THE IMPACT OF THE 1962 DRUG AMENDMENTS ON R AND D PRODUCTIVITY IN THE ETHICAL PHARMACEUTICAL INDUSTRY

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Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
July, 1973

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PREFACE

The 1962 Drug Amendments caused a substantial change in the economic character of the ethical pharmaceutical industry in the United States. It is the purpose of this study to ascertain what impact these amendments have had upon the productivity of research and development in the drug industry. The methodology employed uses a multiple regression model which is analagous to a production function. Comparisons between this production functionand that of a similar production function for a period prior to the 1962 Drug Amendments are given as the primary evidence of this impact on R and D.

I wish to acknowledge many people who were important to this study and to my graduate education. To my committee, Professors Larkin Warner, Mitchell Locks, Rudolph Trenton, and Joseph Jadlow, I am very grateful. I would especially like to thank Professor Jadlow for his interest and support in completing this study, and for his generating my interest in industrial organization and the drug industry.

In addition, I would like to thank all of the faculty of the Department of Economics and especially Professors Richard Leftwich, Frank Steindl, Michael Edgmand, and Gerald Lage for making my graduate education a rewarding and stimulating experience. I would also like to express my gratitude to the Pharmaceutical Manufacturers Association whose Doctoral Dissertation Research Grant was indispensible to the completion of the study.

Finally, I would like to acknowledge my family. To my parents, Walter and Irene Cocks, whose heritage, sacrifice, and encouragement made all of my education possible. To my wife, Donna, whose help and encouragement are immeasurable; and, to my children, Kristin, Andrew, and Christopher who are a constant inspiration.

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CHAPTER I

INTRODUCTION

In recent years the ethical pharmaceutical industry has become a subject of great social and economic concern. Its importance stems from two basic sources. First, it is an integral part of the broader health-care industry which is of importance to all members of society. Secondly, the ethical drug industry has been identified as a technological progressive industry, and thus it can be important in depicting what factors are necessary for technological advancement in the United States economy.

The present study deals with some of the economic aspects of technological change in the ethical pharmaceutical industry. Specifically, it deals with the particular institutional setting of the industry as it is established by the regulatory framework of the Food and Drug Administration, and what economic impact a change in this setting has had upon the research and development activity of the industry. The 1962 Drug Amendments represent a major change in the institutional setting of the industry, and the impact of this legislation is analyzed.

The significance of the 1962 Drug Amendments to the institutional framework of the U. S. ethical drug industry is apparent for several reasons.

(1) These amendments represent the first major change in United States drug law since the passage of the 1938 Federal Food, Drug, and Cosmetic Act.[1, 2]

(2) The amendments charged the Food and Drug Administration with the responsibility of close regulation of all the stages of the testing of new drugs. Special emphasis was placed on the scrutiny of the testing of new drugs in clinical trials. This is the testing stage in which new drugs are extensively evaluated in humans. The increased reporting and evaluating procedures required for the testing of new drugs were intended to increase the safety of these products.

(3) The 1962 Drug Amendments also gave the FDA the responsibility of requiring the proof of efficacy of new drugs. Prior to the amendments only proof of safety was required, but with the amendments the stated effectiveness of new drugs must be substantiated. This was implemented by requiring formal evaluating and reporting procedures.

(4) With the increased regulation of the research and development activity of the industry, it appears that the costs of this R and D have been significantly increased. The increased evaluating and reporting procedures appear to be the primary cause of these increased costs.

Two time periods are being used to assess the effects of the changes in the institutional setting. The first is a time period prior to the 1962 Drug Amendments--1955 to 1960. This is a time period in

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[1] 52 Stat. at L. 1040 (1938).

[2] Joseph M. Jadlow, Jr., "The Economic Effects of the 1962 Drug Amendments," (Unpub. Ph.D. dissertation, University of Virginia, August, 1970), p. 1.

which the drug industry has been previously studied by William S. Comanor,[3] and it will serve as a reference point for comparing the post-1962 period. The second time period is 1965 to 1970; it was selected with the view that the full effects of these amendments would be evident by this period.

Four hypotheses are presented for analysis in this study. First, however, it will be determined whether a regression model analagous to a production function can usefully explain the R and D activity of the drug industry. This model has new drug products as its dependent output variable and R and D inputs, size of firm, the interaction between the size of firm and the scale of research effort, and diversification as the independent variables.

Hypothesis 1, which is the primary hypothesis of the study, deals with the productivity of professional research and development personnel in the drug industry. It is expected that the amendments have had a severe negative impact on the additional output that can be obtained by adding one more professional researcher.

Prior to the amendments Comanor found this marginal relationship between professional R and D inputs and new drug output to be positive up to a size of firm that was very large.[4] It is hypothesized that the increased regulatory procedures required by the amendments have caused this relationship to become negative for all sizes of firms.

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[3]William S. Comanor, "Research and Technical Change in the Pharmaceutical Industry," Review of Economics and Statistics, 47 (May, 1965), pp. 182-190.

[4]Ibid., p. 185.

Hypothesis 2 deals with the impact of the 1962 Drug Amendments on economies of scale in doing durg R and D. As economists use the term, economies of scale usually concern the production processes of the firm where a proportionate increase in each of the productive inputs results in a more than proportionate increase in the output of the firm.

In this study only one aspect of the firm will be considered--its R and D activity--and the term economies of scale will only apply to this aspect. A direct measure of R and D scale economies is not possible because data on the magnitude of all R and D factor inputs is not available. Economies of scale will be looked at by observing the effect on R and D output of the relationship between the size of the firm and the level of its R and D labor inputs. It is expected that since the passage of the amendments there is a positive effect on the R and D output of the firm as both its size and its scale of R and D increases. This is due to the increased regulatory procedures which could make the use of specialization of labor, high speed computers and specialized equipment more conducive to the production of new drugs. For the 1955-1960 period Comanor found this relationship to be negative.[5]

Comanor investigated "economies of scale" by observing the percentage increase in output that is achieved when R and D labor inputs are increased by one percent. If the percentage change in output was greater than one percent, he concluded that this indicated economies of scale.[6] For the purposes of this study, it is felt that this is an

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[5] Ibid., p. 185.

[6] Ibid., pp. 187-188.

incorrect measure of scale economies. It is more precisely the output elasticity of one input. Scale economies relate to all available inputs.

Hypothesis 3 concerns the type of scale economies that have been experienced since the passage of the 1962 Drug Amendments, and states that supporting R and D personnel now contribute positively to the R and D output of the firm. Comanor found the reverse of this to be true for the 1955-1960 time period.[7] This result is expected because the increased reporting and record keeping necessitates greater use of this type of research and development personnel.

Hypothesis 4 states that the effects of the 1962 Drug Amendments have been so great that they have altered the input-output relation of the industry. Not only may the R and D output of the industry be determined in the manner of the original model, but it may be that the R and D output of the industry determines the level of research and development inputs. This result is anticipated because the firms introducing new products are R and D intensive and this emphasizes their R and D competitiveness. This competitiveness feeds upon itself such that their R and D effort produces new products which enhances their profitability which in turn allows them to reinvest funds back into their R and D process. Comanor found this not to be the case for the period prior to the amendments.[8]

Each of these hypotheses is investigated using a simple multiple regression technique based on the model discussed above. In order to

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[7] Ibid., pp. 188-189.

[8] Ibid., p. 189.

make as reliable comparisons between the two periods as possible, the techniques and data sources of Comanor's original study are duplicated as closely as possible.

In addition to this introductory chapter, the study is organized into five chapters. Chapter II presents a description of the basic industrial organization framework of the study as well as a description of the ethical pharmaceutical industry and its research and development characteristics. Chapter III summarizes those aspects of the 1962 Drug Amendments that might have an effect on the industry's R and D, presents the hypotheses as to these effects, and gives a brief summary of the previous literature on the economic impact of the amendments on drug R and D. Chapter IV describes the methodology and data sources and characteristics of the present study. Chapter V presents the empirical results of the study, and Chapter VI summarizes the conclusions of the study.

CHAPTER II

ECONOMIC ASPECTS OF THE DRUG INDUSTRY AND ITS R AND D ACTIVITY

The present chapter presents a discussion of the industrial organization framework which forms the basis for the present study of the ethical pharmaceutical industry. The chapter also focuses on the economic aspects of the ethical drug industry--its structure, conduct, and performance. Finally, there is a discussion of the research and development activity of the drug industry.

Microeconomic Theory, Industrial Organization, and Research Development

One of the important concerns of economists about the purely competitive model is whether this market structure results in the incentives that will induce a high rate of technological progress. Technological progress occurs on two fronts. First, there are some firms that are able to lower the costs of producing existing products. They provide the process innovations in an industry.[1] Some economists state that one of the benefits that can be expected from pure competition concerns this type of technological innovation:

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[1]Werner Z. Hirsch, "Technological Progress and Microeconomic Theory," American Economic Review, LIX (May, 1969), p. 36.

> Because of the pressure of prices on costs, entrepreneurs may have especially strong incentives to seek and adopt cost-saving technological innovations. Indeed, if industry capacity is correctly geared to demand at all times, the only way competitive firms can earn positive economic profits is through leadership in innovation. We might expect therefore that technological progress will be more rapid in competitive industries.[2]

Secondly, there is the technological progress by those firms that produce new or improved products.[3] This type of innovation is not easily adapted to the theory of the firm as it relates to pure competition. The essence of this type of innovation is that it deals with the demand for products. A new demand is being created thus the traditional theory of the firm does not adequately handle this. It is this type of innovation that occurs in the drug industry and this aspect of the industry is dealt with more fully in subsequent sections.

There has been a great deal of discussion both on a priori and on an empirical basis as to what type of market structure is most conducive to technological change. As has already been mentioned, there are those who feel that a structure of pure competition maximizes the rate of technological change. At the other extremes there are those who feel that it is necessary to have monopoly power in order for technological change to occur. This issue is still being explored and no conclusive statements as to which view is valid can be made.

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[2] F. M. Scherer, Industrial Market Structure and Economic Performance (Chicago, 1970), p. 13.

[3] Hirsch, p. 36.

[4] This view has become to be known as the Schumpeterian hypothesis as first expressed by J. A. Schumpeter, Capitalism, Socialism, and Democracy (New York, 1942) and more recently elaborated by John K. Galbraith, American Capitalism: The Concept of Countervailing Power (Cambridge, 1952).

The theoretical model of pure competition serves as a reference point for the empirical sub-discipline of industrial organization. In order to make this model pragmatic, the concept of workable competition has been developed in the analysis of industries. This concept forms the basis of the industrial organization framework.[5]

The industrial organization method of analysis has been characterized by F. M. Scherer in the following manner:

> In the field of industrial organization, we try to determine how market processes direct the activities of producers in meeting consumer demands, how these processes may break down, and how they can be adjusted (i.e., through government intervention) to make actual performance conform more closely to the ideal.[6]

This method of analysis is divided into three aspects that are not mutually exclusive. These aspects of an industry are its structure, conduct, and performance. The concepts of workable competition attempt to establish norms for these aspects and empirical tests are then related to these norms.[7]

This study utilizes the basic industrial organization framework in dealing with the ethical pharmaceutical industry. The primary emphasis of the study deals with the market performance aspect of economic progressiveness--the drug industry's research and innovation. The

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[5]For a complete discussion of the various approaches to workable competition, see Stephen H. Sosnick, "A Critique of Concepts of Workable Competition," Quarterly Journal of Economics, LXXII (August, 1958), pp. 386-387.

[6]Scherer, p. 2.

[7]Representative summaries of the industrial organization framework and its method of analysis are provided in Richard Caves, American Industry: Structure, Conduct, Performance (Englewood Cliffs, New Jersey, 1967), pp. 16-54 and pp. 96-114 and Scherer, pp. 1-7.

conduct features of this research and innovation are discussed also. An understanding of the research and development activity of the drug industry is very important because the firms in this industry have been identified as being very technologically progressive.[8] This understanding may be helpful in establishing valid models of the firm for these progressive firms.

Drug Industry--Its Structure, Conduct, and Performance

Since the early 1960's there have been several studies published which concern the structure, conduct, and performance of the ethical drug industry. The next four sections of this chapter deal with these issues.

Ethical Pharmaceutical Industry Defined

This study concentrates on the research and development activities in the ethical pharmaceutical industry. The industry has been identified in the following manner:

> The ethical drug industry includes firms primarily engaged in the fabrication, finishing, or sale of drug products or preparations in finished dosage forms such as pills, capsules, tablets, etc.[9]

The industry is known as the ethical drug industry because these products are primarily sold through a written prescription. This is in

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[8] Hirsch, p. 43.

[9] Leonard G. Schifrin, "The Ethical Drug Industry: The Case for Compulsory Patent Licensing," Antitrust Bulletin, XII (Fall, 1967), p. 893.

contrast to drugs that are known as proprietary drugs which are advertised to the general public and sold over-the-counter without a written prescription.[10]

In addition to these definitional considerations, the way products are identified in the ethical drug industry has important economic significance that is brought out later in this chapter. These products are designated in three ways. (1) Most drugs are derived chemically and thus they have chemical names.[11] (2) All ethical drug products are given generic names which are basically common names.[12] This is the name that is usually assigned by the discoverer when it is determined that the chemical substance has desirable pharmaceutical properties.[13] (3) In addition to these chemical and generic names some drug firms utilize trade-names or brand-names; each of these is an original trademarked name given to a product by a firm for its own particular drug. Thus, the same generic product sold by two or more firms could have many distinct trademarked brand-names.[14]

There are varying degrees of complexity associated with these names. The chemical names are very complex, the generic names less so, and the brand-names are usually very simple.

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[10]Jeremii W. Wesolowski and Zdzislaw P. Wesolowski, "The Economics of Research and Development in the Pharmaceutical Industry," Marquette Business Review, XIV (Fall, 1970), pp. 159-160.

[11]Hugh D. Walker, Market Power and Price Levels in the Ethical Drug Industry (Bloomington, 1971), p. 18.

[12]Schifrin, p. 893.

[13]Walker, p. 18.

[14]Schifrin, p. 893.

Structure of the Ethical Drug Industry

One of the most unusual characteristics of the ethical drug industry is the nature of the demand for the product. The demander of the product is not the one who makes the decision on its purchase. This is due to the fact that the purchase of this product requires a written prescription from a physician who makes the decision as to product choice. This characteristic was clearly elucidated by Estes Kefauver:

> As was pointed out often during the hearings, the ultimate consumer--the patient--is captive. The doctor, in writing the prescription, places the order for the merchandise; the consumer foots the bill. Thus the man who orders does not pay, and the man who pays does not order.
>
> Clearly, the physician is pivotal in the scheme of things; he is the person who determines whether a drug will or will not be sold.[15]

Given this purchase condition, it is felt that the physician is relatively price insensitive and the price elasticity of demand is considered to be quite low. Feldstein has roughly computed this elasticity for the products of a typical firm and found the coefficient interval to be 1.46 to 2.23. He concluded that this is relatively low.[16]

In addition, many states have anti-substitution laws which make it illegal for pharmacists to substitute generically equivalent drugs

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[15]Estes Kefauver, In A Few Hands: Monopoly Power in America (New York, 1965), pp. 8-9.

[16]Martin S. Feldstein, "Advertising, Research and Profits in the Drug Industry," Southern Economic Journal, XXXV (January, 1969), p. 242.

for the trade-name drugs prescribed by the physician. This also reduces the price elasticity of demand.[17]

There has been some disparity as to the number of firms in the ethical pharmaceutical industry. Walker states that the industry is comprised of approximately 520 firms, 33 of which could be classified as large.[18] Table I shows Walker's breakdown of concentration in the industry.

TABLE I

WALKER'S CONCENTRATION ESTIMATES*

	Number of Firms	Total Sales Millions $	Percentage of Total Sales
Large firms	33	1,750	80.00%
Small firms selling under generic name	379	234	10.68%
Small firms selling under brand name	108	204	9.32%
Totals	520	2,188	100.00%

*Distribution of 1961 sales of Ethical Drugs by Class of Firm.

Source: Hugh D. Walker, Market Power and Price Levels in the Ethical Drug Industry (Bloomington, 1971), p. 8.

[17] Jadlow, p. 70.

[18] Walker, p. 5.

The Pharmaceutical Manufacturers Association has indicated that there are approximately 700 firms,[19] and this is the number that is used by Schifrin. Schifrin states that the 20 largest of these 700 account for over 90 percent of sales and 12 to 15 additional firms account for half of the remainder.[20]

Comanor states that the drug industry is moderately concentrated, and he points out that it would be classified as a Type Two oligopoly according to Kaysen and Turner's classification scheme.[21] A Type Two oligopoly is one in which the eight largest firms account for at least 33 percent of total sales and the 20 largest firms account for 75 percent or more of industry sales.[22] Comanor's concentration estimates are presented in Table II.

The concentration data presented in these tables is somewhat misleading in that it is too aggregative. A more precise presentation of concentration data looks at the substitutability of drug products. The relevant market in the drug industry has been defined by some economists by looking at various therapeutic categories. These categories are viewed as a set of products which are grouped because

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[19]Pharmaceutical Manufacturers Association, Prescription Industry Fact Book (Washington, D. C., 1962), p. 2. A later edition of this book indicates that the "drugs" industry was comprised of 1325 firms in 1964, Pharmaceutical Manufacturers Association, Prescription Industry Fact Book (Washington, D. C., 1968), p. 15.

[20]Schifrin, p. 901.

[21]William S. Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," Economica, XXXI (November, 1964), pp. 374-375.

[22]Carl Kaysen and Donald F. Turner, Antitrust Policy: An Economic and Legal Analysis (Cambridge, 1965), p. 27.

there are similarities in the diseases treated and in the treatment of these diseases.[23]

TABLE II

COMANOR'S CONCENTRATION ESTIMATES*

	Sales	
	Millions of Dollars	Percentage
Largest 3 companies	$ 384	20%
Largest 7 companies	800	41%
Largest 15 companies	1,190	61%
All companies	1,945	100%

*Pharmaceutical Industry: Concentration Ratios, 1958.

Source: William S. Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," Economica, XXXI (November, 1964), pp. 374-375.

There have been two studies conducted by Arthur D. Little, Inc. that deal with the concentration in various therapeutic categories. Table III presents the results of the Little study in 1960. Table IV presents the results of a subsequent Little study on market concentration in 17 therapeutic categories for the period 1956-1965.

Both Tables III and IV indicate that concentration in almost all of these drug markets is relatively high. It is also apparent, however,

[23]Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," p. 377.

TABLE III

CONCENTRATION RATIOS IN TWENTY THERAPEUTIC MARKETS--1960

Therapeutic Market	Market Share of Top Five Firms (Percent)
Analgesics	59
Antacids	70
Antibacterials and Antiseptics	70
Antibiotics	60
Antihistamines	58
Antiobesity Preparations	71
Antispasmodics and Anticholinergics	55
Biologicals	66
Cardiovascular Preparations	58
Cough and Cold Preparations	45
Dermatological Preparations	50
Diabetic Therapy Agents	78
Diuretics	72
Hemantinic Preparations	57
Hormones and Nonhormonal Antiarthritics	50
Laxatives	66
Psychotherapeutics	69
Sedatives and Hypnotics	62
Sulfonamides	62
Vitamins and Nutrients	52

Source: Jesse W. Markham, "Economic Incentives in the Drug Industry," Drugs in Our Society, ed. Paul Talalay (Baltimore, 1964), p. 169.

TABLE IV

CONCENTRATION RATIOS IN 1956-1965
SEVENTEEN THERAPEUTIC
CATEGORIES

Therapeutic Category	Average Percent Share of Market by Dollar Volume 1956-1965 Top Four Products	Average Percent Share of Market by Dollar Volume 1956-1965 Top Eight Products
Analgesic, nonnarcotic	55.9	73.9
Antiarthritics, nonsteroidal	69.5	84.1
Antibiotics, broad and medium spectrum	48.0	67.7
Antibiotics, penicillins	61.3	78.6
Antihistamines	66.7	85.4
Antiobesity, amphetamines	68.5	79.1
Ataraxics	71.1	88.6
Rauwolfia-diuretic combination	73.4	92.2
Coronary vasodilators	64.3	74.8
Diabetic therapy, other**	99.4	99.8
Diuretics	69.6	80.0
Hormones, corticoids	52.4	68.5
Corticoids with antiinfectives	48.6	66.6
Oral muscle relaxants	53.2	71.8
Psychostimulants	69.2	82.7
Sedatives, barbiturate	62.6	70.8
Sulfonamides	57.4	68.7

*Covers the period 1959-1965.
**Covers the period 1957-1965.

Source: Arthur D. Little, Inc., "Trends in Market Shares for Ethical Pharmaceutical Products," reprinted in U. S. Senate Select Committee on Small Business, Subcommittee on Monopoly, Hearings on Competitive Problems in the Drug Industry, Part 5, 90th Cong., 1st Sess. (1968), pp. 1,788-1,805.

that the turnover of leading firms in certain markets can be high. This factor was discussed by Markham and he computed an index of firm turnover for the 1960 Little study. In 9 of the 20 therapeutic markets at least 50 percent of the largest firms in 1951 did not appear among the largest in 1960.[24] Comanor has also observed this turnover phenomenon and he attributes it to the expansion of pharmaceutical research facilities and to the rapid rate of product obsolescence that is the goal of the research effort in the industry.[25]

According to the available evidence the drug industry is highly concentrated. However, certain analysts assert that the therapeutic classifications used to determine these market shares do not represent meaningful economic markets, and the concentration data would appear differently if better definitions were employed. More research is required to deal with this problem.

Another important aspect of an industry's structure is its entry barriers. "The term entry barriers refers to obstacles preventing new firms from engaging in the production of a particular category of output."[26]

It is widely accepted that there are no economies of scale entry barriers in the production of ethical drugs.[27] The most prominent entry

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[24]Jesse W. Markham, "Economic Incentives in the Drug Industry," Drugs in our Society, ed. Paul Talalay (Baltimore, 1964), p. 168.

[25]Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," pp. 376-377.

[26]Douglas Needham, Economic Analysis and Industrial Structure (New York, 1969), p. 97.

[27]Henry Steele, "Monopoly and Competition in the Ethical Drugs Market," Journal of Law and Economics, V (October, 1962), pp. 132-133.

barrier in the drug industry is the patent.[28]

Product differentiation is also considered an important entry barrier. Product differentiation in the drug industry has two facets. First, the research and development activity of the industry is directed toward the achievement of scientific and chemical product differentiation.[29] Second, once the R and D effort has yielded a patentable drug product a tremendous selling effort is used to get the prescribing physicians to use a particular brand-name drug.[30]

The ethical drug industry is one in which product competition prevails through its R and D activity and its selling effort directed not at the ultimate consumer but at the physician "purchasing agent." The patent and economies of scale in research and development and advertising are considered by some economists to be the most important entry barriers in this industry.

Market Conduct in the Ethical Drug Industry

The primary characteristics of the pricing behavior of an oligopolistic industry is that pricing decisions are made with a regard to the impact of these decisions on a firm's rivals. A firm in this type of industry must take into account the collective interactions of its decisions with the rest of the industry. There are several

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[28] Jadlow, p. 78.

[29] Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 182.

[30] Steele, "Monopoly and Competition in the Ethical Drugs Market," p. 141.

explanations for the manner in which pricing decisions are made in oligopolistic industries.[31]

Certain aspects of the pricing behavior of firms in the drug industry were brought out in the Kefauver hearings. It was observed that where only one or a few firms sold a particular product, prices had a tendency not to vary widely. Specific examples of this are shown in the antibiotic drugs and corticosteroid hormones. Prices among a few firms became extremely rigid after a period of time.[32]

The antibiotic tetracycline renders an illustration of another type of behavior relating to market conduct in the ethical drug industry. It has been suggested that the existence of the cross-licensing of patents in the drug industry could enhance the collusive behavior of its members. Costello suggests that such a meeting of the minds was evident among the producers of broad spectrum antibiotics in what he terms the "tetracycline conspiracy."[33]

It is hypothesized by many economists that the conduct of the ethical drug industry is characteristic of an oligopolistic industry. These aspects of conduct are consistent with the concentration and entry barrier patterns discussed previously.

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[31]For a discussion of these decisions see Richard Caves, American Industry: Structure, Conduct, Performance (Englewood Cliffs, New Jersey, 1967), pp. 40-45.

[32]Henry Steele, "Patent Restrictions and Price Competition in the Ethical Drugs Industry," Journal of Law and Economics, XII (July, 1964), p. 203.

[33]Peter M. Costello, "The Tetracycline Conspiracy: Structure, Conduct, and Performance in the Drug Industry," Antitrust Law and Economics Review, I (Summer, 1968), p. 397.

The theory of oligopoly has been somewhat lacking in the sense that no standard model has been devised that can explain the pricing and output decisions of firms in this type of market structure. One of the main reasons for this is that the behavior of firms in this type of structure takes on many facets. These many facets do not allow a systematic analysis of the pricing and output decisions of the firms. One approach that has been used to analyze the rivalry in oligopoly is the theory of games.[34]

The theory of games is relevant to considerations of oligopoly because it deals with conflict situations. Conflict situations are those in which there are two or more opponents and the actions of one side depend in part on the actions of its rivals. The theory of games involves the mathematical techniques for analyzing these conflict situations and relies on simplified formal game models. The outcomes of these formal game models are known as payoffs. Games can be two-person games or n-person games. Games are also classified as zero-sum games or non-zero-sum games. A zero-sum game is one in which the sum of the payoffs is zero. This means that one wide loses exactly the same as the other side wins. Non-zero-sum games are those in which the sum of the payoffs is not zero. The strategy of a participant in one of these conflict situations consists of the rules which determine his choices in all possible situations. Games can be either finite or infinite. A

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[34]Scherer presents a concise discussion of the role of game theory as it relates to oligopoly in his Industrial Market Structure and Economic Performance, pp. 140-145.

finite games is one in which the participants have a finite number of strategies.[35]

The new product rivalry that exists in the ethical drug industry fits very well into a simple two-person, non-zero-sum game model.[36] The payoff structure in this model results in what is known as the prisoner's dilemma. This means that the participants end up using strategies that place them in a position that is worse than is necessary. This prisoner's dilemma model has also been suggested by Scherer as being applicable to advertising and new product rivalry in oligopoly.[37]

The prisoner's dilemma strategies that are open to ethical drug firms in their product rivalry have been alluded to by Comanor:

> The introduction of new products affects the competitive position of the firm in a quite different manner. To the extent that rivalry takes the form of competition between products which are priced at the same or similar levels, the number and character of new products which are introduced directly affect the demand for the firm's output. If the firm introduces new products which do the job 'better', then its output and total profits may be higher even if the costs of the new products are greater than those of their predecessors and profit margins correspondingly reduced. The firm that falls behind in the race to introduce new products may find its demand and profits lower than its rivals', even if it should succeed in reducing the costs of producing its older products. This will be the case especially if the price elasticities of demand for its products are relatively low.

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[35] E. S. Venttsel, An Introduction to the Theory of Games (Boston, 1963), pp. 1-12.

[36] The use of this game model in analyzing product rivalry in the drug industry was suggested by Professor Joseph M. Jadlow, Jr. and is patterned after an unpublished paper of his entitled, "The Financial Crisis in Intercollegiate Athletics and the Prisoner's Dilemma."

[37] Scherer, p. 143.

> This explanation involves the question of profit maximization under conditions of oligopoly. Where profit rates are minimal, the pressures to reduce costs via the introduction of new techniques are likely to be substantially less. But new products may be similar to those existing in the competitive model. Here the introduction of competitive new products by a firm's rivals may result in a large, and in some cases fatal, decline in the demand for the firm's output. ...it appears likely that the prevention of declines of profit is more important than the making of gains, that the maintenance of existing market shares through the introduction of new products is more important than the reduction of cost, and that a firm will work harder for the former purpose than for the latter. This means, merely, that in an uncertain world firms operate under some kind of minimax strategy. On this basis, firms will emphasize new products rather than new processes in their research efforts.[38]

This situation can be depicted using two firms, A and B, each with two possible strategies as shown in Figure 1. One possible strategy would appear feasible because, as pointed out by Comanor, the firm could stand to make gains due to the reduction of research and development outlays. This strategy could possibly result in substantial gains to the firm.

The second strategy would be for the firm to emphasize R and D for new products. This is feasible for it can be used, as stated by Comanor, to prevent the decline of profits and to maintain existing market shares. Figure 1 shows the profit payoffs that might occur to typical firms in this prisoner's dilemma situation. The numbers above the diagonals in the profit matrix are the profit possibilities for firm B and those below the diagonals are for firm A.

The worst that can happen to firm A if it deemphasizes R and D for new products is a profit gain of $2 million. The worst that can happen to firm A if it emphasizes R and D for new products is a profit gain

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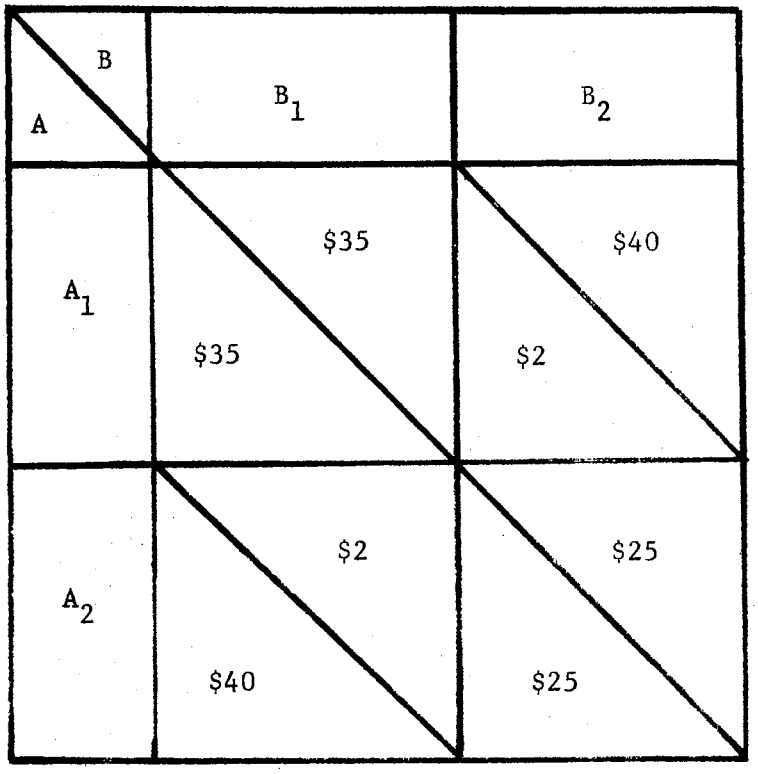
[38]Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," p. 378.



A_1 - deemphasize R and D for new products by firm A.
A_2 - emphasize R and D for new products by firm A.
B_1 - deemphasize R and D for new products by firm B.
B_2 - emphasize R and D for new products by firm B.

Figure 1. Payoff Matrix

of $25 million. This is the situation for firm B as well so that the emphasizing strategies of A_2, B_2 dominate. Both firms would be better off if they deemphasized R and D for new products, strategies A_1, B_1, but their most conservative strategy dictates that, given the uncertainty of their situation, they choose to emphasize R and D. This paradox, then, is the drug firms' prisoner's dilemma.

One qualification to this analysis must be pointed out. In the real world, the emphasizing strategies, A_2, B_2, may in actuality have payoffs that are greater than those of the deemphasizing strategies, A_1, B_1, e.g., because the R and D associated with new products may act as an effective entry barrier that enhances the profit possibilities of this activity.

Performance of the Ethical Drug Industry

The performance aspects that are dealt with in this section concern the economic efficiency of the industry--especially as they concern profit levels and the price-cost relationship of firms in the industry. The economic progressiveness of the industry is discussed separately in a following section.

It is generally accepted among industrial organization economists that monopoly power yields profit levels that are above "normal." One of the noticeable characteristics of the ethical drug industry is the persistence of excessive profits.[39] Several studies have revealed high profits in this industry.

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[39]Schifrin, pp. 908-909.

Four studies that have looked at profitability in the drug industry place it first, second, or third in terms of rate of return.[40] This high level profitability has been maintained over a fairly long period of time as indicated by these studies. The competitive norm allows excess profits to be made for short time periods but as new firms enter an industry these profit levels will be driven to a normal level. If the average profit rate of all industries in these studies indicates a normal rate of return, the drug industry has been able to maintain a rate that is considerably above the norm.

It has been argued that the high profit levels in the drug industry are warranted by the fact that it is subject to a great deal of risk in providing health-sustaining new drugs and these high rates reflect the necessary risk premium. Two of the previously mentioned studies--the Fisher and Hall and the Conrad and Plotkin papers--took into account risk as an aspect of profits. The Fisher and Hall study shows that, with risk taken into account, the drug industry still has the highest rate of return of the 11 industries studied.[41] The Conrad and Plotkin

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[40]These studies include Gordon R. Conrad and Irving H. Plotkin, "Risk and Return in American Industry," reprinted in U. S. Senate, Select Committee on Small Business, Subcommittee on Monopoly, Hearings on Competitive Problems in the Drug Industry, Part 5, 90th Cong., 1st Sess. (1968), p. 1841; Federal Trade Commission, "Rates of Return for Identical Companies in Selected Manufacturing Industries," reprinted in U. S. Senate, Select Committee on Small Business, Subcommittee on Monopoly, Hearings on Competitive Problems in the Drug Industry, Part 5, 90th Cong., 1st Sess. (1968), p. 1833; Irving Fisher and George R. Hall, "Risk and Corporate Rate of Return," reprinted in U. S. Senate, Select Committee on Small Business, Subcommittee on Monopoly, Hearings on Competitive Problems in the Drug Industry, Part 5, 90th Cong., 1st Sess. (1968), p. 1835; and, Hugh D. Walker, Market Power and Price Levels in the Ethical Drug Industry (Bloomington, 1971), p. 27.

[41]Fisher and Hall, "Risk and Corporate Rate of Return," p. 1,835.

study shows that the drug industry is the fourth riskiest of the 59 industries studied.[42]

One final consideration of these rates of return for the drug industry must be noted. It has been observed that for accounting purposes, drug firms tend to expense their expenditures for research and development in the current period rather than capitalizing these expenditures. This causes the accounting rate of return to appear somewhat higher than that of not so research intensive industries. It is hypothesized that the capitalization of these R and D expenditures in the drug industry would make the rate of return for the industry lower and more representative of the economic profit rate.[43]

Other indicators of monopoly power than excess profits can be examined when the efficiency of an industry is being evaluated. One of these indicators is the relationship of the price of the product to the costs of its production. In the purely competitive model the price of a good equals its marginal cost. Under many circumstances the demand for a good represents its social valuation and the long-run marginal cost represents the social cost of producing the product. For firms with monopoly power the marginal value of the good is greater than the costs of production so that society would be better off if more resources were devoted to the production of that good.[44]

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[42]Conrad and Plotkin, "Risk and Return in American Industry," p. 1,831.

[43]Thomas R. Stauffer, "The Measurement of Corporate Rates of Return: A Generalized Formulation," Bell Journal of Economics and Management Science, 2 (Autumn, 1971), pp. 467-468; and, Jesse J. Friedman and Murray N. Friedman, "Relative Profitability and Monopoly Power," Conference Board Record, IX (December, 1972), pp. 49-58.

[44]C. E. Ferguson, Microeconomic Theory (Homewood, Illinois, 1969), p. 275.

A certain amount of evidence was presented in the Kefauver hearings showing the relationship between the manufacturing cost and the price of several drugs. From the examples chosen it was apparent that the prices of some drug products were substantially greater than their marginal costs.[45]

Walker has made estimates of the differentials of the prices of the brand-names of large manufacturers and generic drugs of small firms. Here it is assumed that the generic products approximate fairly closely the competitive situation so that the price and marginal cost of these are relatively close. Walker concluded from his estimates that drugs that are sold by large firms under brand-names are on the average 2.14 times as great in price as drugs sold under generic names by small firms.[46]

The preceding aspects of the performance of the ethical pharmaceutical industry are offered as limited evidence of certain economic inefficiencies. The excess profits and the persistence of monopoly as indicated by the cases of prices exceeding marginal costs result in the misallocation of resources in this industry. As already indicated, the progressiveness aspects of the performance of the industry are dealt with in detail in a later section of this chapter.

To summarize the preceding sections, the structural conditions of the drug industry indicate an industry that is characterized by a relatively high level of market concentration with the existence of

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[45]U. S. Senate, Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, Hearings, Administered Prices in the Drug Industry, 86th Cong., 2nd Sess., (1960), pp. 15-24.

[46]Walker, p. 26.

several important entry barriers. The market conduct of the industry takes on many characteristics of an oligopolistic industry. And, finally, the performance aspects discussed indicate a considerable degree of resource misallocation in the ethical drug industry.

R and D Activity in the Drug Industry

The last two sections of this chapter deal with the economics of research and development. The first of these sections presents a general discussion of the economics of R and D, emphasizing those facets most directly related to the drug industry. The last section specifically discusses the R and D activity of the ethical drug industry.

Economics of R and D

Research and development has been characterized by Mansfield in the following manner:

> 'Research' is original investigation directed to the discovery of new scientific knowledge, and 'development' is technical activity concerned with nonroutine problems encountered in translating research findings into products and processes. Although there is no clear line between research and development, they are by no means the same thing. Whereas research is conducted to obtain new knowledge, development is required to reduce the knowledge to practice.[47]

It is customary to distinguish between invention and innovation when dealing with R and D. Invention is basically the discovery of some unique new product or process. Innovation is the application of a newly invented product or process in a commercial manner. It is the commercial application of an invention that gives it its economic

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[47]Edwin Mansfield, Industrial Research and Technological Innovation: An Econometric Analysis (New York, 1969), pp. 6-7.

significance.[48] Innovation is of primary importance in the ethical pharmaceutical industry.

The output of the research and development activity carried on by business firms is referred to as technological change. Technological change is an advancement in the state of learning that results in a change in the make-up of equipment, products, or organization that were previously in use.[49] The technological change of the drug industry is the development of marketable new drugs.

Much of the work in the area of research and development has concentrated on what determines the level of R and D activity within the firm. The major determinants of the amounts of resources or the expenditures a firm makes on R and D include the expected profitability of its R and D program. This implies that the same factors that influence the output of any good influence a firm's R and D. Thus, the factors of demand, cost, and supply all play a role.[50, 51]

Mansfield has applied an econometric analysis of a small sample of firms in the drug industry to determine the important factors of research and development expenditure. These factors included the lagged actual R and D expenditures, the sales of the firm in the current

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[48]Richard R. Nelson, "The Economics of Invention: A Survey of the Literature," Journal of Business, XXXII (April, 1959), p. 102.

[49]Mansfield, Industrial Research and Technological Change: An Econometric Analysis, p. 4.

[50]Ibid., p. 5.

[51]These factors were also found by Edwin Mansfield and Richard Brandenburg, "The Allocation, Characteristics, and Outcome of the Firm's Research and Development Portfolio: A Case Study," Journal of Business, 39 (October, 1966), pp. 447-464, to be the primary determinants of the R and D activity of the research component of one large U. S. firm.

period, the expected rate of return on the firm's R and D program, and the firm's lagged profits.[52]

Grabowski has also analyzed the determinants of R and D expenditures in the drug industry using an econometric model. Grabowski's model found that the significant determinants of R and D expenditures included an index of the research productivity of the firm which was the patent output of the firm obtained from its scientific personnel inputs, a lagged profit variable, and an index of diversification.[53]

R and D and its resultant technological change does two things. First, it develops new techniques that affect the production functions for existing products. Second, as an alternative, it develops new products. The resources and expenditures used in achieving these results are important, as indicated by the aforementioned studies, but in the drug industry it is not the expenditures that are the important measure. The development of new products serves as the technological change in the drug industry. It is necessary to know the rationale behind this new product development. A major portion of this rationale comes from the apparent oligopolistic structure in which there is product competition acting as a defense mechanism. This aspect was discussed in terms of the prisoner's dilemma.

This is not the complete rationale for the persistant desire for firms in the drug industry to increase their output of new products.

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[52]Edwin Mansfield, "Industrial Research and Development Expenditures: Determinants, Prospects, and Relation to Size of Firm and Incentive Output," Journal of Political Economy, LXXII (August, 1964), p. 323.

[53]Henry G. Grabowski, "The Determinants of Industrial Research and Development: A Study of the Chemical, Drug and Petroleum Industries," Journal of Political Economy, LXXVI (March-April, 1968), p. 297.

It is necessary to know how the R and D of the drug firm and its development of new products fit into the production processes of the firm. A possible method of analyzing this is suggested by using a model introduced by Clemens.[54]

Clemens' model deals with multi-product production treated as a problem of price discrimination. New products are an important element of the strategy of the firm, and they are devised with the intent of using a firm's idle capacity.[55] This appears to be important in the operation of ethical drug firms. Drug firms may differentiate their products and create inelastic demands by the introduction of new products. The dynamics of the industry are such that there are high rates of new product introduction and rapid obsolescence so that as a newly patented product of a firm loses market share, the firm experiences higher and higher excess capacity.[56]

This fact is closely interconnected with the defensive nature of R and D by firms in the drug industry. The applicability of Clemens' model to this defensive aspect comes from the following statement: "The invasion of new markets may have the purpose of keeping potential competitors at their distance."[57] This is why drug firms emphasize R

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[54]Eli W. Clemens, "Price Discrimination and the Multiple-Product Firm," Readings in Industrial Organization and Public Policy, ed. Richard Hefelbower and George W. Stocking (Homewood, Illinois, 1958), pp. 262-276.

[55]Ibid., p. 263.

[56]Schifrin, "The Ethical Drug Industry: The Case for Compulsory Patent Licensing," p. 899.

[57]Clemens, "Price Discrimination and the Multiple-Product Firm," p. 263.

and D and why the industry has been characterized as having aspects of an oligopolistic structure.

The relevance of Clemens' analysis with regard to the drug industry is also expressed by the following statement:

> The elimination or addition of a trade-mark, or a few accessories, is the means by which product differences are created to the end that strong and weak markets can be exploited at differing margins of profit.[58]

The essence of Clemens' analysis is that if there is any market where the price of the product is greater than the marginal cost then this encourages the firm to enter that market. Firms will produce to the point where the least profitable unit of output will be produced at marginal cost.

The model presented by Clemens is used here as a means of illustrating how technological innovations in the form of new products are translated into the production activity of the ethical drug firm. Several assumptions are made which include the following. (1) Products are not considered to be homogeneous, but there is a homogeneous unit of output. This means that the firm can produce several products utilizing the same production processes. (2) Closely allied with the first assumption is the assumption that resources are easily transferable within the firm which allows the production of several products. Clemens cites the chemical industry as an example of the relative ease of transferability of resources among products. It is obvious that this relative resource mobility could exist within drug firms. (3) The market characteristics faced by the firm range from strong monopoly to pure competition. This is a realistic assumption for the drug industry.

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[58] Ibid., p. 264.

Newly patented drugs that are widely promoted may have monopoly market positions. As drugs become commercially mature and generic substitutes become available, the closer to pure competition drug markets become. (4) Clemens assumes that the demand curves faced by the firm are not related--the new product areas are relatively diversified. In the past this assumption may not appear to apply for it has been observed that only a few firms deal extensively in each therapeutic market. The results of the present study indicate this may no longer be the case. In order to get new approved products there is an indication that drug firms must diversify their R and D efforts.[59] Thus, there may or may not be related demands faced by the drug firm. (5) It is assumed that the firm has a certain amount of excess capacity which allows the firm to increase production without a great increase in marginal cost. This follows from the way the demand for drug products has a tendency to deteriorate. It has also been indicated that the largest portion of the drug firm's total costs are fixed costs so that marginal costs do not change appreciably when new outputs are added.[60] (6) New markets are invaded in the order of their profitability. This clearly applies to the ethical pharmaceutical industry because firms enter those markets in which R and D activity is directed and results in a patentable product. It is this activity that may yield highly inelastic demands. (7)

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[59]Refer to page 95.

[60]Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," p. 375.

Finally, it is assumed that the firm maximizes profits.[61, 62]

To illustrate his model, Clemens presented an analysis of five markets in which profits are maximized when production is distributed among the five markets in such a manner that marginal revenue in each market is equated with marginal cost. In Figure 2 EMR is the horizontal line depicting equal marginal revenue. This is established by the intersection of the firm's marginal cost curve and the marginal revenue curve for the last market that can be secured profitably. The limit to this is a market with a perfectly elastic demand curve. Each market has its own 0 output axis with a corresponding demand curve. From these demand curves it is possible to get the marginal revenue curves for each market. These demand curves are shown in Figure 2 as D_1 through D_5 with their respective marginal revenue curves, MR_1 through MR_5. In these five markets five product prices are established as P_1 through P_5.[63]

For a drug firm these could be five products with D_1 being the most recently patented drug with the most inelastic demand. The other demand curves could represent maturing brand-name products or, as the demand curves become relatively more elastic, these could represent generic products which the firm is producing to fill out any excess capacity that it might have.

Thus, a drug firm may devise any new drug products to maintain monopoly in these markets and then may fill out the rest of its

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[61] An analysis of the revelance of profit maximizing behavior on the part of drug firms in their R and D activity is presented in Jadlow, pp. 16-23.

[62] Clemens, "Price Discrimination in the Multiple-Product Firm," pp. 266-267.

[63] Ibid., p. 267.

productive capacity in the manner shown. As long as there is a profitable market, a drug firm is encouraged to enter and it will often enter with generic drugs to fill out this productive capacity.

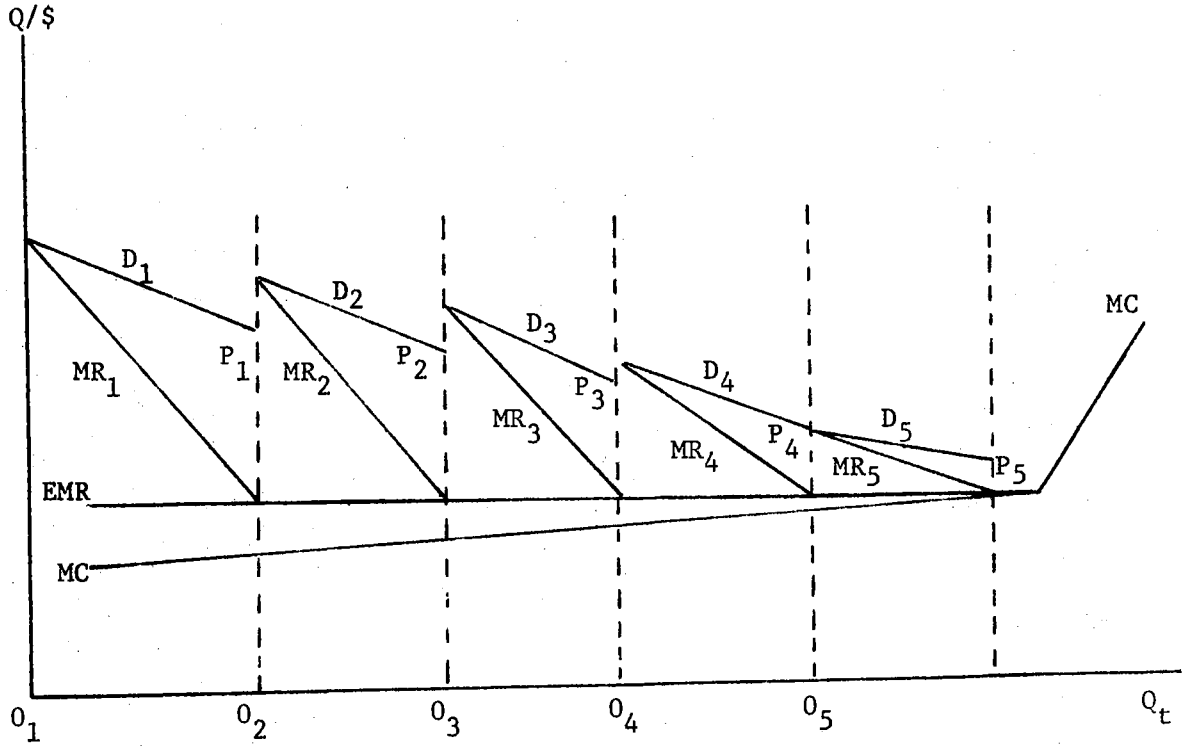

Figure 2. Multi-Product Production

It is the purpose of the research and development units of drug firms to produce new products that can be introduced in the preceding manner. As such, these new products can be viewed as the output of the R and D facility. This is basically the way it is treated by Comanor, and this is discussed more fully in Chapter IV.

Characteristics of R and D in the Drug Industry

The main issues concerning the progressiveness of the industry are whether its R and D effort results in socially desirable new products and whether the patent privilege in its present form is the necessary incentive to assure a flow of these products from the industry. It is difficult to measure the social returns and/or costs of the R and D activity of the ethical pharmaceutical industry. The private returns and/or costs bear heavily in establishing the industrial organization position of the industry and have been referred to previously.

One of the primary conflicts that resulted from the Kefauver hearings on the drug industry concerned the progressiveness of the industry. The Senate Subcommittee on Antitrust and Monopoly concluded that the value of the industry's research and development did not have much social significance. It was stated that most of the medically significant new drugs came from outside the industry, and that the industry concerned itself with "molecule manipulation" which resulted in drugs therapeutically equivalent to those already being sold.[64]

> The drug industry is the most research-conscious of all non-defense industries, with more company-financed research and development in relation to sales than any other industry. In 1964, the all-industry totals for research and development expenditures as a percent of sales was 4.4 percent; for drugs and medicines, 4.7 percent. For company-financed research and development, moreover, the all-industry total was 1.9 percent, as compared to 4.5 percent for drugs and medicine. For the period 1956 to 1964, the average annual increase in research and development expenditures for the drugs and medicines industry was 13 percent, compared to an economy-wide increase of slightly less than 10 percent in total

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[64]William S. Comanor, "The Drug Industry and Medical Research: The Economics of the Kefauver Committee Investigations," Journal of Business, 39 (January, 1969), p. 12.

industry expenditures and between six and seven percent in total company-financed expenditures.[65]

Schifrin also asserts that the drug industry concentrates more on basic research than does the economy as a whole or does the industrial sector.[66] The absolute magnitude of expenditures for research and development is also large in the drug industry where $400 million was devoted to that purpose in 1966.[67]

As indicated by the preceding, the resource use for R and D by the industry is extensive. This is reflected in the manpower utilization of drug firms in the recent past. In 1959 the total number of research and development employees of pharmaceutical companies was 11,400 and increased to an estimated 16,400 in 1965 and is expected to increase to 19,000 by 1968. This represents an annual percentage increase of six percent. The pattern of employment of R and D personnel has been very consistent over the period with 55 percent of the research staffs manned by scientists and 45 percent manned by technicians and supporting personnel. It has also been observed that about 25 percent of the total R and D staffs hold a doctoral degree, 35 percent hold a master's or bachelor's degree, and 40 percent hold less than a bachelor's degree.[68]

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[65]Schifrin, "The Ethical Drug Industry: The Case for Compulsory Patent Licensing," pp. 898-899.

[66]Ibid., p. 899.

[67]Jerome E. Schnee, "Research and Technological Change in the Ethical Pharmaceutical Industry," (unpub. Ph.D. dissertation, University of Pennsylvania, 1970), p. 192.

[68]U. S. Department of Health, Education and Welfare, Resources for Medical Research: Trends in R and D Manpower in the Pharmaceutical Industry 1959-65 and 1968 (Washington, D. C., 1966), p. iii.

In utilizing these resource inputs, Comanor has pointed out that the industry appears to use them in a complementary manner rather than a competitive manner with other users of these inputs. In 1960 the drug industry provided more than 30 percent of the funds for medical research but only used 12 percent of the persons doing research with the Ph.D. degree and only 5 percent with the M.D. degree. He feels that drug R and D provides useful division of labor of R and D inputs and the persons employed by the industry are not really substitutable with non-industry personnel so that the opportunity cost of industry research relative to non-industry research is comparatively low.[69]

The following statement by Walker summarizes the performance aspect of the progressiveness of the ethical drug industry and the dilemma that must be faced in imposing public policy on the industry.

> Investment by the industry in research and development is substantial and, on the whole, socially productive. If policies to reduce market power in the drug industry were introduced, it would be important to ensure that most of this research and development activity were maintained. Thus, if a policy were predicted to impair the willingness or ability of the industry to continue to finance research and development, then the costs of financing this activity by some other method should be charged against whatever benefits arise from the introduction of the policy.[70]

This chapter has outlined the industrial organization framework which serves as the basis for the present study. The chapter also included a summary of the economics of the ethical drug industry and the role of research and development within the industry.

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[69]Comanor, "The Drug Industry and Medical Research: The Economics of the Kefauver Committee Investigations," p. 17.

[70]Walker, p. 141.

CHAPTER III

1962 DRUG AMENDMENTS AND THEIR IMPACT ON R AND D IN THE DRUG INDUSTRY

In 1962 a major institutional change was imposed upon the ethical pharmaceutical industry with the passage of the 1962 Drug Amendments.[1] This chapter outlines the aspects of these amendments that affected the R and D activity of the industry. Certain hypotheses as to the economic impact of these amendments on the industry's R and D are posited. A summary of earlier statements and studies of this R and D impact are also included.

Aspects of the 1962 Drug Amendments Relating to Research and Development

In October, 1962, after several years of investigations by Senator Kefauver's Subcommittee on Antitrust and Monopoly, the 1962 Drug Amendments were enacted into law. The amendments were divided into three parts. The first part deals with the development, naming, and advertising of drugs; the second part deals with the factory inspection of drug

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[1] Drug Amendments, 76 Stat. at L. 780 (1962). These are reprinted in U. S. Senate, Hearings on Interagency Coordination in Drug Research and Regulation, Part 2, pp. 409-425.

manufacturing; and the third part concerns the registration of drug firms.[2]

It is the first part of these amendments that is most important to this study for it contains sections dealing with the requirements for the development of new drugs. One of these sections relates to the effectiveness and safety of new drugs. Prior to the amendments only the substantial proof of safety was necessary to gain approval of new drugs. The amendments required not only the proof of safety of these but also substantial evidence of their effectiveness. If this evidence cannot be provided to the Secretary of Health, Education and Welfare, then there may be refusal to approve the new drug, or withdrawal of prior approval. The evidence that must be provided to prove this safety and effectiveness includes certain monitored investigations which would include clinical investigations under the supervision of qualified experts.[3]

Another section of the first part of the amendments requires that new drug developers maintain certain records which are to be made available to the Secretary of Health, Education, and Welfare upon request. Reports concerning the clinical investigation and other relevant information are to be maintained on approved new drugs.[4] In addition to this, this section of the amendments outlined the following:

> The Secretary is also authorized to require: (a) the submission, before any clinical testing, of 'preclinical tests (including tests on animals)' of a drug that justifies any proposed clinical testing; (b) the sponsor of a new drug investigation to obtain a signed agreement from each investigator (before distribution of experimental drugs) that

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[2]Jadlow, "The Economic Effects of the 1962 Drug Amendments," p. 92.

[3]Ibid., pp. 92-93.

[4]Ibid., p. 93.

> patients administered the drug will be under his supervision; (c) the sponsor of a new drug's investigation to keep records and make reports (including analytical reports of investigators) of information from investigational use of the drug that will enable the Secretary to evaluate the 'safety and effectiveness' of it if a new drug application is later filed. Finally, the section provides that regulations issued about new drug testing shall require sponsors of tests to obtain from investigators using the drugs certification that they will inform human beings (or their representatives) being administered such drugs that they are being used for experimental purposes, and that they will obtain the 'consent' of these people if it is not contrary to these patients' best interests.[5]

In order for a new drug to be put on the market, another section of the amendments requires that the Secretary must approve it as to its safety and effectiveness. A period of 180 days is allowed for the consideration of a new drug application and this period may be extended; furthermore, there is no automatic approval of new drugs once the time period has expired. Hearings may be requested on non-approved new drugs.[6]

Subsequent to the passage of the 1962 Drug Amendments, the FDA issued new regulations[7] in accordance with the provisions of the amendments. These new regulations concentrated on what was necessary for the investigational use of a new drug. Specifically, the regulations outlined the precise information that sponsors of new drugs are to make available to clinical investigators and also the records and reports that clinical investigators are to keep and maintain. These regulations increased the necessary requirements in the form of records and reports

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[5] Ibid., pp. 93-94.

[6] Ibid., p. 94.

[7] A complete summary of the regulations is presented in Jadlow, "The Economic Effects of the 1962 Drug Amendments," pp. 98-102.

that were to provide substantial evidence on the safety and efficacy of new drugs.

These amendments and regulations imposed a major institutional change upon the ethical drug industry, and more specifically, upon the research and development activity of the industry. This institutional change forms the basis of the several hypotheses that are offered to assess the impact of this change on the R and D activity of the drug industry.

Review of the Literature on the Economic Impact of the 1962 Drug Amendments on Drug R and D

Soon after the effective date of the amendments several industry sources verbalized the expected economic impact. None submitted any real evidence of this impact, but they did indicate some *a priori* predictions about this impact.

Beyer indicated that these amendments would prove very costly to the research and development activity of the drug industry.[8] He also anticipated the type of scale economies that might be expected as a result of the amendments:

> The new regulations require a more precise and current auditing of the on-going activity of each clinical investigation than either we or the physician have been used to in the past. Whether or not this is worth the added effort and expense, it certainly does encourage the use of mechanical

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[8]Karl H. Beyer, Jr., "The Effect of the New F. D. A. Regulations on the Drug Industry," Clinical Pharmacology and Therapeutics, 5 (January-February, 1964), p. 1.

> data processing equipment to minimize both delay and the tremendous amount of detailed clerical work that would be required otherwise.[9]

Gibson noted that the average cost of doing clinical research would be increased substantially as a result of the amendments and regulations.[10] Gibson also noted the type of scale economies that might exist due to the increased reporting and record keeping, and how these might put the small firm at a comparative disadvantage.[11] "The legislation bearing Senator Kefauver's name has not lowered drug costs nor helped the small manufacturer."[12]

One of the first economic studies of the effects of the 1962 Drug Amendments was conducted in 1966 but was not published until 1970. This is a study by Wesolowski and Wesolowski. The primary evidence offered in this study indicated that the amendments have significantly reduced the number of new single chemical entities.[13] The cost effects on R and D were noted by relating the industry's lagged total expenditures with the number of new drugs introduced to get an "average cost" for new products. This computation showed a marked increase in this average cost between 1962 and 1963.[14] Without citing any significant

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[9]Ibid., p. 5.

[10]Augustus Gibson, "The Effect of the Investigational Drug Regulations on Drug Research and Development," Food, Drug, and Cosmetic Law Journal, 19 (March, 1964), p. 155.

[11]Ibid., p. 159.

[12]Ibid., p. 161.

[13]Jeremii W. Wesolowski and Zdzislaw P. Wesolowski, "The Economics of Research and Development in the Pharmaceutical Industry," Marquette Business Review, 14 (Fall, 1970), p. 167.

[14]Ibid., pp. 169-170.

evidence the authors also stated that the pharmaceutical industry is obtaining diminishing returns from its R and D activity. These diminishing returns are attributed to higher research costs due to the increased cost of all research inputs, the growing difficulty in solving certain medical problems, and the reduction in the number of new drugs approved by the FDA.[15] Wesolowski and Wesolowki, again without any evidence, indicated that the new drug regulations would impose a heavy burden on small firms which they classified as having sales under $10 million.[16]

In an extensive study of the determinants of research and development in one drug firm, Jerome Schnee hypothesized that development costs have been significantly increased due to the amendments. His sample of post-1962 new drugs was too limited for him to measure the increased costs or the overall impact of the 1962 Drug Amendments on the individual firm.[17]

A recent econometric study by Baily has attempted to assess the impact of the amendments on the R and D activity of the industry. He used an industry-wide input-output relation to investigate the R and D activity of the pharmaceutical industry. His output variable was the number of new drugs introduced and his input variable was the R and D expenditures of the industry. Baily found that the simple correlation between these expenditures and the rate of new drug development is negative. The possible explanation that is given for this contradiction

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[15] Ibid., p. 17.

[16] Ibid., pp. 171-172.

[17] Schnee, p. 95.

is that the FDA regulations of 1963 had a tremendous impact on the industry, and this threw the relationship off because of the great increase in the average cost of new drugs. To allow for this impact, Baily assumed that his functional relationship had shifted due to the amendments, and he looked at the data prior to and after 1962 independently. This removed the negative coefficient for R and D expenditures, but the magnitude of the coefficients and their statistical significance were not considered to be plausible. Baily explained that this phenomenon resulted because the new regulations were not the sole reason for the increased costs of developing new drugs.[18]

One of the most comprehensive analyses of the economic effects of the 1962 Drug Amendments is provided in the 1970 University of Virginia Ph.D. dissertation of Joseph M. Jadlow.[19] The study utilizes an industrial organization framework to study all facets of the amendments' effects on the drug industry. An important element of this study concerns the effects of the amendments on the R and D activity of the industry.

The conclusions of Jadlow's study concerning the impact of the legislation on research and development include the following:

(1) The 1962 Drug Amendments were responsible for significantly increasing the costs of doing drug R and D. This conclusion is based on the observation that the average expenditure per new single chemical entity has risen considerably since the enactment of the amendments.

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[18]Martin Neil Baily, "Research and Development Costs and Returns: The U. S. Pharmaceutical Industry," Journal of Political Economy, 80 (January-February, 1972), pp. 71-72.

[19]Jadlow, "The Economic Effects of the 1962 Drug Amendments."

There was an observed upward trend in these costs prior to 1962, but the increase in costs after 1962 was in excess of the pre-1962 trend.[20] In addition, the average expenditure per all new drug products as a measure of average cost was observed. Again, the average cost for the development of a new marketable drug increased significantly after 1962.[21]

(2) The second major conclusion concerns the economies of scale in R and D issue. It was hypothesized that "there are some economies of scale associated with the activities firms must perform to satisfy the new amendments and regulations."[22] This hypothesis was tested by observing the relationship of the average R and D costs per professional R and D employee for small firms with the same relationship for large firms. If the research costs per professional employee have risen faster for the small firm relative to the large firm, then this would indicate that scale economies are indeed present.[23] Using this type of a test it was found that subsequent to the amendments and new regulations, the costs per professional employee for small firms had risen the greatest. This indicates that scale economies are present.[24]

(3) The last major conclusion of the Jadlow study on the impact of the amendments on R and D deals with the reduction in the flow of new drug products. Two hypothesized reasons were given for the reduction in this flow. One of the reasons was that the proof of efficacy

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[20] Ibid., p. 149.

[21] Ibid., pp. 151-153.

[22] Ibid., p. 157.

[23] Ibid., p. 159.

[24] Ibid., p. 161.

requirements have caused part of this reduction in new drugs. The other reason was that the increased costs of drug research and development have precipitated part of the decline in new drug output.[25]

To test the hypothesis concerning the efficacy requirements, the sharp reduction in all new drugs since 1962 was noted. In addition, it was assumed that three types of new products would more precisely reflect the impact of the efficacy requirements. There would be a reduction in the number of new combination products, new dosage forms of old products, and new duplicates of old single chemical entities. A reduction could be expected in the last two because when approval of these was made before the amendments only proof of safety was required. After the amendments, firms would have to have extensive proof of efficacy of these products.[26] Regarding the new combinations, it had been shown that the risks associated with these new drugs were greater so that it was expected the FDA would now more heavily weigh these risks against the effectiveness of these combination products, and they would be less likely to approve these new drugs. The sharp reduction in the number of these three categories of new products was given as evidence that the efficacy requirements have reduced the number of new products going to the market.[27]

To test the reduction of new products due to increased R and D costs, the study concentrated on the reduction in the number of new single chemical entities. Since these are the most innovative of new

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[25]Ibid., p. 163.

[26]Ibid., p. 164.

[27]Ibid., p. 167.

drug products, the efficacy requirements would have relatively less of an impact on these than it would on the other categories of new drugs. Thus, it was assumed that a reduction in the number of new single chemical entities would reflect the impact of rising R and D costs on the flow of new drugs. A sharp reduction in the number of these new products was observed subsequent to the passage of the amendments. It must be noted, however, that a downward trend in this category of new products had begun prior to the amendments so the conclusion on this aspect is not quite as clear.[28] To further evaluate this situation, a categorization of new single chemical entities as significant advances was made. Using this approach a sharp reduction in the number of significant advances was observed after the 1962 Drug Amendments.[29]

Hypotheses Concerning the Economic Effects of the Amendments on R and D in the Drug Industry

The 1962 Drug Amendments and the new regulations require substantial proof of the efficacy and safety of new drugs before they may be marketed, and they provide for a substantial expansion of reporting and clearing procedures for the clinical testing of experimental new drugs. It seems likely that these requirements have raised the costs of doing drug research. Limited evidence has already been gathered on the raising of these costs.[30]

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[28] Ibid., pp. 168-170.

[29] Ibid., pp. 171-172.

[30] Ibid., p. 156.

In order to gauge the impact of the 1962 Drug Amendments, a model of technical change or research output will be utilized. This model is patterned after a model previously introduced by William S. Comanor[31] and is analagous to a production function. This model incorporates R and D inputs, size of firm, the interaction between size of firm and research inputs, and diversification as determinants of research output.

The main thrust of the present study is to investigate the effects of the 1962 Drug Amendments on the productivity of professional R and D personnel in the drug industry. This is a positive investigation and the major hypothesis (Hypothesis 1) is:

> Given the significant institutional change caused by the 1962 Drug Amendments, it can be expected that during the 1965-1970 period the marginal productivity of professional research and development personnel has become negative.[32]

The implications of this hypothesis are that professional R and D personnel are needed just to satisfy the increased requirements of the amendments and the new regulations and this has adversely affected the output flow of new drugs. The necessary proof of safety and efficacy would require more animal and clinical studies that would tend to increase the utilization of these personnel.

Another factor that bears on the increased utilization of professional R and D personnel is the increased record and reporting procedures set up by the new drug regulations for investigational new

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[31] Comanor, "Research and Technical Change in the Pharmaceutical Industry."

[32] The assumption that the marginal productivity of professional R and D personnel is positive prior to the amendments is based on the results of Comanor's study for the 1955-1960 period; see Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 188.

drugs. It has been estimated that before these drugs can be sent out almost 11 different "statements" must be forwarded to the FDA. Three of these statements must be forwarded for each clinical investigator in the study. Many types of periodic reports must be made to the FDA, and at least three sets of records must be maintained. In addition to these, the clinical investigators must maintain comprehensive and detailed records and reports.[33] Thus, the increased requirements for the proof of safety and efficacy and the increased record keeping have diverted a portion of the effort of professional R and D personnel and have adversely affected their productivity as it relates to providing new drug products.

It might be expected that after the passage of the 1962 Drug Amendments, scale economy benefits can be experienced for larger firms in the drug industry. Scale economies are where a proportionate increase in all inputs results in a proportionately greater increase in output--output in this case being limited to innovative new drugs. These scale economy benefits are implied if the relationship between the size of the firm and the scale of research personnel inputs have positive influence on the research and development output of the industry.[34] These influences lead to a second hypothesis (Hypothesis 2):

> Since the passage of the 1962 Drug Amendments, the interaction between the size of firm and the scale of research inputs now has a positive influence on the R and D output of firms in the

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[33] Jadlow, "The Economic Effects of the 1962 Drug Amendments," pp. 122-123.

[34] This is the reverse of what Comanor found in his previous analysis of the industry for the 1955-1960 time period. See pages 56 and 63.

industry. This relationship is indicative of the scale economy benefits now available.

The possibility that scale economy benefits are now available is based on the notion that it now takes a certain minimum staff of people to organize and maintain the records and reports as required by the amendments and regulations. As firms are large, both in size of firm and size of R and D component, they may be more able to establish and maintain this minimum staff of people. Thus, it takes some minimum number of professional R and D personnel as well as supporting or auxiliary personnel to engage in research and development in the industry.[35]

In addition to this, it may be possible for drug firms to benefit from R and D specialization of labor and from the use of large-scale computer facilities.[36] It is expected that large firms may have a comparative advantage in dealing with these increased research costs.

An important aspect of the economies of scale issue in drug research and development concerns the role of supporting personnel. If Hypothesis 2 can be supported, then it can be expected that supporting personnel now play a more important part in drug R and D. This stems from the idea that it takes some minimum level of technicians and clerical personnel just to satisfy the increased requirements of the regulations and these people can be a positive influence on the R and D

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[35]This study will distinguish between two types of personnel involved in drug R and D activity--professional and supporting or auxiliary. These are more clearly defined in Chapter IV.

[36]Jadlow, "The Economic Effects of the 1962 Drug Amendments," p. 125.

output of drug firms.[37] In addition it may now be that larger firms obtain scale economy advantages from the use of these personnel because they can utilize specialization and division of labor in meeting the requirements of the regulations. This hypothesis (Hypothesis 3) concerning this aspect of the impact of the amendments is:

> Supporting personnel relative to professional R and D inputs are now significant contributors to the research output of drug firms. The importance of these supporting personnel leads to scale economy benefits for larger sized drug firms.

A final consideration of the 1962 Drug Amendments' impact on the R and D activity of the drug industry is the possibility that the amendments have changed the relationship between technical change in the industry and the scale of research activity. It may be that in addition to, or now independently of, the fact that R and D output is primarily determined by the level of R and D inputs, the scale of research and development is now determined by the level of R and D output. This result could be expected because the basis for selecting firms for this study is that they introduced at least one new single chemical entity during the 1965-1970 time period. Thus, it appears that these firms were extensively committed to research and development and this extensive R and D may serve as an effective entry barrier in the industry. It appears that a good many of the competitive forces within the drug industry take place through this R and D. It is thus conceivable that this activity feeds upon itself in the following manner: extensive R and D serves as an effective entry barrier and it produces new drug products which in turn create profits, and finally these

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[37] This is the opposite of what Comanor found in his previous study of the industry. See page 67.

profits can then be reinvested for new and expanded research and development activity.[38] The final hypothesis (Hypothesis 4) of the study deals with this issue:

> The 1962 Drug Amendments have increased the R and D entry barriers to the extent that it is now evident that not only may R and D output be determined by R and D inputs, but the scale of R and D inputs are now determined by research output.

Each of these hypotheses represents a significant change in the R and D activity of the ethical pharmaceutical industry since enactment of the 1962 law. Substantiation of these hypotheses would indicate the great impact that the 1962 Drug Amendments have had upon the research and development activity of the industry.

The present chapter has outlined the 1962 Drug Amendments and the FDA regulations that followed that relate to research and development. A summary of several of the studies that have dealt with the possible economic impact on R and D of these amendments was given. Finally, four hypotheses have been advanced as to what impact these amendments and regulations have had on the research and development activity of the ethical drug industry.

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[38]This is the opposite of Comanor's previous results. See pages 67-68.

CHAPTER IV

METHODOLOGY AND DATA SOURCES

The present chapter provides a description of the basic model that is used in this study to explain the research and development activity of the ethical pharmaceutical industry. This chapter also includes a description of the data sources used and the characteristics of the sample of firms for the period 1965-1970.

Summary of Comanor's Study

In 1963, William S. Comanor[1] completed a study of research and development activity in the pharmaceutical industry for the years 1955-1960. Comanor's investigation focused on such things as whether large size was necessary for firms to engage in research and development, and whether R and D grows more or less than in proportion to increases in the size of the firm. Comanor also investigated the relationship between R and D and the rate of technical change, and the relationship between the size of the firm and R and D productivity.[2]

One of Comanor's most important conclusions was that there were substantial diseconomies of scale in R and D for moderate and large

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[1]William S. Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," (unpub. Ph.D. dissertation, Harvard University, June, 1963).

[2]Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 182.

sized firms. On the other hand, he concluded that there were economies of scale in the research and development activity of small firms.[3] Comanor used the term economies and diseconomies of scale in the traditional sense such that, for example, economies of scale exist when a doubling of inputs results in more than a doubling of output.

Comanor used a multiple regression technique on a firm cross sectional basis to explain various aspects of drug research and development activity. The following equation represents the estimated relationship which he used:

$$Y = b_0 + b_1R + b_2R^2 + b_3S + b_4I + b_5D \qquad (4.1)$$

where b_0, b_2, $b_3 > 0$ and b_1, b_4, $b_5 < 0$.

Comanor assumed that the introduction of new products is the primary objective of the research and development activity of drug firms. He suggested that the purpose of this introduction of new products is to achieve scientific and chemical product differentiation.[4] Two separate designations of new product introduction were used by him to measure technical change in the drug industry.

"New single chemical entities," which usually represent the most innovative new products, was one of the designations used. These are unique new drugs (each with one active ingredient) which have not been marketed in the United States before. The other designation was all of the new products introduced by the various drug firms. These designations served as the dependent variable of the regression equation. In order to assess the economic impact of these variables, they were

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[3] Ibid., p. 190.

[4] Ibid., p. 182.

weighted on the basis of their sales for two calendar years after their introduction.

In his study, Y_1 is the total dollar sales of all of the new single chemical entities for the first two years after a firm introduces them. Y_2 is the total dollar sales of all new products, including new single chemical entities, duplicate single chemical entities, new combinations of active ingredients, and new dosage forms of previously introduced products.[5]

The first independent variable, R, is the scale of research and development variable. This is also designated in two ways. The first designation, R_1, is the average number of professional R and D personnel employed by the firm in 1955 and 1960. R_2 is the average number of total R and D personnel employed in the research facilities during the two years. This R_2 variable includes all professional and supporting personnel in these R and D facilities.[6]

For the most part professional personnel are defined as those persons who hold either the Ph.D. or the M.D. degree. Although the precise definition of professional personnel was not given, it appears that persons with training constituting at least the four-year college degree were included if they had the skills to engage in scientific investigation. Supporting personnel includes all personnel involved in the R and D function who hold something less than these degrees. This

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[5]Ibid., p. 183.

[6]Ibid.

includes a wide range of personnel down to, and including, clerical personnel.[7]

These definitions are similar to those of other manpower studies of the pharmaceutical industry. As an example, the study of the manpower trends in the ethical drug industry made for the National Institutes of Health by the Pharmaceutical Manufacturers Association defines these accordingly:

> R & D Scientific and Professional Staff includes all persons whose work requires the application for research and development of knowledge, skills, and scientific techniques, in the life, physical, engineering, or mathematical sciences, acquired through the completion of a four-year college course (or its equivalent) with a major in these fields or in medicine or other health professions. Exclude persons who have formal training in the sciences but who are not actively engaged in research and development.
>
> Technicians and Supporting Personnel for the R & D staff includes persons who may hold some academic degrees at the bachelor's level or above. Technicians include persons actually engaged in technical work at a level which requires knowledge of the life, physical, engineering, or mathematical sciences comparable at least to that acquired through technical institutes, junior colleges, or other formal post-high school training less extensive than four-year college training or through equivalent on-the-job training experience. Supporting Personnel includes persons who provide literature, clinical, statistical, or other services specifically for R & D staff.[8]

R^2 is a quadratic term for the above R and D variables that is introduced to account for the fact that there is a curvilinear relationship between research effort and technical change.[9] S is the size variable and it was computed as the average of yearly prescription and

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[7]Bowker Associates, Inc., Industrial Research Laboratories of the United States, 13th Edition (Washington, D. C., 1970), p. viii.

[8]U. S. Department of Health, Education, and Welfare, p. 17.

[9]Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 185.

hospital dollar sales between 1955 and 1960. I is an interaction variable which is the product of scale of research and the size of the firm. D is a variable that accounts for the degree of diversification of the drug firm. This was measured in three ways. D_1 was computed as the average dollar sales by the firm in each therapeutic market. These average sales were not picked up unless they accounted for at least two percent of the firm's total sales. D^2 was computed according to the following:

$$D_2 = 1 - \frac{\text{firm's sales in largest market}}{\text{firm's total sales}} . \qquad (4.2)$$

The sales used in the computation of D_2 are based on averages for the six-year period. D_3 is the product of D_1 and D_2. In order to account for the problem of heteroscedasticity, Y, R, and R^2 are deflated by the size of the firm.[10]

The relationship investigated by Comanor is analagous to a production function. Y measures the output of the R and D facility of the drug firm and the primary input is the number of research personnel. This does not incorporate the level of the capital input, but the labor inputs represent one of the most important aspects of the drug firm's R and D effort.

The analysis of the various forms of the regression equation caused Comanor to conclude that as the firm increased in size the gains resulting from new product introduction increased in greater proportion. He also concluded that for small firms economies of scale in R and D were present and diseconomies appeared as the size of firm increased.[11]

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[10] Ibid., p. 184.

[11] Ibid., p. 187.

Comanor elaborated on this economies of scale issue in the following manner. By multiplying equation 4.1 by S, it can be expressed in the general form:

$$Y = a + bR + cR^2, \tag{4.3}$$

where a, b, and c are parameters whose values are derived from the regression coefficients of his multiple regression model. $b = - e - fS^2$ where e and f are again parameters derived from the regression coefficients, and a is a functionof S and D. Taking the partial derivative of equation 4.3 expresses the marginal productivity of R and D personnel:

$$\partial Y/\partial R = b + 2cR. \tag{4.4}$$

Due to the fact that b is inversely related to S, $\partial Y/\partial R$ is inversely related to S. For given values of R, $\partial Y/\partial R$ declines with the square of S. He concludes from these relationships that the marginal productivity of professional research personnel is inversely related to the size of the firm.[12]

The elasticity of research innovation was also considered. The relevant dependent variable was new single chemical entities and the elasticity was expressed as $\partial Y/\partial R \cdot R/Y$. The elasticity was computed at three separate points in the size distribution of firms. This looks at the percentage change in research output with a unit percentage change in R and D activity with S being held constant. At a firm size considered to be small the elasticity was 1.39; for a size considered to be moderate the elasticity was computed to be 0.61; and for a size considered to be large the computed elasticity was 0.51. These

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[12] Ibid.

elasticities support the results on scale economies implied by the regression equation.[13]

McGee has criticized Comanor's use of the term returns to scale in research and development in his studies of the pharmaceutical and other industries:

> What does 'return to scale' mean? In general, economists say there are increasing returns to scale if, with constant technology (!) when a firm, say, doubles the inputs of all factors of production per unit time, output per unit time more than doubles. Now make something called 'research resources' a factor of production along with (the usual) 'labor' and 'capital', and waive the complication of lags. In the usual sense, presumably, there would be increasing returns if doubling of labor, capital, and research more than doubled outputs. What Comanor found, at most, is that his measure of 'research' inputs does not increase proportionally with (an imperfect measure of) the overall size of firm. His situation therefore, is <u>not</u> a question simply related to returns to scale as that phenomenon is commonly understood. It seems, rather, to be a case of variable proportions and what he wants to say hinges on the question of whether 'research' and other factors are complementary in production, and to what extent.[14]

McGee contends that if the returns to scale issue deals with the relationship of research costs to research output when research and development is taken alone, then the method of looking at R and D in a production function sense is logically flawed.[15] These criticisms are important to the present study for they have significant implications relative to the impact of the 1962 Drug Amendments on drug research and development. These implications are more fully discussed in the empirical results chapter.

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[13] Ibid., pp. 187-188.

[14] John S. McGee, <u>In Defense of Industrial Concentration</u> (New York, 1971), p. 105.

[15] Ibid.

Table V summarizes the empirical results of Comanor's study. Y_1 represents the dependent variable defined as the first two year sales of new single chemical entities. Y_2 represents the two year sales of all new products. R_1 denotes professional R and D inputs, and R_2 takes into account total personnel working in a drug firm's research and development facility. I_1 and I_2 represent the interaction variables when R_1 and R_2 are used respectively, and D stands for diversification.

Comanor concluded that the data fitted the model better as it is expressed by equation 4.5 in Table V. Thus, technical change is statistically better defined when it appears as the sales of new single chemical entities. Professional R and D personnel is also the more important input designation in explaining this technical change.[16]

In Comanor's estimates the R and D input variable, R_1, had a negative sign which he stated was not due to the research process in the industry, but was due to the fact that in some of the estimates there were zero values for the dependent variable. This caused statistical problems which would make the sign of the regression coefficient become negative.[17]

The quadratic term for R and D input had a positive sign associated with it and was found to be highly significant. This significance appeared for both designations of the R and D input.[18]

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[16] Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 184.

[17] Ibid.

[18] Ibid.

TABLE V

COMANOR'S REGRESSION ESTIMATES

$Y_1 = \underset{(.136)}{.422} - \underset{(1.285)}{4.671R_1^*} + \underset{(.107)}{.547R_1^{2*}} + \underset{(.0000083)}{.0000344S^*} - \underset{(.000000031)}{.000000128I_1^*} - \underset{(.040)}{.130D^*}$	$(\underline{R}^2 = .40)$	(4.5)
$Y_2 = \underset{(.222)}{.873^*} - \underset{(2.098)}{.060R_1} + \underset{(.175)}{.557R_1^{2*}} + \underset{(.0000136)}{.0000289S^{**}} - \underset{(.000000051)}{.000000106I_1^{**}} - \underset{(.066)}{.111D^{**}}$	$(\underline{R}^2 = .22)$	(4.6)
$Y_1 = \underset{(.150)}{.471^*} - \underset{(.981)}{1.989R_2^*} + \underset{(.031)^2}{.112R_2^{2*}} + \underset{(.0000102)}{.0000300S^*} - \underset{(.000000017)^2}{.000000051I_2^*} - \underset{(.044)}{.120D^*}$	$(\underline{R}^2 = .28)$	(4.7)
$Y_2 = \underset{(.232)}{.932} + \underset{(1.513)^2}{1.381R_2} + \underset{(.047)^2}{.118R_2^2} + \underset{(.0000157)}{.0000194S} - \underset{(.000000027)^2}{.000000034I_2} - \underset{(.068)}{.100D}$	$(\underline{R}^2 = .18)$	(4.8)

* Indicates statistical significance at 99% confidence level.
** Indicates statistical significance at 95& confidence level.
Statistical significance for the regression coefficients is determined by one-tailed t-test, and the significance of the R^2 by the F-ratio test.

Source: William S. Comanor, "Research and Technical Change in the Pharmaceutical Industry," Review of Economics and Statistics, 47 (May, 1965), p. 185.

The size of firm variable in three of the four equations in Table V was found to be significant and is positively related to research output.

> Since new products have been weighted by their sales during their first two years after introduction, we should expect our measures of technical change to be influenced by such factors as distribution facilities, selling effort, and firm reputation. To the extent that these factors are correlated with firm size, the size variable introduced into the equations will be positive. Firm size appears to have acted to increase the gains resulting from new product introduction, and these gains increased more than proportionately with size of firm.[19]

Because it was necessary to deflate by size of firm to deal with the problem of heteroscedasticity, the interaction variable was introduced to incorporate a scale factor in the relationship. This interaction variable was also used to explain scale economies of drug research and development.

In an input-output relationship, economies of scale exist if a proportionate increase in inputs results in a greater than proportionate increase in output. Diseconomies of scale are indicated by less than proportionate increases in output from proportionate increases in inputs.[20] The usual explanation for these diseconomies of scale is that there are managerial problems of coordination and control that exist in large scale operations.[21] This is the same approach used in looking at the research output of the drug industry, and the interaction variable is an important element in dealing with the scale economies issue.

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[19] Ibid.

[20] James M. Henderson and Richard E. Quandt, Microeconomic Theory, (New York, 1958), pp. 202-208.

[21] Richard H. Leftwich, The Price System and Resource Allocation, (Chicago, 1966), p. 145.

The interaction variable allows an analysis of the problems of management coordination and the control of large scale R and D facilities. The inclusion of the size variable alone resulted in competing effects on the research output of the firm. On one hand, size allows the firm to benefit more from its research output through the use of large promotional and distribution facilities. On the other hand, these advantages may be offset by the decrease in efficiency in the research facility due to the coordination and control problems associated with large size. Using the size variable alone in the regression equations would absorb the variation from these competing effects. This is why Comanor introduced the interaction variable. Thus, the size variable in the regression equation would pick up the promotional and distributional advantages of large firms and the interaction variable would allow for the inefficiencies of large size as reflected by the negative sign of the coefficient.[22]

> At the lower range of the distribution of firm size, I is small relative to deflated values of RD,[23] so that the primary impact of research is designated by the coefficients of RD. For small firms, there appear to be increasing returns to scale of research. At the upper range of the distribution, however, I may be large relative to RD/S and the major determinant of research output comes from the coefficient of the interaction variable. In this case, research and development may exhibit decreasing returns to scale. It appears that we cannot deal with the question of economies or diseconomies of scale in research without considering the size of the firm in which the research is undertaken. While increasing returns may persist so long as the firm is small, there is likely to be decreasing returns when the firm becomes large. Thus,

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[22] Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 137.

[23] Comanor refers to the R and D inputs as RD whereas this study uses R.

there is probably a point beyond which a research establishment becomes relatively inefficient.[24]

All three of Comanor's diversification variables were found to be statistically significant. The sign of these was always negative and this indicated that higher research output can be achieved when a firm concentrates in a few product areas, other things being equal.[25]

The scale economies issue was further explored by Comanor as he determined the marginal productivity of R and D and the elasticity relationships from his estimated equations. The true expression for equation 4.5 when the deflation factor is incorporated is:

$$Y/S = .422 - 4.671R/S + .547R^2/S + .0000344S - .000000128R \cdot S - .130D. \quad (4.9)$$

Multiplying both sides of the equation by S renders the equation in the form of equation 4.3:

$$Y = .422S = 4.671R + .547R^2 + .0000344S^2 - .000000128(R \cdot S^2) - .130(D \cdot S). \quad (4.10)$$

Rearranging equation 4.10, it can be expressed as:

$$Y = .422S + .0000344S^2 - .130(D \cdot S) + (- 4.671 - .000000128S^2)R + .547R^2. \quad (4.11)$$

Equation 4.11 allows the calculation of values for a, b, and c in equation 4.3:

$$a = .422S + .0000344S^2 - .130(D \cdot S),$$

$$b = - 4.671 - .000000128S^2,$$

$$c = .547.$$

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[24]Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 140.

[25]Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 184.

From these estimates the empirical estimate of the marginal productivity of research and development for the period studied could be given as:

$$\partial Y/\partial R = - 4.671 - .000000128S^2 + 2(.547)R. \qquad (4.12)$$

By using selected values for three firm sizes, Comanor estimated the elasticities ($\partial Y/\partial R \cdot R/Y$) that were given earlier. These were given to support his scale economies conclusions.

Comanor also considered some alternative hypotheses to this main hypothesis that technical change in the drug industry is determined by the factors of research inputs, size of firm, the interaction between firm size and scale of research, and diversification. One of these hypotheses concerned the role of supporting personnel in relation to the professional R and D inputs. Specifically, he looked at whether a large ratio of supporting personnel (i.e., technicians and clerical workers) to professional personnel was necessary to increase the efficiency of the research facility. This was investigated by introducing an additional variable into the regression equations; this variable was the ratio of supporting personnel to professional R and D personnel, averaged for 1955 and 1960. The coefficient for this added variable was found to be statistically insignificant and was negative.[26]

The idea was also investigated that the causal relationship between technical change in the drug industry and R and D inputs was such that the introduction of new products determines the level of R and D for the drug firm. This could come about because these new products could

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[26]Ibid., pp. 188-189.

increase the profits of the drug firm which would in turn allow the firm to increase its investment in research and development.[27]

This alternative hypothesis means that the R and D intensity of the drug firm is greatly influenced by new product introduction. This was tested by looking at various lead-lag alternatives for the period covered. If R and D intensity is determined by technical change, then it could be expected that technical change at the start of the period would be better correlated with the R and D inputs at the end of the period. If the R and D inputs at the beginning of the period are better correlated with the new product output at the end of the period, then this supports the original hypothesis. Comanor performed these tests and found that the test of the alternative hypothesis was not statistically significant, and the lead-lag structure consistent with the original hypothesis was highly significant.[28]

Comanor had three main sources for his data. The information on new drug products was supplied by Paul de Haen, a consultant to the drug industry. The data on the sales of these new products and the total sales for firms during the 1955-1960 time period were supplied by R. A. Gosselin and Company, Inc., which is a market research firm. The data on the number of R and D inputs was available in the tenth and eleventh editions of the National Academy of Sciences--National Research Council publications, Industrial Research Laboratories of the United States. These gave a breakdown of the number of research personnel in a drug

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[27] Ibid., p. 188.

[28] Ibid.

firm and presented them according to whether they were professional or supporting personnel.[29]

From these data sources a sample of 57 firms was chosen. These were restricted to U. S. drug firms and were also restricted so as not to include firms that involved pharmaceutical mergers during the period investigated. If a pharmaceutical firm merged with a non-pharmaceutical firm and it appeared that the integrity of the drug firm was maintained then it was included in the sample. Also, pharmaceutical mergers that occurred in 1960 were allowed.[30]

Comanor's sample is essentially non-random and it is not dominated by large firms. The size distribution is J-shaped and one-third of the observations fell in the smaller size class.[31]

The scale of the research facilities in Comanor's study had a range of 4.0 - 590.5 when using professional R and D personnel, and 7.0 - 1103.0 when total personnel were counted. The means were 74.7 and 158.4 respectively, and the standard deviations were 112.6 and 246.5.[32]

Techniques of Present Study

The present study is based on the period 1965 to 1970, a period in which the full effects of the 1962 Drug Amendments should be evident. The techniques that were utilized by Comanor are being duplicated as closely as possible so that a valid comparison of the two time periods

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[29] Ibid., p. 183.

[30] Ibid.

[31] Ibid., pp. 183-184.

[32] Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 120.

can be attempted. Thus, a model of technical change in the drug industry is employed in this study in a like manner to that of Comanor.

Since Comanor's work, new single chemical entities have become recognized as the most innovative output of drug research and development. For this reason this study will first look at the initial two year sales of new single chemical entities. This definition of R and D output was found to be the most significant in Comanor's study, and this is considered the ideal measure of the inventive output of the industry because it takes into account the economic impact of drug innovation. This impact is important for it represents the innovative demand of new drugs before the influence of the promotional effort on the part of drug firms becomes effective.[33]

In addition to this measure, however, the present study uses the number of new single chemical entities to represent the output of the research and development facility of a drug firm. This has some limitations since it does not weight the economic importance of the R and D effort,[34] but it has been used in previous studies of the drug industry and other industries. Mansfield has used a weighted count of the number of innovations for the chemical, oil and steel industries to show inventive output.[35] Baily has recently used the number of new drugs on an unweighted basis as the measure of aggregate R and D output

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[33]Grabowski, p. 294.

[34]Part of the economic impact is accounted for in this measure since only those drugs that had some positive dollar sales are counted.

[35]Mansfield, Industrial Research and Technological Innovation: An Econometric Analysis (New York, 1969), pp. 40-41.

for the drug industry.[36] The count of new single chemical entities seems preferable to the number of total new drugs since the former are generally more innovative. Also, carrying the analogy of the production function further, the number of new single chemical entities as the output in physical units is consistent with the typical production function which measures the output and the inputs in physical units.

The research and development variable is used in the two forms presented by Comanor, and all of the other variables are employed in the manner of Comanor's presentation. The model is an input-output model for research and development and is expressed in equation 4.1. A summary of the definitions of the variables used in the present study follows:

Y_1 - total two year sales of new single chemical entities.

Y_2 - total number of new single chemical entities produced by the drug firm.

R_1 - total professional R and D personnel, average for 1965 and 1970.

R_2 - total R and D personnel including supporting personnel, average for 1965 and 1970.

S - size of firm as measured by the average prescription and hospital sales for the period 1965-1970.

I - interaction, scale variable which is the product of S and R.

D - diversification variable measured in the three ways used by Comanor.

T/P - ratio of supporting personnel to professionals, average for 1965 and 1970.

Given the significance of the model of technical change in the drug industry, changes in the model for the two time periods should reflect

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[36] Baily.

the impact of the 1962 Drug Amendments on the R and D activity of the industry. Acceptance or rejection of the alternative hypotheses should also be an indication of the impact of the amendments.

Data Sources and Sample Characteristics

Data Sources

The data sources for the present investigation are virtually the same as those used by Comanor. There are three primary data sources. The new single chemical entities introduced in the relevant period are presented by Paul de Haen in the Journal of Clinical Pharmacology.[37] The two year sales of these new single chemical entities and the total hospital and prescription sales by firm have been supplied by the market research firm, R. A. Gosselin and Company, Inc. The data on research and development personnel are available in Industrial Research Laboratories of the United States.[38]

The Gosselin data are based on two annual audits performed by the firm, the National Prescription Audit and the National Hospital Audit. These audits are very much the same as those that were used for Comanor's study.[39] The National Prescription Audit attempts to measure the "retail outflow" of prescriptions. The audit is based on a sample of 400 pharmacies which have been chosen to measure the preferences of

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[37] Paul de Haen, "Drugs Released for Clinical Use," Journal of Clinical Pharmacology and New Drugs, 5-10 (1965-1971).

[38] Bowker Associates, Inc., Industrial Research Laboratories of the United States, 12th and 13th Ed., (Washington, D. C., 1965 and 1970).

[39] Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," pp. 101-104.

prescribing physicians. Thus, this sample is supposed to reflect the distributions of the prescriber and prescription universe. The sample has been chosen so that it is proportionate by geographical location and type of retail concern. It was also chosen so that it would represent a wide cross section of prescribers. Of the 400 stores selected, 229 or 57 percent, collected data on new prescriptions and 171, or 43 percent, collected new and refill prescription data. Thus, the sales data that have been collected for this study include both new and refill prescriptions.[40]

The National Hospital Audit is derived from a sample of 60 "Non-Federal Short Term General Hospitals" in the U. S. This sample is statistically supposed to represent the purchasing activity of all hospitals in the population of "Non-Federal Short Term General Hospitals."[41]

There are two main limitations to the data derived from the Gosselin audits. First, they do not cover the sales of all drugs in the U. S. Notably, they do not include sales to governments and other institutional organizations. Secondly, the National Prescription Audit has had a tendency to concentrate on large retail outlets.[42]

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[40]This is one of the main differences in the data for the present study and the data of Comanor's study. Comanor did not have information on refill prescriptions, and he had to extrapolate to get estimates of refill prescription sales.

[41]The description of these data is based on the descriptions contained in the forewards of the National Prescription Audit and the National Hospital Audit.

[42]Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 101.

The data collected from the editions of Industrial Research Laboratories of the United States is virtually the same as that collected by Comanor. Two exceptions, however, must be noted. Previous to 1965, the data had been collected and published by the National Academy of Sciences/National Research Council. The twelfth and thirteenth editions were published by Bowker Associates, Inc. Although it appears that the questionnaire technique and the basic data collected are the same, it might be expected that some differences might arise when the compilers are two different groups.

The data presented in these volumes list the R and D personnel according to whether they are professional or auxiliary, supportive personnel. In addition, the major research activity of the research facility was identified. In many cases firms that had subsidiaries with separate research components were broken into their respective organizational units.[43]

One of the major problems associated with using these volumes for this R and D data was the fact that some firms were included in one of the editions but not the other. In these cases, a simple method of extrapolation was utilized which incorporated the projected growth of research personnel in the industry during the period under consideration. As stated previously, it has been estimated that the average rate of growth of research personnel in the industry for the period 1959-1965 was six percent per year, and that this would continue until 1968. This was based on the estimate made by the Pharmaceutical

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[43]Bowker Associates, Inc., pp. vii-viii.

Manufacturers Association for the National Institutes of Health.[44] It is assumed in this study that this projection would carry over into 1970 so that a forward or backward extrapolation is made based on this six percent rate. Thus, if a firm is listed in the 1965 edition of Industrial Research Laboratories and not in the 1970 edition, it is assumed that its research inputs increased by 36 percent from 1965 to 1970. Likewise, if a firm is listed in the 1970 edition but not in the 1965, it is assumed that the number of research personnel is 36 percent less in 1965 than in 1970.

The obvious disadvantage of this approach is that it could not be expected that any single firm would adhere to the average rate of change in personnel. If this procedure had not been adopted, however, the sample of firms in the study would have been greatly reduced.

McGee has criticized Comanor's use of this type of R and D personnel data for two primary reasons. (1) There are quality differences among research and development personnel, and these differences may consistently occur among different types and sizes of firms. (2) There may also be differences in the quantity of non-human research inputs, and these may consistently vary among different types and sizes of firms.[45] These are valid criticisms but insufficient information does not allow these factors to be taken into account.

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[44] U. S. Department of Health, Education, and Welfare, p. 3.

[45] McGee, p. 104.

Sample Characteristics

The sample of ethical drug firms for this study was chosen on the basis that only firms which introduced at least one new single chemical entity during the period 1965-1970 were included, and only U. S. firms were included. In addition, the number of firms involved was restricted by the availability of data on sales and R and D inputs. Drug firms that merged with other drug firms during the time period were excluded except for those firms that merged in 1970. If a pharmaceutical firm merged with a non-pharmaceutical firm and it appeared that the pharmaceutical firm retained its ethical pharmaceutical integrity, then the firm was included in the sample.

One of the characteristics of the sample of the R and D activity for the 1965-1970 period that must be noted first is the level of the R and D output for the industry as a whole. During this period the output of new single chemical entities was 96. All of these are not included in the final sample for the reasons outlined above.

When this output is compared with Comanor's period of study before the 1962 Drug Amendments, the difference is striking. For the period 1955-1960 the total number of new single chemical entities was 276.[46] Thus, since the 1962 Drug Amendments there has been a drastic reduction in the innovative output of the ethical drug industry.

The preceding considerations yielded a sample of 31 firms that is essentially non-random. These 31 firms on the average accounted for 75 percent of the total hospital and prescription sales in the United States, including refill prescription sales. Table VI shows the primary

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[46]Walker, p. 130.

TABLE VI

CHARACTERISTICS OF 31 FIRM SAMPLE
FOR 1965-1970 PERIOD

	Firm	Ethical Drug Sales (000)	Number of New Single Chemical Entities 1965-1970	R and D Activity: Professional R and D Personnel	R and D Activity: Technical R and D Personnel	Diversification (D_1)
1.	Eli Lilly	$199,698	4	789	875	7.2
2.	American Home Products	196,048				
	2a. Wyeth		1	422	190	7.5
	2b. Ayerst		3	216	221	8.2
3.	Merck, Sharpe and Dohme	156,870	8	752	785	5.8
4.	Smith, Kline and French	123,855	2	408	420	9.3
5.	Upjohn	118,396	5	371	356	4.3
6.	E. R. Squibb	99,506	2	341	370	9.8
7.	Abbott	97,460	2	462	384	9.8
8.	Lederle	92,861	3	307	292	8.6
9.	Parke, Davis	88,124	3	147	405	9.0
10.	Pfizer and Roering	87,156	7	174	411	8.8

TABLE VI (Continued)

Firm	Ethical Drug Sales (000)	Number of New Single Chemical Entities 1965-1970	R and D Activity: Professional R and D Personnel	R and D Activity: Technical R and D Personnel	Diversification (D_1)
11. G. D. Searle	$ 65,330	1	152	225	5.8
12. A. H. Robins	58,310	3	58	49	11.0
13. Warner-Lambert	52,270	2	262	440	9.3
14. Sterling	50,367	3	282	316	9.2
15. Schering	48,940	4	264	185	7.3
16. Johnson and Johnson	47,733				
16a. McNeil		3	85	61	8.8
16b. Ortho		1	97	97	3.2
17. Wallace	25,675	1	41	17	6.6
18. Baxter	25,263				
18a. Hyland		1	31	8	1.0
18b. Flint		1	79	64	3.0
19. Merrell	23,686	1	134	140	10.0
20. Norwich	21,898	1	121	200	2.0
21. Cutter	12,927	1	53	26	2.2
22. Stuart	9,636	1	10	12	9.0

TABLE VI (Continued)

Firm	Ethical Drug Sales (000)	Number of New Single Chemical Entities 1965-1970	R and D Activity		Diversification (D_1)
			Professional R and D Personnel	Technical R and D Personnel	
23. Warren-Teed	$ 5,651	1	21	28	5.0
24. Allergan	3,531	1	23	11	3.5
25. Rowell	1,622	1	7	8	8.2
26. Philips-Roxane	1,284	1	18	54	5.3
27. Central	270	1	3	9	8.6
28. duPont	116	1	45	132	.8

data that is used in the regression analyses that are performed in the following chapter. The sample contains realtively more larger firms than the 57 firm sample of Comanor where one-third of the firms in his J-shaped distribution fell in the smallest size class. This smallest class was considered to be those firms who had sales less than $1 million[47] which can be considered a rather arbitrary designation. From Table VI it appears that the distribution of firms for the 1965-1970 sample period falls into three distinct class sizes. These class sizes are apparent by looking at the relative size in average sales and at the scale of research and development inputs.

The smallest class size in the distribution of firms in the present study is considered to be firms whose average sales range from $1.0 million to $26 million. The range of professional R and D inputs for this size class is 7 to 134. The average level of sales is $14.2 million and the average scale of research inputs is 48.9 for professional research personnel. The medium class size is designated as the firms whose sales range from $30 million to $66 million and the research inputs range from 58 to 282. The average sales for this medium size class is $53 million and the average number of professional research personnel is 171.4. The large class size is designated as firms whose sales range from $85 million to $125 million and whose employment of professional research personnel ranges from 147 to 462. The average level of sales for this size class is $101.1 million and the average number of professional research inputs is 315.7.

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[47] Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 109.

The mean size for the 1965-1970 sample is $64 million. The average number of professional research inputs for the sample is 199.2.

These size characteristics of the 1965-1970 sample are indicative of the type of impact that the 1962 Drug Amendments have had on the R and D activity of the ethical drug industry. Comparing the present sample of firms introducing new drug innovations with the 1955-1960 sample, larger firms are now more predominant.

Another striking comparison that can be made between the sample of firms for 1955-1960 and that for 1965-1970 is the difference in the scale of research and development activity. This is reflected in Table VII which compares this aspect of the present sample with Comanor's.

TABLE VII

DIFFERENCES IN SCALE OF R AND D ACTIVITY
BETWEEN 1955-1960 AND 1965-1970

	Number of Personnel		
	Mean	Standard Deviation	Range
Professional R and D - 1955-1960*	74.7	112.6	4.0 - 590.5
Total R and D - 1955-1960*	158.4	246.5	7.0 - 1103.0
Professional R and D - 1965-1970**	199.0	470.9	3.0 - 789.0
Total R and D - 1965-1970**	410.0	407.3	12.0 - 1664.0

Sources: *William S. Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," (unpub. Ph.D. dissertation, Harvard University, June, 1963), p. 120; **Bowker Associates, Inc., Industrial Research Laboratories of the United States, 12th and 13th Ed., (Washington, D. C., 1965 and 1970).

The magnitude of research and development personnel in 1965-1970 is considerably greater than that of the 1955-1960 period. This is noticeable in both professional R and D personnel and total personnel, where both are greater than two and one-half times the level in 1955-1960.

A final characteristic of the sample of firms for the 1965-1970 period that must be noted concerns the treatment of firms that had one or more pharmaceutical subsidiaries. The size variable for this situation is computed as the total for all of the pharmaceutical subsidiaries of the firm. As an example, American Home Products had three subsidiaries that made pharmaceutical sales during the period studied. These three subsidiaries were Wyeth, Ayerst, and Ives Laboratories, and their sales were combined to get the size variable. This combined sales figure is used because it is assumed that the size influences must come from all of the pharmaceutical activity of the parent firm.

For this subsidiary situation the R and D output and input variables were calculated for each individual subsidiary. This is based on the assumption that the research and development facilities are relatively autonomous once the size of the firm has been taken into account. Thus, for American Home Products its Wyeth and Ayerst subsidiaries had new single chemical entity output during the relevant period so that these outputs were counted separately, and they had different scales of research facilities as measured by R and D inputs. These were also counted separately.

Utilizing this data base, the model of research and development output for the ethical pharmaceutical industry is employed in the next chapter to ascertain the impact of the 1962 Drug Amendments on R and D

in the industry. In that chapter, appropriate comparisons are made with Comanor's study in making the assessment of this impact.

CHAPTER V

EMPIRICAL RESULTS

The preceding chapter has outlined the basic model of technical change and the data that are used in the present chapter to judge the impact of the 1962 Drug Amendments on the R and D activity of the pharmaceutical industry. This chapter presents the results of the various regression analyses that have been performed to ascertain this impact.

Empirical Results Using Comanor's Techniques

The first analysis which is presented here duplicates Comanor's study. Thus, it is assumed that the output of the R and D facility can be determined by using the model expressed by equation 4.1. The relevant output for this model is the two year sales of new single chemical entities, Y_1. All of the other variables are those outlined in Chapter IV. This is the ideal technique, given the significance of Comanor's results, for it allows the most valid comparisons of the two time periods.

Equation 5.1 represents the estimated relationship using Comanor's techniques:

$$Y_1 = 1.085 - 3.42R_i + .836R_i^2 + .005S - .013I$$
$$\qquad\qquad (-1.289)\ (1.447)\ \ (.499)\ \ (-.646)$$
$$- .076D_1. \quad (R^2 = .159) \qquad (5.1)$$
$$(-.670)$$

The significance of the $\underline{R}^2$ is judged by the F-ratio test and the significance of the regression coefficients by one-tailed t-tests which are in parentheses under the regression coefficients.[1] Based on these tests the estimated equation is highly insignificant. The regression coefficients for the variables representing research and development inputs do have significance at the 90 percent confidence level, but on the whole the significance of this relationship in explaining the R and D output of the drug industry for this time period is not very high.[2]

One comparison with the Comanor estimates that must be noted deals with the signs of the regression coefficients. The coefficients for the 1965-1970 period take on the same signs as those of the 1955-1960 period when the techniques of Comanor's model are duplicated.

In addition to performing the regression analysis utilizing the deflated two year sales of new single chemical entities, Y_1, and the number of professional R and D personnel, R_1, as shown in equation 5.1, the total number of R and D personnel was also used as the input

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[1] As done previously in Table V, the coefficient of determination, $\underline{R}^2$, is underlined so that it will not be confused with the research variable, and this will be continued throughout this study.

[2] In this and the following multiple regression estimates the data for some of the variables have been scaled so as to express them in the same order of magnitude. This is recommended by J. Johnston, Econometric Methods (New York, 1963), p. 12, and is necessary to assure that there will not be too few significant numbers in some of the estimates. This is also important because the computer program used would only calculate regression coefficients to five significant places. Appropriate adjustments will be made to these coefficients in order to account for these scaling factors in a later section of this chapter.

independent variable. With these variables the relationship is also highly significant.

Based on these estimated equations it is concluded that a model with the first two years sales of new single chemical entities as the dependent variable and research inputs, size of firm, the interaction between the size of the firm and scale of research inputs, and diversification as the independent variables is not statistically relevant to the 1965-1970 time period. This conclusion follows from the insignificance of the regression coefficients that are reflected in the t-values, and from the value of the coefficient of determination as well as its F-statistic which measures its significance. The F-value for this estimated relationship is .9124.

Empirical Results Using Number of New Single Chemical Entities as Output Variable

Output Model Using Revised Techniques

The regression analysis was also performed when the dependent output variable was expressed as the number of new single chemical entities, Y_2, produced by each of the firms during the 1965-1970 time period. Both definitions of the R and D inputs are used in conjunction with Y_2. The other variables in the estimates are the same as those used by Comanor and as defined in Chapter IV. In all of these estimates the dependent variable and the scale of research and development

variables, R and R^2, are deflated by the size of firm in order to deal with the problem of heteroscedasticity.[3]

Table VIII presents the estimated regression equations when Y_2 is the dependent variable. Equations 5.2 - 5.4 are the estimates when R_1 and D_1, D_2, and D_3 are used respectively. Equations 5.5 - 5.7 are the estimates when R_2 and D_1, D_2, and D_3 are used respectively. As done previously, the one-tailed t-test is used to judge the significance of the regression coefficients, and the F-ratio test is used to judge the significance of the $\underline{R}^2$. As shown, the t-tests indicate that all of the regression coefficients for the model using Y_2 and R_1 are significant at the 95 percent confidence level with the exception of the linear R and D term which is significant at the 99 percent confidence level. The F-ratio indicates that all six of the estimated equations are significant at the 99 percent confidence level. The F-values for equations 5.2 - 5.7 are 42.53, 43.68, 44.26, 73.65, 74.86,

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[3]In Comanor's sample there was a wide range in firm size which made him assume there would be a difference in the error terms of the various observations, and thus he assumed heteroscedasticity, Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," p. 124. The present sample also has a wide range in firm size so that it is assumed that there is heteroscedasticity. In light of this assumption it is also assumed that the error terms of the observations have a variance that is proportional to the size of the firm as expressed by its total pharmaceutical sales. The constant of proportionality that is used to reduce the possibility of heteroscedasticity, then, is the size of the individual firm. It is also assumed that the size disturbances would affect both the output variable and the scale of research variables so that both are deflated by the size of firm. See Pothuri Rao and Roger LeRoy Miller, Applied Econometrics (Belmont, California, 1971), pp. 127-129 and pp. 141-145. To ascertain whether heteroscedasticity might still exist once the above transformation is performed, a test suggested by H. Glezser, "A New Test for Heteroskedasticity," Journal of the American Statistical Association, 64 (March, 1969), pp. 316-323, is employed. Using this test on the regressions it appears that "mixed" heteroscedasticity may still exist, but an adequate constant of proportionality could not be ascertained to deal with this problem.

TABLE VIII

REGRESSION ESTIMATES FOR 1965-1970

$Y_2 = -.046 + .4496R_1^{*} - .503R_1^{2**} - .008S^{**} + .017I^{**} + .083D_1^{**}$ $\quad\quad (4.349) \quad (-2.237) \quad (-2.210) \quad (2.212) \quad (1.884)$	$(\underline{R}^2 = .89)$	(5.2)
$Y_2 = -.037 + .318R_1^{*} - .489R_1^{2**} - .008S^{**} + .016I^{**} + 1.124D_2^{**}$ $\quad\quad (6.728) \quad (-2.091) \quad (-2.195) \quad (1.950) \quad (2.012)$	$(\underline{R}^2 = .90)$	(5.3)
$Y_2 = -.195 + .321R_1^{*} - .534R_1^{2**} - .009S^{**} + .020I^{**} + .103D$ $\quad\quad (6.789) \quad (-2.256) \quad (-2.488) \quad (2.296) \quad (2.096)$	$(\underline{R}^2 = .90)$	(5.4)
$Y_2 = -.251 + .456R_2^{*} - .076R_2^{2*} - .0005S + .0003I + .038D_1$ $\quad\quad (5.819) \quad (-3.720) \quad (-.190) \quad (.153) \quad (1.196)$	$(\underline{R}^2 = .94)$	(5.5)
$Y_2 = -.318 + .443R_2^{*} - .072R_2^{2*} - .0005S + .00004I + .594D_2$ $\quad\quad (5.491) \quad (-3.402) \quad (-.191) \quad (.058) \quad (1.355)$	$(\underline{R}^2 = .94)$	(5.6)
$Y_2 = -.246 + .453R_2^{*} - .075R_2^{2*} - .0004S + .00005I + .060D_3$ $\quad\quad (5.771) \quad (-3.670) \quad (-.161) \quad (.062) \quad (1.605)$	$(\underline{R}^2 = .94)$	(5.7)

*Indicates statistical significance at 99% confidence level.
**Indicates statistical significance at 95% confidence level.
Statistical significance for the regression coefficients is determined by one-tailed t-tests, and the significance of the $\underline{R}^2$ by the F-ratio test.
The t-values are in parentheses under the regression coefficients.

and 77.10, respectively. In addition, it must be noted that the $\underline{R}^2$'s for equations 5.2 - 5.7 are markedly greater than the $\underline{R}^2$ for equation 5.1.

Based on the significance of the regression coefficients, it is concluded that the equations utilizing the number of new single chemical entities, Y_2, as the output variable and the number of professional research personnel, R_1, as the input variable are the most significant relationships determining the R and D activity of the drug industry for the period under investigation. Equations 5.2 - 5.4, based on the test criteria, appear to be equally significant.

The only differentiating feature of equations 5.2 - 5.4 is the three diversification designations, and all three are statistically significant. It is concluded that all three of the definitions of diversification are equally satisfactory.[4]

Using the estimated regression equations 5.2 - 5.4, it is concluded, then, that a production function type of model can be utilized to investigate the R and D activity of the ethical drug industry for the period 1965-1970. This model has the number of new single chemical entities that a drug firm introduces as its dependent output variable. The independent variables include research personnel inputs, size of firm, the interaction between firm size and scale of research inputs, and diversification.

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[4]These diversification measures when used by Comanor were also equally satisfactory; Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 184. Due to the fact that all three definitions of diversification are significant in both Comanor's study and the present study, the further use of the regression equations for additional analysis will use only one of the definitions--D_1.

The definition of the dependent variable used in this model to investigate the impact of the 1962 Drug Amendments is not the exact same definition used for the 1955-1960 period, but the similarities should be enough to allow the assessment of this impact. The difference in the definitions that is necessary to make the model statistically significant may even be indicative of this impact. It must also be noted that the difference in model significance due to the difference in dependent variable definition may be due to some unknown statistical qualities of the two samples involved.[5]

Using equation 5.2 as the representative relationship for the R and D output of the ethical drug industry, the first consideration that must be dealt with is the signs of the coefficients. The linear R and D term is positively associated with R and D output in the drug industry which is an a priori expectation. This contrasts greatly with Comanor's empirical results which indicated that the linear input variable was negatively associated with the output variable. He stated that this was incongruous with the hypothesized relationship, and he attributed

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[5]The regression estimates that are presented in Table VIII are based on the definitions of the variables contained in Chapter IV. One of the important designations is the size of firm variable which was defined as the sales of all the subsidiary units of a corporate entity, whereas the other variables were measured relative to the individual subsidiary units. To insure that this definition of firm size was not causing anomalous results, the size of firm variable was redefined so that it only accounted for the sales of the subsidiary unit of the parent corporate entity. This did not alter the results significantly. The regression estimate based on this analysis is contained in the Appendix. In addition, the estimated results contained in Table VIII indicacated that the residual associated with one observation (Central Pharmacal) was relatively high. The regression estimates were then run with the removal of this observation. This reduced the magnitude of the various regression coefficients. The results of these analyses are also presented in the Appendix.

it to a statistical problem associated with having a number of zero values for the dependent variable.[6]

As shown, the value of the quadratic R and D term is negative, and there may be an a priori reason to expect this because the production function may be subject to decreasing marginal productivity at some level of research inputs. Comanor found the term to be positive.[7]

The regression coefficient of the variable used to denote the size of firm, S, has a negative value. This may be somewhat anomalous in the light of similar studies which have looked at R and D output and the size of firm. Schnee's study of the drug industry looked at the relationship between the number of drug innovations, a linear size variable, and a quadratic size variable. For the period 1950-1962 his regression results are as follows:

$$n_j = .31 + .07S - .003S^2, \tag{5.8}$$

where n_j is the number of innovations for the j th firm and S is the size variable. As can be seen the linear size term is positive.[8]

A similar technique, but one in which a scale of R and D factor is incorporated, has been used by Mansfield to study the chemical industry:

$$n_i = R_i(2.38 + .404R_i - .024S_i). \tag{5.9}$$

Here the size of coefficient has a negative sign, but this is somewhat misleading because the scale of R and D (for his purposes R and D expenditures) is a multiplicative factor in front of the parenthesis.

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[6]Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 185.

[7]Ibid.

[8]Schnee, p. 176.

Thus, the size of firm variable is multiplied by the scale of research which is more like the interaction variable of the present study.[9]

As indicated previously, Comanor stated that a positive sign could be expected for the size of firm variable because this would reflect such things as the firm's distribution facilities, selling effort, and reputation. He concluded that firm size in his 1955-1960 period acted to increase the gains from technical change.[10]

This type of conclusion does not seem to apply to the present study due to the fact that the R and D output variables are different. In Comanor's study the dollar sales of the new drug innovations were used as the dependent variable and these sales could be affected by distribution facilities, selling effort, and reputation. It should be expected that these factors would not be important when only physical R and D output is considered.

Given the negative sign of S for the present study, it may be that this variable reflects the usual negative impact that size alone has upon this aspect of a firm's output. It thus appears that since 1962, firm size alone results in decreasing gains to R and D output which could be attributed to the usual types of management coordination and control problems as these problems arise in connection with the research and development of the firm.

This interpretation can also be seen from the partial correlation coefficient which is also negative and has a value of - .404. The

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[9]Mansfield, Industrial Research and Technological Innovation: An Econometric Analysis, p. 41.

[10]See pages 64-65.

partial correlation coefficient is a measure of the proportion of the variation in Y_2 unaccounted for by R_1, R_1^2, I, and D that is explained by the addition of S.[11]

As an additional check on the sign of this variable, the simple correlation between R and D output and the size of firm was computed. This is done to ascertain whether the other variables in the total relationship might have rendered the sign negative. The estimated relationship is as follows:

$$Y_2 = 1.015 - .008S. \qquad (\underline{R}^2 = .09) \quad (5.10)$$

Although the relationship itself is not statistically significant, the negative sign of the size variable is consistent with the previous results.

The sign of this size variable is the first clue to the impact of the 1962 Drug Amendments. Even though the sign of the size variable when Comanor's techniques are exactly duplicated is the same as Comanor's result, the negative sign that results when only physical R and D output is used as the dependent variable is an important indicator of the effects of the amendments on drug innovation. It must be noted that even though the sign of the size coefficient in the present study is negative and indicates decreasing output gains, this does not necessarily show decreasing returns to scale as it is used in this study. Decreasing or increasing returns for the present study relate to the scale of R and D inputs and size of firm as they affect R and D output.

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[11] Johnston, p. 61.

Finally, the possibility that the sign of the size variable is incorrect must be considered. This can occur when there are certain unknown qualities of the sampling distribution. This usually means that the regression coefficient is not statistically different from zero, but with the computed t-value indicating that the coefficient is significant at the 95 percent level, there is good reason to accept the value of the sign.[12]

The sign of the interaction variable, I, for the 1965-1970 time period is positive. This again differs greatly with the 1955-1960 period where the value was negative. The negative sign for Comanor's I allowed for two competing effects on the R and D output of the drug firms in the industry. The size variable alone, in Comanor's study, picked up the distributional and promotional advantages of large size, while the interaction variable would allow for the offsetting disadvantages occurring in the research facility.[13]

The sign of the interaction variable of the present study is another clue as to the impact of the amendments. In 1955-1960 the inefficiencies of large sized firms relating to their R and D facility were reflected in the negative sign. For the 1965-1970 period it appears that certain inefficiencies due to large size have now been to a certain degree offset.

For the present study the negative sign of the size variable may reflect the management coordination and control problems that can arise when R and D is associated with a large sized firm. On the other hand,

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[12]Rao and Miller, p. 46.

[13]See pages 65-66.

the positive sign of the interaction variable, which occurs when both designations of R and D inputs are used, may reflect certain R and D facility scale efficiencies. Thus, the positive sign that appears when R_1 is used may reflect the fact that professional R and D inputs when associated with the size of firm exert a positive impact on the R and D output of the firm. The positive sign that appears when R_2 is used may reflect the better use of clerical personnel and technicians, computing facilities and specialization of labor that occurs within the research facility and becomes more important when the size of the firm becomes larger and when the scale of the research facility becomes larger. The positive sign of the interaction variable may also reflect the fact that as both the size of firm and the scale of research activity become larger, the firm is able to attract more capable personnel which increases its R and D output. All of the apparent efficiencies that are indicated above are directly related to the provisions of the new drug regulations.

The sign of the diversification variable as shown in Table VIII is positive when each of the three definitions is used. To Comanor the negative sign of this coefficient in his study indicated that the output of the drug firm would be greater when the firm concentrated its research effort in a few areas. Given the significance of the variable for the present study, the positive sign may indicate that the research effort must be spread over a wider area of product categories in order for it to find a marketable new drug product. This sign change could also reflect an effect of the amendments on the R and D effort of the industry. Because of the proof of efficacy requirement for all types of

drugs, as discussed in Chapter III, the firm may now have to extend its research activity into many areas in order for it to develop a new drug which will be approved by the FDA for introduction on the market. This would have the tendency of involving the firm in several markets and thus diversifying the R and D activities of the firm.

The observed signs of the variables for the present study are offered as preliminary evidence as to the impact of the 1962 Drug Amendments on the R and D activity of the drug industry for the 1965-1970 time period. The estimated relation given in equation 5.2 will now be used to investigate the major aspect of this study.

Scale Economies and the Use of Supporting Personnel in Drug R and D

Equation 5.2 expresses the estimated relationship between the research and development output of drug firms for the period 1965-1970 and these firm's R and D inputs, their size, their interaction with size and personnel inputs, and their degree of diversification. For computational expediency the variables in this relationship were scaled to obtain these estimates. Scaling of variables in an estimated relationship does not effect the significance of the regression coefficients that are obtained, but it does affect the values of the regression coefficients themselves.[14] It is necessary to take into account these

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[14] E.g., if it is assumed that a three variable linear model has been estimated thusly,

$$\overline{Y} = a + \overline{B}_1 X_1 + \overline{B}_2 X_2, \qquad (5.a)$$

then the estimated regression coefficient for the independent variable X_1 is computed in this model by:

scaling factors to get the true magnitude of the regression coefficients that are shown in equation 5.2. This is especially necessary for the present study because the values of the regression coefficients are used to determine R and D marginal productivity and output elasticity that exists for drug firms for the 1965-1970 time period. When the scaling factors are accounted for, the true expression of equation 5.2 is:

$$Y = -3.568 \times 10^{-5} + .04496R - 5.032 \times 10^{-4}R^2 - 8.05 \times 10^{-9}S + 1.731 \times 10^{-11}R \cdot S + 8.3 \times 10^{-5}. \quad (5.1)$$

Comanor used the regression coefficients from his 1955-1960 sample to explore what he termed the "economies of scale" of drug R and D. The same technique is used in the present study to look at drug R and D but the implications of the technique do not necessarily reflect economies of scale as the term is generally used in the theory of production.

$$\bar{B}_1 = \frac{(\Sigma yx_1)(\Sigma x_2^2) - (\Sigma yx_2)(\Sigma x_1 \Sigma x_2)}{(\Sigma x_1^2)(\Sigma X_2^2) - (\Sigma x_1 x_2)^2}, \quad (5.b)$$

where the variables in equation 5.b are expressed in deviation form. However, if the variables have been scaled for computational expediency, it is necessary to adjust the regression coefficients derived from equation 5.b so that the true value of $\bar{B}$ can be determined. Thus, if the scale factors of k_1, k_2, and k_3 are used on Y, X_1, and X_2 respectively, then it is necessary to make adjustments for these scale factors. The mathematics of this adjustment for $\bar{B}$ is shown in equations 5.c, 5.d, and 5.e:

$$\bar{B}_1 = \frac{(\Sigma k_1 y k_2 x_1)\left[\Sigma (x_2 k_3)^2\right] - (\Sigma k_1 y k_3 x_2)(k_2 x_1 k_3 x_2)}{\left[\Sigma (x_1 k_2)\right]\left[\Sigma (x_2 k_3)^2\right] - \Sigma (k_2 x_1 k_3 x_2)^2}, \quad (5.c)$$

$$\bar{B} = \frac{k_1 k_2 k_3^2\left[(\Sigma yx_1)(\Sigma x_2^2) - (\Sigma yx_2)(\Sigma x_1 x_2)\right]}{k_2 k_3\left[(\Sigma x_1^2)(\Sigma x_2^2) - (\Sigma x_1 x_2)^2\right]}, \quad (5.d)$$

$$\bar{B} = \frac{k_1\left[(\Sigma yx_1)(\Sigma x_2^2) - (\Sigma yx_2)(\Sigma x_1 x_2)\right]}{k_2\left[(\Sigma x_1^2)(\Sigma x_2^2) - (\Sigma x_1 x_2)^2\right]}. \quad (5.e)$$

The true value of the regression coefficient is then expressed as:

$$\bar{B}_1 = \bar{B}_1 \frac{k_2}{k_1}. \quad (5.f)$$

When the deflation factor is taken into consideration, equation 5.11 can be expressed as:

$$Y/S = -3.568 \times 10^{-5} + .04496R/S - 5.032 \times 10^{-4}R^2/S - 8.05 \times 10^{-9}S + 1.731 \times 10^{-11}R \cdot S + 8.3 \times 10^{-5}D. \quad (5.12)$$

Multiplying both sides of equation 5.12 by S yields the following:

$$Y = -3.568 \times 10^{-5}S + .04496R - 5.032 \times 10^{-4}R^2 - 8.05 \times 10^{-9}S^2 + 1.731 \times 10^{-11}R \cdot S^2 + 8.3 \times 10^{-5}D \cdot S. \quad (5.13)$$

Rearranging equation 5.13 it can be expressed as:

$$Y = -3.568 \times 10^{-5}S - 8.05 \times 10^{-9}S^2 + 8.3 \times 10^{-5}D \cdot S. + (.04496 + 1.731 \times 10^{-11}S^2)R - 5.032 \times 10^{-4}R^2. \quad (5.14)$$

Using equation 5.14 it is possible to obtain values for a, b, and c as originally indicated by equation 4.3 in Chapter IV:

$$a = -3.568 \times 10^{-5}S - 8.05 \times 10^{-9}S^2 + 8.3 \times 10^{-5}D \cdot S \quad (5.15)$$

$$b = .04496 + 1.731 \times 10^{-11}S^2 \quad (5.16)$$

$$c = -5.032 \times 10^{-4}. \quad (5.17)$$

Using the general form for the marginal productivity of research and development as indicated in equation 4.4 in Chapter IV, it is possible to express the marginal productivity for the 1965-1970 period as:

$$\partial Y/\partial R = .04496 + 1.731 \times 10^{-11}S^2 - 2(5.032 \times 10^{-4})R. \quad (5.18)$$

In this estimated relationship b is positively related to S and 2cR is negative so that the value of $\partial Y/\partial R$ is determined by the relative values of b and 2cR. Given the firms that appear in the 1965-1970 sample, the value of 2cR is absolutely larger than b and the value of $\partial Y/\partial R$ is always negative.

Thus, during the 1965-1970 period the marginal productivity of research and development personnel is negative. This is a striking

result and it supports Hypothesis 1 which stated that the 1962 Drug Amendments would cause the marginal productivity of professional R and D personnel to become negative. This contrasts to the results for the 1955-1960 period, where Comanor found the marginal productivity of R and D personnel to be positive, but the relationship was such that $\partial Y/\partial R$ was inversely related to S,[15] and it was only at very large values that the marginal productivity of R and D personnel inputs would be negative.[16]

In order to investigate the implications of this marginal productivity relationship, the sizes of the firms in the present sample are classified into three arbitrary class sizes. These class sizes are chosen on the basis of Table VI in Chapter IV. From this table it appears there are three class sizes of firms in the 1965-1970 time period which are classified as small, medium, and large. The small class size includes firms whose sales are in the range of $1 - $26 million. The medium size class includes firms whose sales range from $30 - $66 million, and the large class size includes firms in the $85 - $125 million sales range. In addition the size range for the total sample of firms is $166 thousand to $200 million. Those firms that fell within these class ranges formed the basis for computing the marginal productivity for each class. The value for S is computed as the average size of all the firms that fell within a particular class range. Thus, the S value for the small class is $14.2 million, for the medium class

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[15] See page 60.

[16] Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 188.

$53.9 million and for the large class $101.1 million.[17] The average value for the total sample is $64.0 million.

Average values for R_1 are calculated in a similar manner. The values for R_1 are 48.9, 171.4, and 315.7 for small, medium, and large firms, respectively. The value for the total sample is 199.2.

Using these computations and equations 5.15, the marginal productivity of R and D inputs for the three class sizes and the total sample were calculated. For small firms the marginal productivity is - .00075; for medium firms the marginal productivity is - .079; and, for large firms the marginal productivity is - .09601. The marginal productivity of research personnel for the total sample is - .08195.

The negative marginal productivity for R and D personnel inputs for the 1965-1970 period is an important implication concerning the impact of the 1962 Drug Amendments on the output of new single chemical entities. Whereas all firm sizes had marginal productivities that were positive for the 1955-1960 period, these appear to have been rendered negative since 1962.[18]

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[17] The class intervals that have been chosen for the present study are larger than those selected by Comanor. These larger class sizes are based on the natural size breaks that appear in Table VI and they should account for growth in the industry. Comanor's size class ranges are the following: small, S = $1 million, R_1 = 13.1; medium, S = $10 million, R_1 = 59.2; large, S = $50 million, R_1 = 353.3. Comanor, "Research and Technical Change in the Pharmaceutical Industry," pp. 187-188.

[18] As pointed out previously, the regression estimates were also calculated where the size of the firm was measured as the size of the individual subsidiary unit as opposed to the size of the total pharmaceutical corporate entity. The marginal productivity calculations were also made based on these regression estimates, and the values of these marginal productivities were not significantly affected. These results are presented in the Appendix. However, the marginal productivity calculations were also computed on the basis of the regression estimates where the high residual observation (Central Pharmacal) was removed.

The implications of these amendments on marginal productivity can be evaluated further by looking at the maximum or minimum characteristics of the drug output relationship. The general relationship for drug R and D output was expressed in equation 4.3. Given the values for a, b, and c that are derived from the estimated relationship in equation 5.14 and are expressed in equations 5.15, 5.16, and 5.17, this general expression becomes:

$$Y = a + bR - cR^2. \tag{5.19}$$

To test whether this function has a maximum or minimum it is necessary to take the first derivative with respect to R and set this equal to zero which determines the critical value.

$$\partial Y/\partial R = b - 2cR, \tag{5.20}$$

$$0 = b - 2cR, \tag{5.21}$$

$$- 2cR = - b, \tag{5.22}$$

$$R = b/2c \quad \text{(critical value)}. \tag{5.23}$$

The functional relationship reaches a maximum if for the critical value the second derivative with respect to R is less than zero. The second derivative of equation 5.19 is:

$$\partial^2 Y/\partial R^2 = - 2c. \tag{5.24}$$

This means that equation 5.19 reaches a maximum at a level of research and development personnel that is equal to the critical value expressed in equation 5.23.

This had the effect of causing the values of the marginal productivities for large and medium firms to be relatively the same as previous calculations. It did cause the marginal productivity for small firms to become positive, but its value is very close to zero. These calculations are also presented in the Appendix.

In order to compare these critical values within the actual levels of R and D personnel, the critical values for each of the class sizes of firms for the 1965-1970 sample period have been calculated. For small firms the critical R is 48.1 and the average actual value of R for this class size is 48.9. For medium sized firms the critical R is 92.9 where the average actual value is 171.4. Firms in the large sized class have a critical R of 220.3 compared with an actual average of R equal to 315.7.

Figure 3 graphically illustrates the relative differences between these critical values and the actual average values for the three size classes of firms. Point A is the actual average for small firms, and point B is the computed critical value. Point C is the actual average for medium firms and D represents the computed critical value. Point E is the actual average value of R for large forms and point F represents the critical value for large firms.

The R and D production function that is used here implicitly assumes that R and D personnel are the variable input which is being applied to a fixed factor of production. These results imply, then, that all sizes of drug firms are operating in Stage III of the stages of production when R and D personnel are the variable input. (Small firms are operating fairly close to Stage II, however.) This means that these firms are using too many professional R and D personnel such that their use is not profit maximizing. Thus, it may be that the 1962 Drug Amendments have forced drug firms to over-utilize professional R and D personnel at the expense of using them in a profit maximizing manner.

In addition, since there is symmetry in the stages of production, this means that the fixed factor of production is under-utilized.[19]

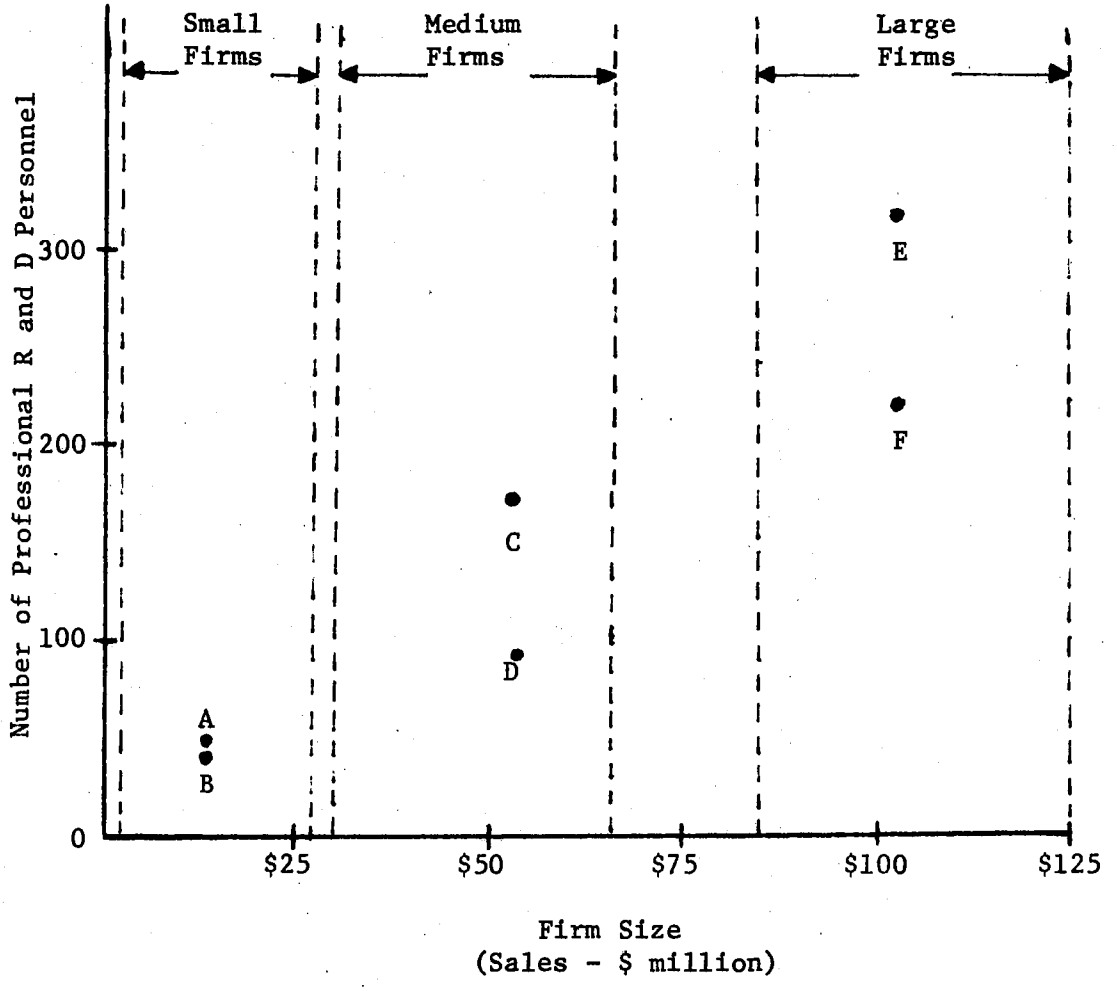

Figure 3. Comparison of Critical Values with Actual Average R Values

[19]Leftwich, pp. 111-116.

At first glance these marginal productivity computations suggest that, during the 1965-1970 period, small firms may be better at judging the profit maximizing level of R and D inputs for they are much closer to the critical value as it is expressed in equation 5.23. It appears that medium and large sized firms are much further away from this critical value of professional R and D personnel, and thus have not been as successful at determining the profit maximizing level of these inputs.

However, these conclusions may be misleading for several reasons. (1) The production function that is used to measure the R and D output of the drug industry is one in which there is only one variable input, R, and it really reflects variable proportions.[20] In conjunction with this, the relationship may not be expressing the complementarity of R and D inputs with the other factors of production within the firm, and the output of new single chemical entities does not express the true output of R and D personnel when these personnel may be involved in the production processes of the firm.

(2) As indicated above, new single chemical entities may not reflect the true R and D output of drug firms. In addition to the "output" that R and D personnel may contribute to the production processes of the firm, they may also produce new product forms which may have economic significance. These new product forms may be new dosages or new forms such as an injection as opposed to a tablet or capsule.

(3) The output of drug research in this study is measured as the number of new single chemical entities as opposed to the dollar sales

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[20] McGee, p. 105.

of new single chemical entities for some specified period of time. A two year count of the dollar sales of new single chemical entities would more adequately account for their economic impact as indicated in Comanor's study. Not using the first two year sales of new single chemical entities as the output variable may have rendered the marginal productivities of the three class sizes negative.

To show the importance of the initial two year sales of the new single chemical entities for the 1965-1970 period, Table IX shows the average first two year sales of the new single chemical entities of the three class sizes of firms for the 1965-1970 time period. As shown in this table, the economic significance of the new single chemical entities is greater for medium and large firms than it is for small drug firms. The increased economic significance is not accounted for by merely counting the number of new single chemical entities.

(4) Table IX may also be indicative of the idea that medium and large sized firms only introduced new drugs that have economic significance. These firms do not market new drugs unless the economic impact of these new drugs is substantial. Large firms with large investments in research and development and marketing may not introduce new single chemical entities unless the anticipated marginal revenues of these products is large enough to cover the marginal costs of these activities as well as their production costs. On the other hand, small firms with more modest R and D and marketing costs will be more willing to market any new product of their R and D effort. Although it cannot be substantiated here, it may be that the economic significance of new single chemical entities reflects their medical significance, and

thus, medium and large firms are introducing the more significant new drugs.[21]

TABLE IX

ECONOMIC SIGNIFICANCE OF NEW SINGLE CHEMICAL ENTITIES

Firm Size Class	Average First Two Year Sales of New Single Chemical Entities (000)
Large	$2,384
Medium	4,810
Small	467

(5) Given that medium and large sized firms are substantially above the critical level of professional R and D inputs as indicated above, this may reflect the idea that these firms have found it necessary to use these highly trained personnel to comply with the requirements of the amendments. This would indicate that the amendments have substantially raised the costs of doing drug research without increasing the flow of new drug output.

[21] As indicated in Chapter II, some economists feel that the economic significance of new drugs is primarily a result of the extensive promotional activity on the part of large firms.

Utilizing the preceding estimated regression equations and the three class sizes of drug firms, it is possible to compute the elasticity of R and D output with respect to professional R and D personnel. This elasticity is represented by $(\partial Y/\partial R)(R/Y)$. The numerical value for $\partial Y/\partial R$ can be calculated by using equation 5.18, and a numerical value for Y is obtained by using equation 5.14.

For small firms the elasticity of R and D output is - .01478; for medium sized firms the elasticity is -2.1743; and, for large firms the elasticity is -5.6894. These elasticity measures indicate the percentage by which R and D output will increase or decrease when there is a one percent increase in R and D inputs.[22]

The above elasticity measures are somewhat misleading because the Y values that are computed from equation 5.14 do not reflect the actual average level of Y for this time period. The value of Y for small firms when equation 5.14 is used is 5.3 times the actual average value for the period. If the actual average value of 1 is used for this class size, the elasticity is - .03668 which is 148 percent greater than the value when Y is computed in equation 5.14. For medium sized firms the actual average value of Y is 2.4 compared to the Y obtained from equation 5.14 which is 8.117, and the elasticity is - 5.575. For large firms the actual average value of Y is 3.4 compared to the computed Y of 8.933, and the elasticity when the actual value is used is - 8.841.

Comanor used the elasticity measures as an indication of the economies or diseconomies of scale that exist within the research and

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[22]The elasticity measurements were also computed with the alternative subsidiary definition and with the high residual observation removed. These elasticities are presented in the Appendix.

development facilities of drug firms. Comanor's use of the term economies of scale has been brought into question by McGee.[23] As the term is usually used, all inputs are variable and a proportionate increase in all of these inputs results in a greater than proportionate increase in output. As discussed previously, Comanor was really dealing with the question of variable proportions because not all inputs were variable in his method; only one input was variable--research and development personnel.

The elasticity measure that was used by Comanor and is used in the present study is really an expression of the output elasticity of an input which is the input's marginal product divided by its average product. Thus, the elasticity measures computed above are the output elasticities of professional R and D personnel.

The preceding empirical results indicate that Hypothesis 1 is supported which means that the marginal productivity of professional R and D personnel has become negative since the passage of the 1962 Drug Amendments. In addition, these results were elaborated on by looking at the output elasticities of these R and D inputs.

These elasticity measures do not reflect the economies of scale that exist in the R and D components of drug firms. In order to get an idea of the scale economies that might appear in these facilities it would be necessary to have estimates of the capital and other factors of production used in these components and this data is not available.

The above results concerning the marginal productivity and elasticity of output of R and D inputs indicate the severe impact

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[23] See page 61.

the 1962 Drug Amendments have had upon the research and development activity of the ethical pharmaceutical industry. It is very likely that these amendments have caused drug firms to expand their R and D components so as to meet the requirements of the amendments, and this has had a negative impact on their output of new single chemical entities. The previous results are based on R and D output being measured as new single chemical entities. This is a somewhat limiting definition of R and D output and if a more comprehensive measure were employed, the results may be significantly different.

If the limitations of the output measure that is used in the present study are ignored, it also appears that the amendments have made it more difficult for drug firms to achieve the profit maximizing level of their R and D inputs. This is especially apparent with medium and large sized firms. However, it should be kept in mind that medium and large firms introduced new single chemical entities that had more economic significance.

Since it is not possible to measure the economies of scale of drug R and D directly, it is necessary to use more implicit means of dealing with this issue. There are two primary indicators that relate to scale economies in drug and research development.

The first indication of the effects of the amendments on scale economies during the 1965-1970 period is shown in the regression estimates from the previous section. Hypothesis 2 expressed the view that the amendments have affected the industry to such an extent that the interaction between the size of the firm and its scale of research now exerts a positive influence on the R and D output of the industry.

Rejecting or not rejecting this hypothesis yields another indication of the impact of the amendments on R and D scale economies.

Equation 5.2 shows that the sign of the interaction variable, I, is indeed positive for the period of the present study. Thus, Hypothesis 2 cannot be rejected. The implication of this positive sign for the interaction variable is that as the size of the firm increases in conjunction with its scale of R and D facility, for which R serves as a surrogate, the firm can experience efficiencies which previously were not available. The types of economies that can be obtained are the same as those discussed in Chapter III. Greater division of labor, utilization of computers, and larger laboratories and laboratory equipment are all among the scale economies available as the firm increases in size.

The most important scale economy was mentioned in the previous section concerning the interpretation of the signs of the variables.[24] There it was pointed out that the inefficiencies of large size could now be offset by the efficiencies of using clerical personnel and technicians to adhere to the requirements of the amendments. Thus, supporting personnel have become much more important in the R and D process of the drug industry. And, it may be that many of the scale advantages that large size yields come from the use of supporting personnel in complying with new drug regulations. This is the essence of Hypothesis 3 which states that supporting personnel relative to professional R and D personnel now make a significant contribution to the research output of the drug firm and thus allow larger firms some scale economy benefits.

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[24]Refer to pages 94-95.

To test the importance of these supporting personnel, the regression estimates were computed again using an additional variable calculated as the ratio of supporting R and D personnel to professional R and D personnel. This variable was calculated on the basis of the average number of each type of personnel for 1965 and 1970--the two years the data were available in Industrial Research Laboratories of the United States. Table X presents the results of these regression estimates with the sixth dependent variable, the ratio of supporting personnel to professional personnel being added. This added variable is represented by the symbol T/P, indicating the designated ratio.

Table X shows that, using the t-test to judge the significance of the regression coefficients, all of the coefficients are significant at the 95 percent level of confidence when the R and D input variable, R_1, is used. The one exception to this is the diversification variable that in all three cases is only significant at a 90 percent confidence level. When R_2 is used as the input variable, only the two R and D input variables are significant.

The F-ratio test is utilized to test the significance of the $\underline{R}^2$, and in all six estimated equations this indicates a significance at a 99 percent confidence level. Based on the t-tests of the regression coefficients and the F-ratios, it is concluded that the model is most significant when the professional R and D input variable is used.

In addition to these tests, the simple correlation coefficient for the dependent variable and this measure of the ratio of supporting to professional personnel can be important in depicting the importance of this added variable. For equations 5.25 - 5.30 these coefficients are .92, .92, .92, .94, .94, and .94 respectively.

TABLE X

REGRESSION ESTIMATES WITH SUPPORTING PERSONNEL 1965-1970

$Y_2 = -.327 + .367R_1^{*} - .366R_1^{2}{}^{**} - .007S^{**} + .014I^{**} + .015D_1^{**} + .370T/P^{**}$ (3.683) (-1.728) (-2.012) (1.940) (1.208) (2.496)	($\underline{R}^2 = .92$)	(5.25)
$Y_2 = -.322 + .276R_1^{*} - .374R_1^{2}{}^{*} - .007S^{**} + .014^{*} {}^{**} + .745D_2 + .362T/P^{**}$ (5.953) (-1.719) (-2.062) (1.801) (1.406) (2.499)	($\underline{R}^2 = .92$)	(5.26)
$Y_2 = -.166 + .278R_1^{*} - .406R_1^{2}{}^{**} - .008S^{**} + .016I^{**} + .069D_3 + .358T/P^{**}$ (5.986) (-1.830) (-2.250) (2.030) (1.478) (2.476)	($\underline{R}^2 = .92$)	(5.27)
$Y_2 = -.251 + .455R_2^{*} - .076R_2^{2}{}^{**} - .0005S + .0003I + .038D_1 + .003T/P$ (4.349) (-2.899) (-.187) (1.48) (1.108) (.019)	($\underline{R}^2 = .94$)	(5.28)
$Y_2 = -.329 + .435R_2^{*} - .070R_2^{2}{}^{**} - .0005S + .00005I + .584D_2 + .019T/P$ (4.130) (-2.646) (-.203) (.068) (1.281) (.119)	($\underline{R}^2 = .94$)	(5.29)
$Y_2 = -.242 + .456R_2^{*} - .076R_2^{2}{}^{**} - .0004S + .00004I + .060D_3 + .006T/P$ (4.354) (-2.889) (-.149) (.057) (1.527) (-.040)	($\underline{R}^2 = .94$)	(5.30)

*Indicates statistical significance at 99% confidence level.
**Indicates statistical significance at 95% confidence level.
Statistical significance for the regression coefficients is determined by one-tailed t-tests, and the significance of the $\underline{R}^2$ by the F-ratio test.
The t-values are in parentheses under the regression coefficients.

Using equations 5.25 - 5.30 and incorporating the language of hypothesis testing, it is possible to deal with Hypothesis 3. The null hypothesis would be that supporting personnel relative to professional research personnel during the 1965-1970 period did not make a significant contribution to the R and D output of the firms in the drug industry. In addition, the use of these supporting personnel leads to scale economies. The alternative hypothesis is the rejection of the null hypothesis. The appropriate test criteria for this hypothesis are the t-test on the regression coefficient T/P and the simple correlation coefficient between new single chemical entity output and the ratio of supporting to professional personnel. As indicated in Table IX, this regression coefficient is always positive and significant at the 95 percent confidence level for all three equations.[25] In addition, all of the simple correlation coefficients are very high. The null hypothesis is then rejected.

Based on this hypothesis testing, it is concluded that since the passage of the 1962 Drug Amendments supporting personnel have played a very important part in the research effort of the drug industry. It is the importance of these supportive personnel that indicates the most important scale economy available to firms in the industry. The increased record keeping and reporting procedures as required by the new drug regulations may have made it such that these supporting personnel are now very important to the R and D output of the industry. It is likely that the larger firms in the industry will be more capable of

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[25]Comanor found this variable to be always negative with no statistical significance, Comanor, "Research and Technical Change in the Pharmaceutical Industry," p. 189.

establishing specialization and division of labor for these supporting personnel which may allow them to take fuller advantage of these scale economies.

An additional aspect of these results must be entered. For the 1955-1960 period Comanor concluded that the insignificance of the regression estimates when total R and D personnel, R_2, was used was an additional indication that supporting personnel do not increase the productivity of professional personnel.[26] With the present study R_1 appears to be the better input measure, but R_2 still renders the estimates significant, according to the F-ratios, so that this adds weight to the importance of supporting personnel relative to the professional R and D inputs.

This section attempts to ascertain the existence and types of scale economies that might prevail in the R and D activity of the ethical drug industry since the passage of the 1962 Drug Amendments. Comanor relied on his elasticity measures to make certain conclusions about these scale economies, but due to conceptual inconsistencies these elasticity measures are not used in the present study to judge scale economies.

The marginal productivity and output elasticity of R and D inputs for the present study do not indicate the tremendous impact the amendments have had upon the output of new single chemical entities. The marginal product of R and D personnel associated with the output of new single chemical entities has been rendered negative since the passage of the 1962 Drug Amendments.

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[26] Ibid.

The primary indicators of the scale economies of research and development that might exist since the passage of the amendments are the sign of the interaction variable and the significance of the ratio of supporting to professional personnel. The sign of the interaction variable is now positive which may indicate that efficiencies may be gained when both the size of the firm and the scale of R and D activity increase. The importance of the ratio of technical to professional personnel may indicate the kinds of scale advantages that can be obtained as a firm and its research facility become larger.

The preceding factors are offered as the primary evidence in looking at one of the most important aspects of this study--the impact the 1962 Drug Amendments have had on the economies of scale in research in the drug industry. It appears that in carrying on research in the 1965-1970 time period, size (as it relates to the firm itself and to the scale of R and D within the firm) has given rise to certain efficiencies that were not available in the 1955-1960 period.

R and D Output Determining R and D Inputs

The preceding sections of this chapter have indicated that the relationship between the size of the firm and its scale of R and D inputs yields some distinct advantages in the research and development productivity of drug firms. One of the implications of these size and R and D scale advantages is that it may be that it is now the R and D output of the drug firm which allows it to expand its R and D facilities.

According to Comanor's results, this was not the case during the period prior to the 1962 Drug Amendments.[27]

It is anticipated that this type of change has occurred since the passage of the amendments primarily because of the entry barriers that are apparent with the increased strictures of these amendments. The scale economies in R and D that were considered in the previous section indicate that there is a cost disadvantage to smaller firms engaged in this activity. This entry barrier is coupled with the entry barrier of the drug patent which it appears may become more important as the size of firm increases. This follows because larger firms may be more successful at developing new products that provide them with greater monopoly power.

There is evidence that these entry barrier aspects do prevail since the passage of the amendments. Even though small firms have been able to enter with new products during the 1965-1970 period, the economic significance of these products is substantially less than that of larger firms. As shown in Table IX, the economic significance of new single chemical entities is significantly greater for medium and large firms. As discussed previously, this economic significance is determined from the first two year sales of new products and this may or may not be greatly affected by promotional effort.[28] However, since only two year sales are counted, these sales should reflect some of the medical significance of these new drugs as it should take some time before the promotional impact can significantly affect sales.

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[27] Ibid., p. 188.

[28] Ibid., p. 183.

Small firms are faced with two difficulties. First, there are the cost disadvantages that appear to be caused by the 1962 Drug Amendments. Second, these firms must enter any new product from their R and D activity with the expectation of recovering as much of their R and D outlays as possible, and these products may not be of enough medical importance to establish a preferred market position. On the other hand, large firms can concentrate on more medically and/or economically important products which allows them to recover their more substantial research and development outlays.

Thus, it is expected that since the passage of the 1962 Drug Amendments, a cycle that feeds upon itself has been set in motion. As size of firm and R and D intensity (measured by scale of R and D inputs) increase, this generates new patented products which may have more medical and/or economic significance. These factors could establish effective entry barriers that increase the revenues of the firm and possibly its profitability. This increased profitability then allows firms to increase their expenditures on R and D. All of these factors highlight the defensive nature of the R and D competition of the industry that was discussed in Chapter II. From these considerations, it is felt that since the passage of the amendments the structure of the industry has been altered to the extent that not only is R and D output determined by R and D inputs, but R and D inputs are dependent upon R and D output.

To investigate this possibility, two basic lead-lag relationships are utilized. The first one is one in which the R and D inputs lead the R and D output of the industry. The same input-output model is used and an arbitrary period for the R and D output is selected--this being the

period 1968-1970. The number of new single chemical entities produced by firms during this period forms the basis of the sample for the dependent variable. The scale of research inputs is the number of professional personnel the firms had in 1965. Thus, the R and D inputs would lead the output, and this is the relationship consistent with the original determination of the research activity of the industry.[29]

The second relationship investigated is one in which the R and D output leads the scale of the research effort. Again, the basic model is utilized, and the output for the industry is the number of new single chemical entities produced by firms during the period 1965-1967 and represents the relevant dependent variable. The primary independent variable, R_1, is the number of professional personnel the firms had in 1970. This relationship is consistent with the idea it is the output that allows firms to increase their R and D inputs.

The other independent variables of the model are compatible with the previous regression estimates, where S is still the average sales of the firms for the five year period. For consistency I incorporates the R_1 relevant to the lead-lag relationship, and D_1 is based on the time period of the lead-lag dependent variable.

If the second relationship where output leads the R and D inputs is found to be significant, this would indicate another meaningful impact of the 1962 Drug Amendments, and it allows the treatment of Hypothesis 4. Table XI presents the regression estimates for the relationships discussed above.

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[29]Ibid., p. 188.

TABLE XI

LEAD-LAG RELATIONSHIPS FOR 1965-1970

(1968-1970) (1965)

$$Y_2 = -.007 + \underset{(1.788)}{.525R_1^{**}} - \underset{(-2.253)}{.157R_1^{2**}} - \underset{(-1.224)}{.001S} + \underset{(1.440)}{.003I} + \underset{(.922)}{.009D} \qquad (\underline{R}^2 = .47) \qquad (5.31)$$

(1965-1967)

$$Y_2 = .410 + \underset{(4.978)}{.448R_1^{*}} - \underset{(-2.439)}{.525R_1^{2*}} - \underset{(-2.620)}{.012S^{*}} + \underset{(2.587)}{.022I} + \underset{(.794)}{.058D_1} \qquad (\underline{R}^2 = .91) \qquad (5.32)$$

*Indicates statistical significance at 99% confidence level.
**Indicates statistical significance at 95% confidence level.
Statistical significance for the regression coefficients is determined by one-tailed t-tests, and the significance of the $\underline{R}^2$ by the F-ratio test.
The t-values are in parentheses under the regression coefficients.

Equation 5.31 represents the first relationship where R and D inputs lead output, and equation 5.32 represents the second relationship where output leads inputs. Again, one-tailed t-tests are utilized to test the significance of the regression coefficients and the F-ratio to test the significance of the $\underline{R}^2$. In equation 5.31 the R_1 input variables are the only variables significant at an acceptable level--the 95 percent level. The F-ratio indicates the $\underline{R}^2$ is not significant at an acceptable level.

In equation 5.32 the t-test indicates that the linear input variable, the size variable, and the interaction variable are significant at the 99 percent confidence level. The quadratic input term is significant at the 95 percent level. The diversification variable is not significant at an acceptable level. The F-ratio test indicates that the $\underline{R}^2$ is significant at the 99 percent confidence level. The signs of the variables are consistent with the results of the previous regression estimates.

Based on these estimates it is now possible to deal with Hypothesis 4. The null hypothesis could state that since the passage of the 1962 Drug Amendments, R and D output does not determine the scale of research inputs. This is because as the size of the firm and its scale of research activity increase this <u>does not</u> contribute positively to the R and D output of the firm, and because with increasing size the economic and/or medical significance of new single chemical entities <u>is not</u> greater. The alternative hypothesis would be to reject the null hypothesis.

The appropriate criterion to test this hypothesis is the F-ratio test on the $\underline{R}^2$ of equation 5.32. Because this test indicates

significance of the $\underline{R}^2$ at the 99 percent confidence level, the null hypothesis is rejected. It is concluded that Hypothesis 4 cannot be rejected, and the significance of the regression coefficients is presented as supportive evidence.

The rejection of this hypothesis implies that as the size and scale of R and D of the drug firm increase, this increases the firm's output of new single chemical entities which in turn increases its sales which in turn increases its profitability which finally allows the firm to increase its R and D inputs. Thus, the output of new single chemical entities is important in determining the level of R and D inputs of drug firms.

It could be construed that the preceding results support the Schumpeterian hypothesis that large size and monopoly power are necessary to achieve technological advancement. Due to the unique institutional framework of the pharmaceutical industry, this would be a misleading conclusion. The industry is unique in its regulatory aspects which impose institutional restrictions upon the industry. The Schumpeterian hypothesis does not necessarily incorporate any outside institutional factors so that applying this to the drug industry is not really appropriate. The preceding results merely reflect the institutional change that has taken place within the drug industry and the impact this change has had on the R and D activity of the industry.

The present chapter has presented the empirical evidence dealing with the four hypotheses of the study. This evidence is based on an input-output model of research and development which has been estimated using multiple regression analysis. Empirical evidence is presented

which may suggest that the 1962 Drug Amendments have had such an impact that they have caused the marginal productivity of R and D personnel to be negative. Likewise this has forced the R and D elasticities of these outputs to be negative. To reflect the economies of scale of R and D in the drug industry for the 1965-1970 period, empirical evidence is presented which shows that the interaction between the size of the firm and its scale of R and D now positively affects the R and D output of drug firms. Further evidence is presented which indicates the type of scale economies that can be expected since the passage of the amendments, not only does the scale of R and D determine R and D output, but the R and D productivity of the drug firm is instrumental in determining the scale of the R and D activity of the firm. This comes about because firms can use profits from previously developed new single chemical entities to expand their research and development effort.

CHAPTER VI

CONCLUSIONS

The ethical pharmaceutical industry is of special economic interest because it is both highly progressive and it constitutes a major part of the health care industry in the United States. The present study uses an industrial organization framework to investigate a specific aspect of the institutional makeup of the industry and how a change in this makeup has affected the research and development activity of the industry.

The tremendous economic impact of the 1962 Drug Amendments has been identified in previous studies, and the present study attempts to elaborate on this impact as it affects the productivity and scale economies of drug research and development. To investigate this impact, the productivity and scale economy conditions of the industry prior to the passage of the 1962 Drug Amendments are summarized. These conditions are then used to make appropriate comparisons with a period sufficiently after the enactment of the amendments to allow the full effects of the amendments to become evident. A multiple regression technique is the major method of analysis for this study.

Four hypotheses are offered to investigate the impact of the 1962 Drug Amendments on the productivity and scale economies. The multiple regression model that is used is one in which the R and D output of drug firms is determined by the scale of research inputs, the size of the firm, the interaction between the size of the firm and the scale of

research, and diversification. The model is found to be significant when the relevant output variable is the number of new single chemical entities firms introduced during the period 1965-1970.

This multiple regression analysis is used to test the four hypotheses of the study. The first hypothesis states that since the passage of the 1962 Drug Amendments, the marginal productivity of professional R and D personnel has become negative. This is expected because of the increased testing, reporting and record keeping that are required by the amendments. This activity has diverted the effort of these personnel thus causing their productivity to become negative. The marginal productivities and the output elasticities of R and D personnel for three arbitrary class sizes of firms are computed, and these measures indicate that the marginal productivity of R and D personnel has become negative since the passage of the 1962 Drug Amendments. However, the marginal productivities and elasticities are based on the output being measured as new single chemical entities and the input as the number of professional R and D personnel. These are somewhat limiting in that they do not totally account for the research and development activity of drug firms.

The second hypothesis deals with the economies of scale of drug research and development that may be apparent since the passage of the amendments. This hypothesis states that since the 1962 Drug Amendments, specifically during the 1965-1970 period, the interaction between the size of the firm and its scale of R and D has become a positive influence on the R and D output of the firm which indicates that economies of scale are present. For this study economies of scale

relate only to research and development, and it means that a proportionate increase in all R and D inputs results in a greater than proportionate increase in R and D output.

Two primary pieces of evidence are used to test this hypothesis. First, it is hypothesized that the sign of the interaction variable is positive rather than the previously observed negative sign. The sign of this variable is positive and this indicates that as both the size of the firm and its scale of research increase together, larger firms may now experience R and D efficiencies not previously experienced. This change in the sign of the interaction variable may reflect the fact that as size and R and D increase there may be increasing efficiencies that come from using more R and D personnel--both professional and technical--and efficiencies may be gained from such things as specialization of labor, more and larger laboratory equipment, computer facilities, and other scale benefits that may arise. It would appear that many of these scale factors are important in complying with the provisions of the amendments as laid out in the 1963 New Drug Regulations.

The second place of evidence relating to the scale economies issue is contained in Hypothesis 3 and it expresses the type of economies of scale that can be expected since the enactment of the 1962 Drug Amendments. It is hypothesized that supporting personnel are now important contributors to the R and D output of drug firms. This is tested by introducing an additional variable into the regression equations; this variable is the ratio of supporting to professional R and D personnel. A positive sign and the statistical significance of the regression coefficient are offered as supportive evidence for this hypothesis.

The last effect of the amendments on drug R and D is depicted in the fourth hypothesis, and it gives an additional clue to the size advantages that may now be available. With the passage of the 1962 Drug Amendments, not only do the R and D inputs determine the level of R and D output, but the reverse is also true. R and D output is now an important determinant of the scale of research activity of the drug firm. This hypothesis is tested by employing two basic lead-lag relationships. The first states that with a regression equation that has the output at the end of the period being determined by the inputs at the beginning of the period would indicate that the hypothesis is not supported. A regression equation that has the output at the beginning of the period being determined by the inputs at the end of the period would indicate the hypothesis can be supported. The first equation is not statistically significant whereas the second is which gives support to the hypothesis.

In dealing with these four hypotheses it is concluded that the 1962 Drug Amendments have had a significant impact on the research and development effort of the drug industry. This impact may be very important in making firm size and the scale of the research and development facility more predominant in determining the R and D productivity of the industry.

This is principally a positive study. In presenting the supportive evidence on the four hypotheses, this study suggests that the 1962 Drug Amendments have heightened the entry barriers of doing research and development in the ethical drug industry. This would explain why the development of new drugs has become increasingly concentrated in the

larger drug firms since 1962.[1] Also, the supporting of the fourth hypothesis gives direct evidence of the type of heightened entry barriers that might prevail in the drug industry.

These conclusions do not necessarily imply that an effective degree of competition may not exist in the drug industry, but they do suggest the notion that when an institutional change is imposed on an industry, it must be recognized that this change can significantly alter the structure of that industry. It appears that the 1962 Drug Amendments have altered the structure of the United States ethical drug industry.

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[1]Jadlow, pp. 175-183.

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APPENDIX

In Chapter IV the size of the pharmaceutical firm was defined as the ethical drug sales for that firm. In those cases where there was a parent corporate entity with one or more subsidiary units, the total pharmaceutical sales of that corporate entity determined the size of each subsidiary unit. All of the other variables were specifically identified with the individual subsidiary units. These definitions determined the values of the observations that were used in the regression estimates in Chapter V.

As an alternative, the size of firm is redefined so that the sales of the individual subsidiary units determine the firm size. All other variables are measured relative to the subsidiary unit. Regression estimates were computed based on this redefined measure of firm size.

Table A-I summarizes the results of these analyses. Equation A.1 is the estimated relationship that is presented in Chapter V where firm size is defined as the ethical drug sales of all the subsidiaries of the parent. Equation A.2 is the estimated relationship where the size of the firm is measured as the ethical drug sales of the individual subsidiary unit only. As shown there is no significant difference between the two regression equations.

The regression analyses that were performed in Chapter V and are exemplified in equation A.1 of Table A-I revealed that the residual associated with Central Pharmacal was relatively high. In order to evaluate the impact of this high residual, the regression estimates are

TABLE A-I

ALTERNATIVE REGRESSION ESTIMATES FOR 1965-1970 PERIOD

Total sample--size defined as sales of total corporate entity. (See Chapter V.)

$$Y_2 = -.046 + \underset{(4.349)}{.4496R_1^*} - \underset{(-2.237)}{.503R_1^{2}}{}^{**} - \underset{(-2.210)}{.008S^{**}} + \underset{(2.212)}{.017I^{**}} - \underset{(1.884)}{.083D_1^{**}} \qquad (\underline{R}^2 = .89) \qquad (A.1)$$

Total sample--size defined as sales of subsidiary units only.

$$Y_2 = -.016 + \underset{(3.996)}{.477R_1^*} - \underset{(-2.169)}{.569R_1^{2}}{}^{**} - \underset{(-2.101)}{.011S^{**}} - \underset{(2.663)}{.023I^{*}} + \underset{(1.949)}{.085D_1} \qquad (\underline{R}^2 = .90) \qquad (A.2)$$

High residual removed--size defined as sales of total corporate entity.

$$Y_2 = -.040 + \underset{(12.825)}{.284R_1^*} - \underset{(-2.901)}{.140R_1^{2}}{}^{*} - \underset{(-2.631)}{.002S^{*}} + \underset{(2.496)}{.004I^{*}} + \underset{(1.509)}{.014D_1} \qquad (\underline{R}^2 = .99) \qquad (A.3)$$

High residual removed--size defined as sales of subsidiary units only.

$$Y_2 = -.064 + \underset{(12.438)}{.305R_1^*} - \underset{(-3.438)}{.188R_1^{2}}{}^{*} - \underset{(-2.820)}{.003S^{*}} + \underset{(3.634)}{.007I^{*}} + \underset{(1.725)}{.016D_1^{**}} \qquad (\underline{R}^2 = .99) \qquad (A.4)$$

*Indicates statistical significance at 99% confidence level.
**Indicates statistical significance at 95% confidence level.
Statistical significance for the regression coefficients is determined by one-tailed t-tests, and the significance of the R^2 by the F-ratio.
The t-values are in parentheses under the regression coefficients.

computed with the Central Pharmacal observation removed. Equation A.3 is the regression estimate where this high residual observation has been removed and where the size of firm variable is designated as the pharmaceutical sales of the total corporate entity. Equation A.4 is the regression estimate in which the high residual observation has been removed and the size of firm variable is designated as the sales of the subsidiary unit only.

The removal of the high residual observation has the effect of reducing the magnitude of the regression coefficients. Those cases in which the observation is removed also has the effect of raising the values of the $\underline{R}^2$'s. Even though there is improvement in the regression estimates when the high residual observation is removed, there is no apparent justification for not including this observation. Thus, the analysis presented in Chapter V is based on equation A.1 in Table A-I.

As indicated in Chapters IV and V, the production function associated with the output of new single chemical entities can be generally expressed as:

$$Y = a + bR - cR^2, \qquad (A.5)$$

where the values of a, b, and c are derived from the estimates of the regression coefficients shown in equation A.1. Using equation A.5, it is possible to compute the marginal productivity of professional R and D personnel, the output elasticity of these inputs, and the critical value of their use. The critical value being the number of personnel where the production function reaches a maximum, thus forming the boundary between Stages II and III of production.

The regression equations A.2 - A.4 found in Table A-I thus allow alternative computations of the marginal productivities, elasticities of

output, and critical values of professional R and D inputs. Table A-II summarizes these computations for each of the regression equations. Redefining the size of firm does not alter these measures to a significant degree. The removal of the high residual observation does have some effect on these measures, and this effect is most noticeable for small firms where the marginal productivities are positive. However, as was the case in Chapter V, the values of the marginal productivity of professional R and D personnel is close to zero.

The greatest effect of these alternative regression estimates is seen with the critical value computations. These reveal that, for small firms, the actual average levels of professional R and D personnel are well within the Stage II-Stage III boundary when the alternative regression estimates are used. As was found in Chapter V, medium and large sized firms are operating in Stage III. It should be noted that there is no way of telling how the actual average values of professional R and D personnel for small firms relate to Stage I of production. It could very well be that these small firms are operating in Stage I.

Figure 4 depicts the relationships of the actual average levels of professional R and D personnel to their critical values for each of the alternative regression estimates. Point A is the actual average value of R for small firms when size is defined as the sales of subsidiary units only. Point B is the critical value of R under this definition. As indicated, the actual value is well below this critical value. Point C is the actual average level of R for medium firms under this definition, and D is the computed critical value. Point E is the actual average value of R for large firms and F is the critical value. For

TABLE A-II

ALTERNATIVE MARGINAL PRODUCTIVITY, ELASTICITY, AND CRITICAL VALUE ESTIMATES

Selected Sample	Marginal Productivities ($\partial R/\partial Y$)			Elasticities ($\partial R/\partial Y \cdot R/Y$)			Critical Values of R_1		
	Large	Medium	Small	Large	Medium	Small	Large	Medium	Small
1. Total sample--size defined as sales of total corporate entity. (See Chapter V.)	-.096	-.079	-.00075	-5.689	-2.174	-.015	220.3	92.9	48.1
2. Total sample--size defined as sales of subsidiary units only.	-.059	-.118	-.012	-13.493	-17.865	-1.26	263.7	206.6	89.8
3. High residual observation removed--size defined as sales of total corporate entity.	-.017	-.008	.015	-1.413	-.319	.333	254.7	143.7	103.0
4. High residual observation removed--size defined as sales of subsidiary units only.	-.016	-.026	.011	-.020	-.039	.018	272.0	134.0	83.8

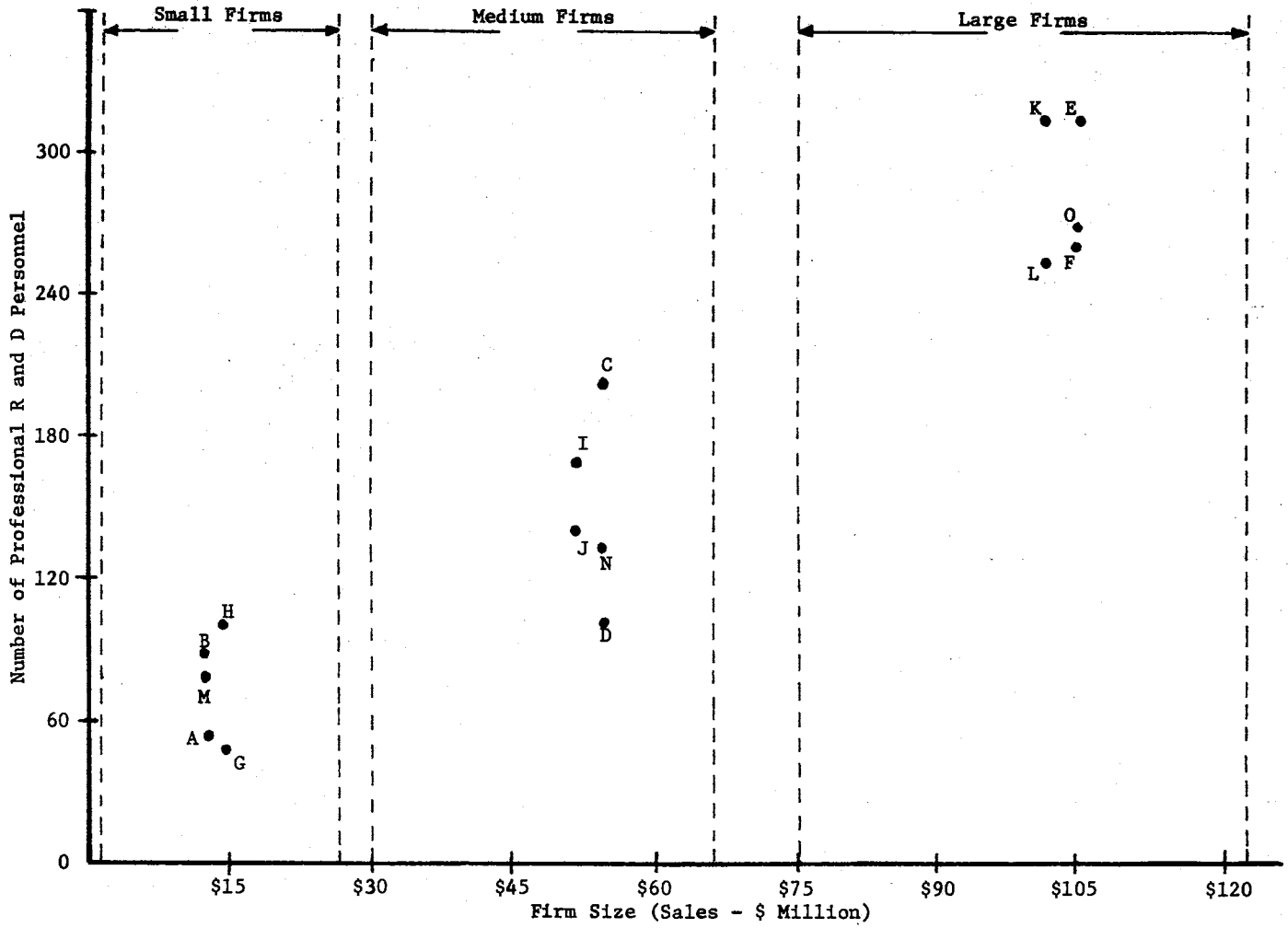

Figure 4. Comparison of Critical Values with Actual Average R Values for Alternative Regression Estimates

medium and large firms the average values are well above the computed critical values.

Point G is the actual average value of R for small firms when the high residual observation is removed and when size is defined as the sales of all subsidiary units combined. Point H is the computed critical value for this definition. Again, the actual average is below the critical value. Point I is the actual average value for medium firms under this definition, and point J is the computed critical value. Point K is the actual average for large firms, and L is the computed value for these firms.

Point A also represents the average value of R for small firms when the high residual observation is removed and when size is defined as the sales of each of the subsidiary units. Point M is the computed critical value for this regression estimate. As with the two previous cases, the average value is less than the computed critical value. Point C is the average value of R for medium sized firms and N is the computed critical value. E is the average for large firms and O represents the computed critical value.

With the exception of the computations associated with small sized firms, the preceding results are essentially the same as those presented in Chapter V. For the most part there is no difference between the regression equations A.1 and A.2 in Table A-I. The computations of marginal productivities, elasticities, and critical values associated with these two regression estimates are also essentially the same. The regression equations with the high residual observation removed do have the same impact on the results, but there is no apparent justification for removing this observation.

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