drugs Industry," J. Law and Econ., 1964, pp. 215-21.

most classes but did not fall by the same amount. This would suggest that there may have been a (relatively small) common component of the fall, since there was a fall in most classes, but also a class-specific component. Second, previous authors did not allow for these class-specific differences in their estimations and, since these appear to be large, they could lead to serious biases in previous regression equations. Third, such biases probably did not influence the estimations for the 1970's presented in Chapter 2. This is because in the pooling tests separate dummy variables were introduced in each class in a fixed effects pooling procedure. The dummies were insignificant, and since theory did not clearly require their presence, they were dropped from the other estimations.[3]

Finally, not only was there a decline in the absolute level of introductions in the early 1960's, but the kind of drugs being introduced changed. Thus if regulation were reduced through a reduction of efficacy standards, the number of drugs being introduced would increase to approximately the levels of the 1950's, but the kinds of drugs would be different.[4]

Section 5.4. Conclusions and Policy Implications

A number of important results have been brought to light in both this chapter and the thesis as a whole. The thesis began by raising some questions about previous empirical work on the effects of regula-

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[3]See Chapter 2, footnote 29.

[4]As shown above, if regulation were reduced to its 1950's levels, then the average introductions, per class, would raise to six. Thus in the six therapeutic classes, there would be about 36 new drugs per year.

tion on the rate of new drug introductions. It was argued that previous empirical work on this issue had relied solely on the decline in the rate of new introductions of the early 1960's and that it had failed to properly account for the role of falling research opportunities in that decline. The inability to accurately measure research opportunities made this work difficult to interpret.

However, in Chapter 2 new estimates of the effect of regulation on new product introductions were derived using disaggregated data from the 1970's. These new drug production function estimations clearly indicated that regulation is a major factor in the supply of new drugs. They implied that regulation has approximately doubled the cost of a new drug. But these estimations were incomplete because they did not take into account the indirect effect of regulation on introductions through its impact on research spending. Therefore, attention was turned to building a model of the R&D decision making process in order to estimate the effect of regulation on research expenditures.

Chapter 3 examined the decision making process used in the R&D divisions of pharmaceutical companies in project selection. In the course of that work it was determined that scientists controlled the decision making process in the 1960's. The scientists did not consider the effects of regulation on the profitability of the individual research project and therefore regulation did not affect project selection decisions. This implied that regulation did not affect research expenditures in that era.

In Chapter 3 it was also determined that, in the late 1960's, non-scientific elements in the pharmaceutical corporations gained access to the decision making processes in the R&D establishments. The primary

change this engendered was an increased concern with the effects of regulation on research profitability. Thus, regulation began to have an impact on the level and allocation of research expenditures.

The fourth chapter presented more evidence on this issue. In that chapter, the proposition that regulation had no effect on research expenditures in the 1960's, but a strong negative effect in the 1970's, was tested econometrically. The econometric results strongly confirmed the evidence gathered in the interviews. And finally, estimates of the 1970's impact of regulation on research spending were derived.

Then, in this Chapter, estimates of the overall effect of regulation on 1970's new product introductions were presented. These incorporated, for the first time, estimates of the direct effects of regulation on introductions with estimates of the indirect effects of regulation through research. The indirect effect through research was shown to be an important additional effect of regulation on the rate of new product introductions. It was shown that in the 1970's regulation sharply decreased the rate of new product introductions.

Finally, attention was returned to the fall in introductions of the early 1960's, which was broken down into its individual therapeutic class components. A rather large fraction of the overall decline was attributed to a single therapeutic class. Further, several sound non-regulatory reasons for this class's decline in introductions were offered. Therefore, even though [illegible] conclusions must be regarded as tentative, it is probably incorrect to attribute the 1960's change in introductions primarily to regulatory factors.

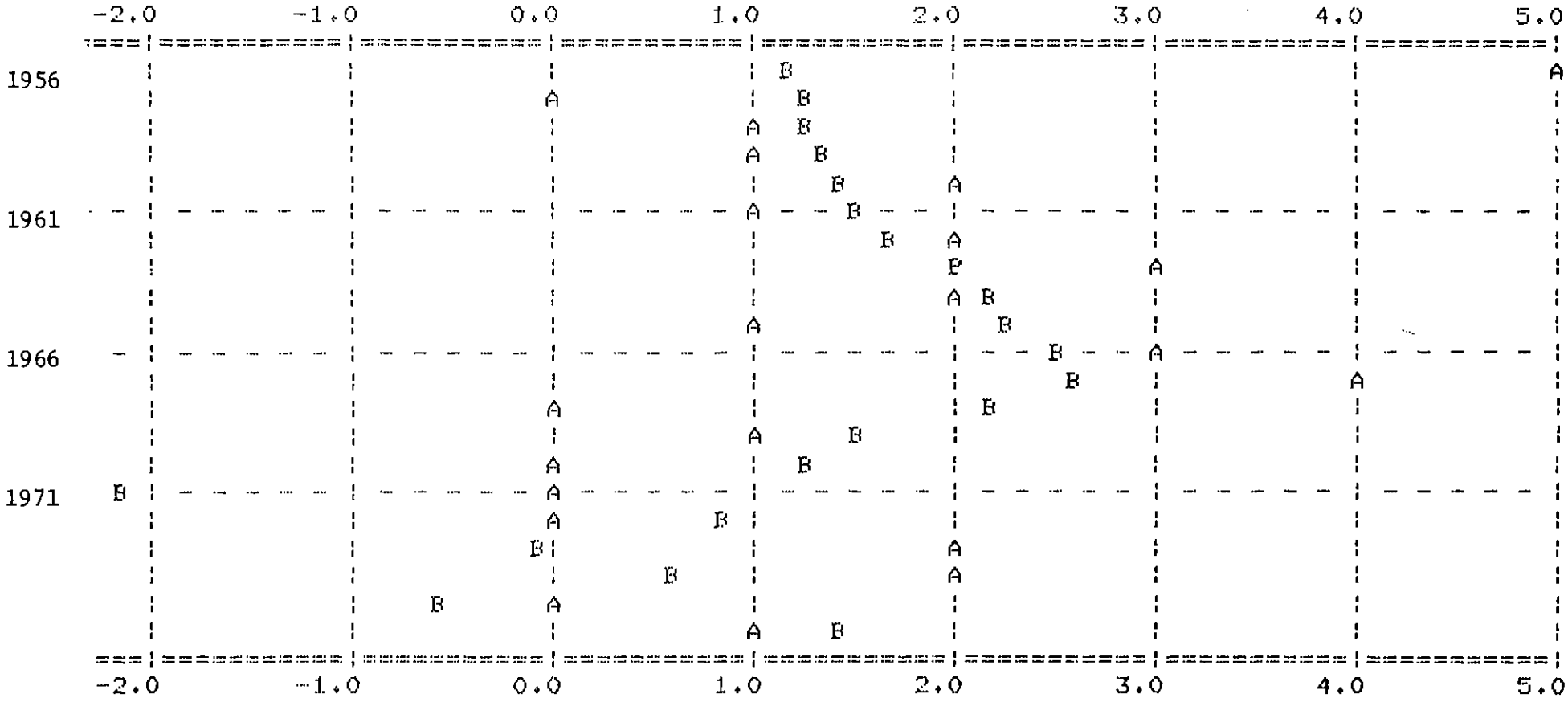
The policy implications of this thesis are quite important. The overriding fact that has been demonstrated is that society faces a steep trade-off between greater confidence that drugs are safe and effective and the number of new drugs that become available. This belies the underlying technological fact that it is difficult and expensive to develop "substantial evidence" that a product is actually effective.

This is a difficult choice to make and it is hoped that some of the information developed in this thesis will be useful in making better social decisions in this area.

Appendix to Chapter 5

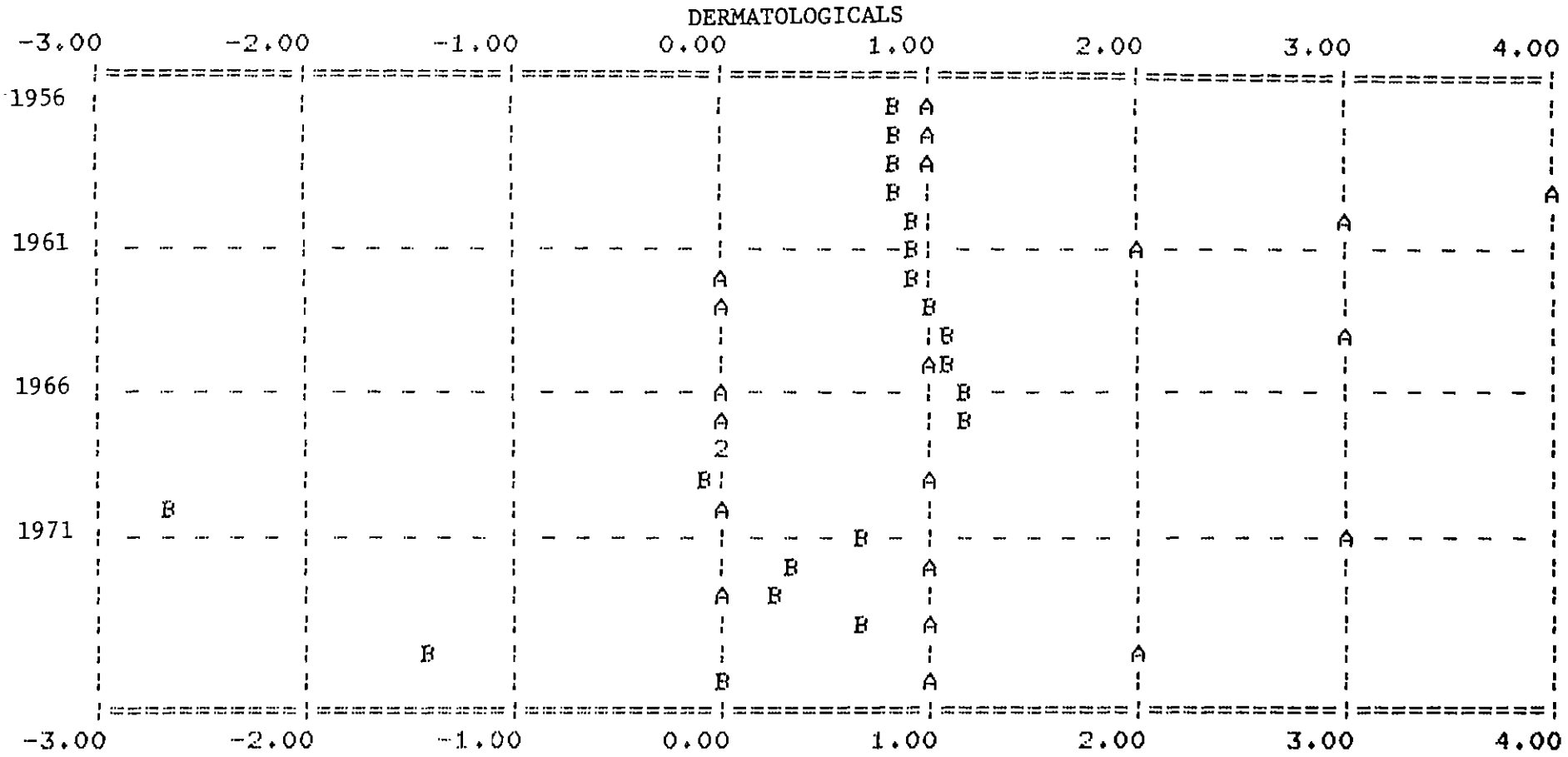
On the following pages the reader will find graphs of predicted and actual new chemical entity introductions. The predicted values are derived from the equations and procedures reported in the text. Notationally, the actual values in various years are denoted "A" and the predictions are denoted "B".

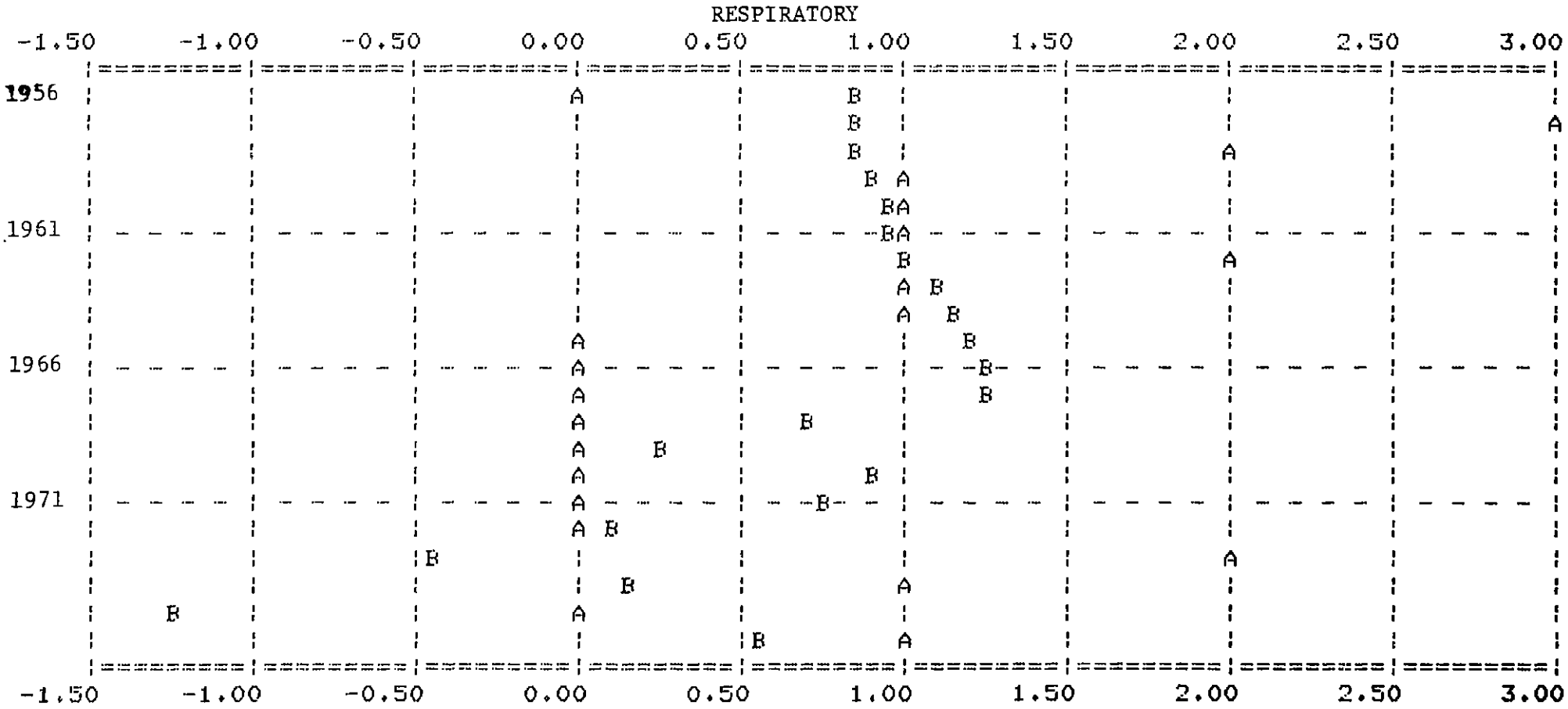
CARDIOVASCULARS

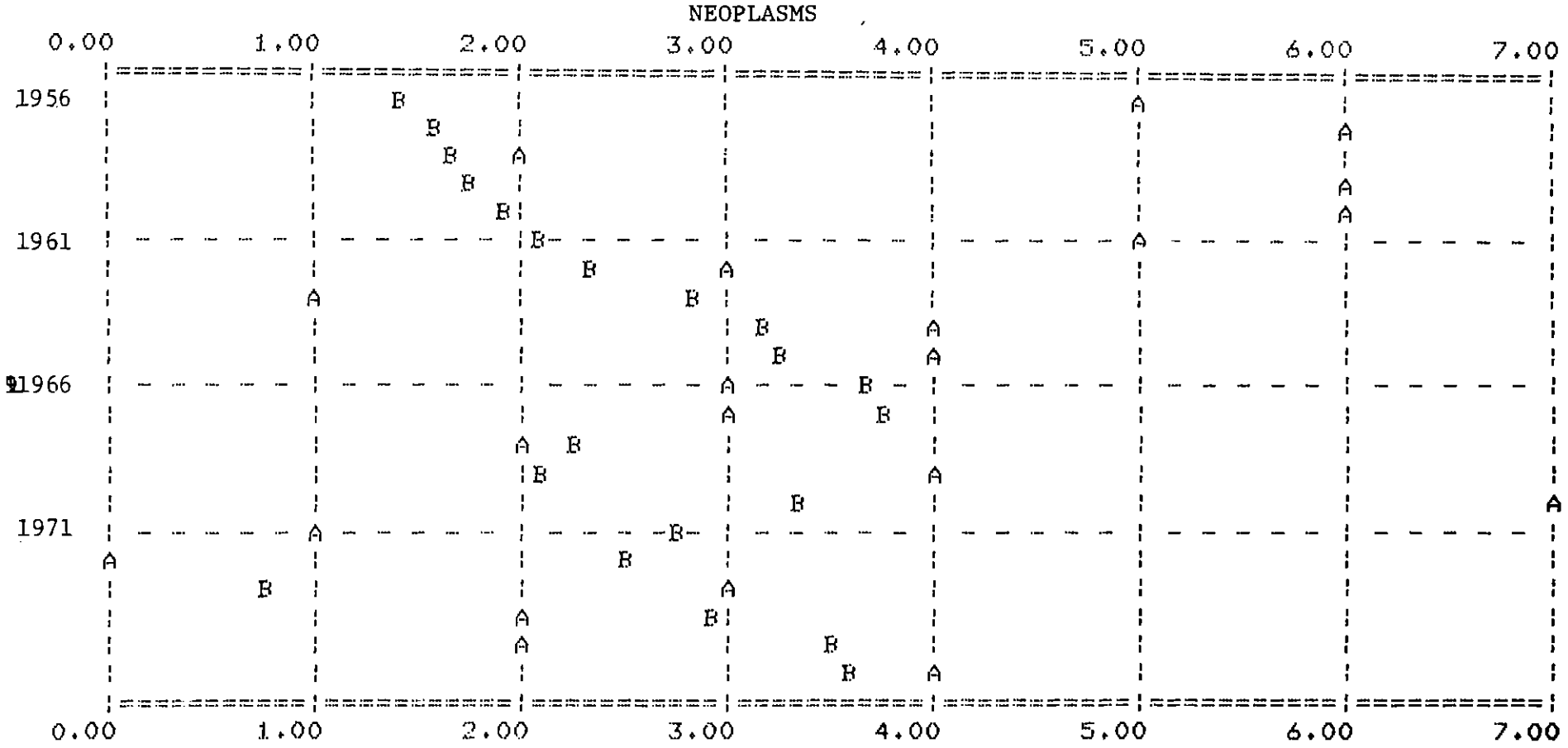


CENTRAL NERVOUS SYSTEM
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
1956
1961
1966
1971

ANTIINFECTIVES


DERMATOLOGICALS
-3.00
-2.00
-1.00
0.00
1.00
2.00
3.00
4.00
1956
1961
1966
1971


RESPIRATORY
-1.50
-1.00
-0.50
0.00
0.50
1.00
1.50
2.00
2.50
3.00
1956
1961
1966
1971


NEOPLASMS
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
1956
1961
1966
1971
A
B

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