PATENTS IN THE ANTIBIOTIC INDUSTRY

MICHIGAN STATE UNIVERSITY

PETER M. COSTELLO

1966

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ABSTRACT

PATENTS IN THE ANTIBIOTIC INDUSTRY

by Peter M. Costello

The thesis explores questions of price and product competition in the antibiotic segment of the ethical drug industry under the influence of product patents. The industry is examined from the early 1940's through 1960 in an attempt to delineate the affects of patents on technical progress, pricing, and on the competitive behavior of firms.

Major sources of data were: (1) The Hearings and Reports of the Senate Subcommittee on Antitrust and Monopoly, (2) briefs and related papers from the Federal Trade Commission v. American Cyanamid Company, et al., case, (3) interviews with the research directors of several antibiotic producers.

The major conclusions of the study were: (1) the narrow spectrum antibiotic market was highly competitive in terms of price and product innovation, while in the broad spectrum market competitive forces were suppressed. The shift in the character of the market was accomplished through the utilization of product patents to exclude entry, refusal to sell in the bulk market, forward integration into direct selling, and collusion among five of the major sellers of broad spectrum antibiotics. (2) The discovery of the broad spectrum drugs

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was the direct result of the invention of a method of inventing, and competitive pressure on profit margins in the narrow spectrum market. With the establishment of patent monopolies the rate of significant antibiotic innovations declined. (3) Tetracycline, the last major broad spectrum drug discovered, was probably not patentable over its substitute chlortetracycline. As a result its corporate inventor found it necessary to practice misrepresentation in the Patent Office to secure the patent thereby preventing unrestricted entry and price competition. (4) In the broad spectrum market entry in the form of substitute products caused the price leader to adjust prices downward. The resulting increased size of the market allowed rivals sufficient sales volume to reach an efficient level of production. The behavior prevents the appearance of price competition and is an alternative to collusive agreements. With the innovation of tetracycline the collusive agreement was substituted for price adjustments. (5) Recent changes in public policy ought to have some effect in improving certain dimensions of the industry's performance. But substantive improvement can only occur with basic changes in the patent statutes.

PATENTS IN THE ANTIBIOTIC INDUSTRY

By

Peter M. Costello

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INTRODUCTION

The 1961 report by the Senate Subcommittee on Antitrust and Monopoly[1] on the practices and performance of the ethical drug industry, is the fourth in a series of investigations of major American industries. While the investigation of the steel industry drew its importance from the basic importance of steel in an industrial economy, ethical drugs draw their importance from their position as a determinant of the health and productivity of human resources. The industry in its invention and innovation of new drugs has been an important factor in relegating certain diseases, such as typhus and typhoid, to the category of medical curiosity. In the case of many other diseases, the period of institutional care has been sharply reduced. In this industry where the basis of its social contribution lies in the productivity of its investment in research and development; where with the innovation of a new drug, market demand grows rapidly and is generally not discouraged by price; where the initial price may be set relative to what the market will bear before competitive substitutes enter; and where the ". . . industry uses the same promotional devices that other businesses use to insure that its new product is used as

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[1]U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Report, Administered Prices, Drugs, Report No. 448, 87th Cong., 1st Sess., 1961.

widely and as soon as possible,"[2] a situation has developed in which the majority of the Subcommittee found much to criticize.

The major conclusions of the Subcommittee can be summarized in the following six points: (1) The patent has been used as a device to restrict domestic and international competition in drugs. By preventing or delaying entry, the firm holding a product patent is in a position to exploit the domestic market and to divide world markets under the guise of the patent. Licensing, which results in duopoly, has often been the result of inadequate manufacturing or sales facilities, while oligopoly has often resulted from simultaneous discoveries. Licensing does not result in price competition nor does it preclude attempts at product differentiation through advertising. (2) Specialization in research and development in combination with patents has led to a high degree of seller concentration in manufacturing, but lower concentration in selling. This, the Subcommittee felt, reflected the major firm's attempt to market a "full line" of drug products indicating that economies of scale may be present in the selling activity. This has led to cross licensing agreements to sell but not to manufacture drug products and accounts for the difference in the levels of concentration. (3) Since the mid-1950's, drug manufacturers have failed to develop significant new drugs although the number of so-called new drugs has increased considerably.

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[2]Dr. Walter Modell, "Hazards of New Drugs," The Wall Street Journal (April 29, 1963).

The majority of the Subcommittee argued that this development was due to excessive allocation of research personnel to patent circumventing research and away from the higher-risk basic research. By marketing a close substitute, the firm's advertising potential could be brought to bear, thereby insuring a share of the market. (4) Both the quality and quantity of the industry's advertising efforts came under sharp criticism. The control over the advertising to physicians through the Food and Drug Administration was termed inadequate. (5) In the matter of price, the Subcommittee compared prices in four product markets with manufacturing costs, prices in foreign countries, and prices of smaller firms where such existed. From such comparisons it was concluded that prices were excessive. (6) In the examination of profit data, the comparison between the rates of profits of the largest drug firms with all manufacturing firms, provided the basis for the conclusion that profit rates in the industry were excessive.

The majority conclusions were debated by representatives of the industry in testimony before the Subcommittee.[3] The essence of the industry's argument was that there has been significant progress in drug therapy as a result of the

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[3]The minority of the Subcommittee did, of course, present criticism of the conclusions of the majority. Unfortunately, their arguments are not well-developed and so dispersed with appeal to non-economic factors (the present Italian law is a product of the Mussolini regime and is hardly one for us to emulate, Subcommittee Report, op. cit., p. 320), as to make them unconvincing. Hence, the industry arguments are developed largely from the Hearings.

patent system. The investment in research in a competitive economy is inherently fraught with risk. These risks fall into three categories. First, there is the risk that the research program will not result in a marketable product. Second, that several firms may discover essentially the same product at the same time. Such a contingency will involve cross-licensing, market sharing, and price competition. Third, that the probability is high that a new drug product will be rendered obsolete within five years of discovery. Thus, product patent protection is necessary to allow firms to recover their past research expenditures through the sale of their innovations.

On the matter of selling costs, the industry argues that relatively large expenditures are necessary to provide a continuous source of information to the physician on new drug products as well as up-to-date information on older products. The size and scope of this activity were held to be essential in maintaining the rapid improvements in the health of the population.

Relative to the charge that the industry's rate of new drug introductions has declined since the mid-1950's, the industry offers two counter arguments. First, that the Subcommittee lacks the technical competence to decide what is, and what is not a significant new drug. Second, in the last twenty years the numbers of new drugs marketed by United States drug manufacturers is significantly greater than by any other country.

Profits are admittedly high --but two factors are offered for consideration on this point. First, the risk of failure in the drug industry is significantly higher than in other industries, hence the rate of return must be greater to attract investors' funds to maintain the level of research spending. Second, that to compare the rate of return to the firm's net worth is not a meaningful measure of the firm's profitability. The significant asset is not capital but rather the scientific staffs. Thus, the better measure is to compare earnings to sales. The logic of the argument here is that if scientific personnel could be treated as an asset this would increase the net worth of the firm and thereby reduce the rate of return. Failing this, earnings to sales are offered as a substitute which accomplishes the same end--reduces the rate of return.

The essences of the arguments focuses on the role of patents. The industry maintains that patents provide the incentive to invest in research which leads to increasingly higher levels of productivity, and that product competition provides a check on monopoly positions established through patents. The Subcommittee argues on the other hand that the patent has the effect of decreasing the level of industry productivity and that product competition is not an efficient check on patent monopolies. The role of the patent then is the heart of the issue.

This study examines the role of patents in its effect on competition. It also will inquire into the traditional

rational of the patent as a device to stimulate investment in research and development. The issue is whether a structure of monopoly or competition tends to yield high levels of technological progress.

In examining these and related questions, two approaches are possible. First, the data developed by the Subcommittee could be reorganized and reworked to test the accuracy of the conclusions. The second approach is a detailed analysis of a particular segment of the ethical drug industry to test the accuracy and applicability of the Subcommittee's conclusions. Within the limits of the available data, the latter approach is followed. The segment of the industry chosen for intensive analysis is the antibiotic sector. The reasons for selecting this particular segment of the industry are: (1) it accounts for the largest dollar volume of sales in the industry, (2) it exhibits a clear contrast between structure and performance under competitive and monopolistic conditions, (3) the conduct with respect to patents can be clearly indicated, and finally (4) the general body of data available is considerably greater than in other segments.

The plan of this study is as follows. Chapter I traces the history of the antibiotic industry from the discovery of penicillin in England, through commercial development in the United States under federal government sponsorship, and up to the discovery of streptomycin. In this period, the patent appears as a minor determinant of industry

conduct. While certain modifications of the basic penicillin drug were patented, and streptomycin with its modification, dihydrostreptomycin, were fully protected by patents, the market for these drugs was essentially competitive. The competitive character of the market was largely a result of the structure of the industry during this period. That is, there was generally separation in drug production from marketing. With the development of forward vertical integration by producers, through merger as well as internal growth, the full potential of the patent as a device to monopolize was realized and utilized. With the discovery of the broad spectrum antibiotics, the patent as a device to exclude entry reached its height.

Chapter II is concerned with the technology of antibiotic research. Here the questions are, what are the characteristics of antibiotic research, where is the research activity located, who discovered these drugs and what was the significance of the various discoveries? The thesis of this Chapter is essentially that the development of a soil screening technique at Rutgers University placed at the disposal of the industry a research technology that was capable of being employed on a mass production basis by relatively unskilled individuals. The resulting discoveries of the broad spectrum antibiotics were a different sort of discovery than that envisioned as rewardable by a grant of monopoly.

The third Chapter analyzes the patent proceedings which led to the securing of the patent on tetracycline. By

the mid-1950's, the value of the exclusive market had been clearly demonstrated. The appearance of tetracycline as a substitute for two established broad spectrum drugs threatened to open the market to competitive entry. The Federal Trade Commission case against five of the six major antibiotic sellers provides the information on the importance of the patent and the extent to which these firms were willing to go to insure the issuance of this patent.

Questions concerning Patent Office proceedings are raised as is the question, should the tetracycline patent have been issued, and did it meet even the Patent Office's rather low standards of invention? In addition the writer raises the basic question of whether any of the broad spectrum antibiotics met the standards of invention in light of the importance of the soil screening technology.

Chapter IV takes up the foreign and domestic licenses which followed the issuance of the tetracycline patent. Were these licenses restrictive to the extent that prices could be controlled? Did they restrict entry in a manner that allowed the development of a cartel in world markets? Does the existence of these agreements explain the apparent differences in drug price among different countries?

Chapter V is an analysis of antibiotic pricing. A utility theory is used to explain the setting of initial prices on new drugs as opposed to some form of target pricing. The Cournot duopoly model is used to explain the type of pricing which develops with entry. The overriding consid-

eration in pricing is found to be joint industry profit maximization, at least with respect to the prescription market. Here also an attempt is made to estimate the competitive price of tetracycline, which in turn is used to estimate the monopoly revenue available to these producers.

The following chapter examines the technological advance of the industry as well as the antibiotic producers. A sample of the largest firms in the industry is selected to test the relationship between research and development expenditures, technological advancement, and size. Here the question is, does monopoly insure a higher rate of new drug discoveries?

The final chapter is largely concerned with specific public policy proposals that have been advanced to improve the performance of the industry. These proposals are examined in increasing order of their effectiveness in improving industry performance.

CHAPTER I

ORIGINS OF THE ANTIBIOTIC INDUSTRY

This chapter traces the early history of the antibiotic industry from the discovery of penicillin in 1928 to the marketing of the broad spectrums in 1956. The chapter is divided into four parts. The first is concerned with the discovery and development of penicillin in England up to 1941. The second covers the efforts of the British researchers and the federal government in securing large scale production. The following section describes the efforts of the Committee on Medical Research and the War Production Board in developing manufacturing capacity in penicillin. The final section discusses the penicillin market structure in its effects upon prices, technological progress, and forward integration.

DISCOVERY AND DEVELOPMENT OF PENICILLIN

The discovery and early development of penicillin can be dated from Fleming's discovery of the antibacterial properties of one of his cultures in 1928, up to 1941 when Florey and Heatley came to the United States in a search for commercial suppliers. This period is primarily concerned with Fleming's work which led to discovery, and with the work of a research group at Oxford College who advanced Fleming's findings to the stage where the clinical effective-

ness of the drug was proven.

Fleming's Research.--This history of discovery begins during the First World War in the search for an antiseptic effective in the treatment of wounds. The search by Fleming, as well as others, was for a substance that would destroy bacteria, leaving tissue unharmed. The research was unproductive in providing a solution, but Fleming continued this work after the war.[1]

In 1928, while employed as a bacteriologist at St. Mary's hospital in London, Fleming succeeded in isolating penicillin. His technique in this series of experiments was to grow cultures of bacteria on plates. When the growth was well advanced, the antiseptic substance was introduced and its effect observed. This set the stage for the accidental contamination of a plate containing a highly developed culture. Normally contamination would have meant the discarding of the culture, but Fleming noted that the bacteria were being destroyed by the contaminating substance. Further work enabled him to isolate the bactericidal substance and identify it as Penicillin rumbrum. In addition, Fleming was able to establish the range of antibacterial activity of his broth, to indicate that it was not toxic to tissue in laboratory animals, and to develop a method of producing the penicillin broth.[2]

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[1]H. W. Florey et al., Antibiotics (London: Oxford University Press, 1949), II, 631.

[2]Ibid., 631-33; also H. T. Herrick, Antibiotics (Brooklyn: Chemical Publishing Co., 1949), pp. 9-15; and Alexander Fleming, Penicillin, Its Practical Application (London: Butterworth & Co., Ltd., 1950), pp. 1-25.

There were, however, certain problems involved with penicillin research that Fleming was unable to solve. First, and of major importance, was the fact that Fleming's method of producing the broth gave quite low yields which limited the amount of the drug available for experimental purposes. Second, was the inability to extract the active substance from the broth. This, combined with the low yields per liter of broth, required large amounts of broth to be produced for each experiment. Finally, the potency of the broth was highly unstable which made comparative tests of its effectiveness difficult.[3] Of these problems, it was the first that regulated penicillin to the status of a laboratory curiosity. Writing in 1940, Fleming said

> we have been using it in the laboratory for over ten years as a method of differential culture. It was used in a few cases as a local antiseptic, but although it gave reasonably good results, the trouble of making it seemed not worthwhile. [4]

Thus, a problem in production became the critical element that remained unsolved in Fleming's research. The discovery that was to provide the foundation for a $360 million industry by 1953 lay relatively unknown in a series of articles in the British Journal of Experimental Pathology.

Florey's Research.--In 1938 interest in antibacterial substances developed at Oxford College's William Dunn School of Pathology. By 1939, Florey and Chain had advanced the

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[3] Florey, op. cit., pp. 633-34; Fleming, op. cit., pp. 11-12, 26-27.

[4] Florey, op. cit., p. 633.

research to the point where an application for funds was filed with the Rockefeller Foundation in New York.[5]

During this period, Fleming's work came to the attention of the Oxford group. The review of the literature turned up confirmations and extensions of Fleming's experiments, but in general the problems that limited Fleming's research on penicillin also limited others.

The Oxford group was finally successful in extracting penicillin from the broth.[6] The extraction of the active substance meant that the potency or stability of the compound was measurably increased, and with the development of assay technique, comparisons and correlations of penicillin samples against bacteria could be made.[7]

In May 1940, the first tests on laboratory animals were carried out which demonstrated the chemotherapeutic properties of penicillin. These results led to further investigations of increased scope with the first patient treated in January 1941. But in these early clinical trials, the problems of sufficient quantities of penicillin were critical. Here the supply restraint was of sufficient importance to limit the patients receiving the drug to children, in the hope that less of the drug would be required to demonstrate and test its effectiveness. In spite of this problem, clinical tests did demonstrate that penicillin was effective in

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[5]Florey, op. cit., p. 636.

[6]Florey, op. cit., p. 638.

[7]Florey, op. cit., p. 637.

treating seriously ill patients in cases where surgery and other drugs were not effective. In addition, these trials showed that penicillin was non-toxic to human tissue.[8]

It is apropos at this point to indicate the contributions of the Oxford group as it was their successes which, to a large degree, stimulated government and commercial interests in the production of penicillin. In this regard it could be said that this group was responsible for the development of penicillin to the state of a "workable drug." Or in slightly different terms they were able to "reduce to practice" the discovery of Fleming. This group was able to solve certain of the technical problems associated with Fleming's discovery and as a result were responsible for taking penicillin out of the realm of a laboratory curiosity. But with success there was also failure. The Oxford group was still faced with the problem of low yields from their broths and it was to this problem that they turned their attention in mid-1940.

In turning to the question of large-scale commercial production of penicillin, the Oxford group had developed a technique for the production of the broth. This technique required a large number of shallow pans to contain and grow the culture medium. These culture mediums were injected with the penicillin mold and growth or fermentation was allowed to take place on the surface of the medium. After a period of some ten days the culture was harvested and the penicillin

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[8]Florey, op. cit., pp. 638-649.

salts drawn off. The process was highly labor intensive, as each pan had to be prepared, injected with the penicillin mold, and finally harvested. In addition, the low yields per liter of broth resulted in high unit value, although we have no estimate of the actual cost. The British chemical firm first approached on the question of large scale production was evidently unable to undertake the necessary research leading to mass production due to supply and personnel restriction resulting from the war.[9] It was in this period that the "battle of Britain" was at its height.

The war in England and the resulting strains on British manufacturing capacity and transportation system led to the decision to attempt large-scale production in the United States. Thus, in July 1941, Florey and an associate, N. G. Heatley, brought to the United States samples of the cultures used in the production of penicillin along with the technical problems of mass production.

It is of interest at this point to attempt an estimation of the costs of the early research on penicillin. Four institutions provided funds to the Oxford group and Florey provides the amounts received from three of these institutions. First, there was the Rockefeller Foundation which between 1940 and 1945 provided $24,560. Second, the Medical Research

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[9] H. W. Florey and E. P. Abraham, "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, VI, No. 3 (1951), 306, cited in Federal Trade Commission, Report on Antibiotic Manufacture (Washington: 1958), Appendix II, p. 310. Hereafter cited as FTC Report.

Council between 1939 and 1945 provided $33,148; and third, the Nuffield Provincial Hospital Trust which provided $22,584 between 1943 and 1945. In addition, Oxford College paid some salaries of the research group as well as the costs of laboratory materials. But of this latter contribution no estimate is provided.[10] The total cost of the research program can then be estimated at about $100,000. That is, $80,290 from the figures provided by Florey and something less than $20,000 provided by Oxford College. There is no estimate of the costs of the research work of Fleming, but one would expect that the sum involved was quite small.

Of the estimated $100,000 cost of penicillin research in England, not all can be allocated to penicillin directly. In the latter years of this period the scope of the Oxford group's research expanded in the search for other substances with properties similar to penicillin.[11] As an estimate a figure of $75,000 is suggested as the cost of reducing Fleming's discovery to practice.

Two conclusions are suggested at this point. First, the data on the costs of penicillin research support the observation that the costs of basic or pure research are generally low relative to other stages in the process of innovating.[12] Here we have classified the research of the

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[10] Florey et al., Antibiotics, pp. 669-70.

[11] Ibid.

[12] See for example the statement of D. Novick, in U.S. Congress, Senate Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, 86th Cong., 2d Sess., 1960, Part 18, p. 10513; and J. Jewkes, D. Sawers, and R. Stillerman, The Source of Inventions (London: Macmillan & Co., Ltd., 1958), pp. 76, 82-90.

Oxford group as basis. The second conclusion is more in the nature of an observation. The process of discovery is the product of the contribution to the stock of knowledge of many individuals. Directly involved in the discovery process of penicillin was not only Fleming and the Oxford group, composed of some twelve individuals and ten assistants,[13] but others who repeated and confirmed Fleming's experiments following their publication. Indirectly involved were those individuals who contributed to that stock of scientific knowledge necessary to those more directly involved.

DEVELOPMENT OF PENICILLIN IN THE UNITED STATES

The development of penicillin in the United States coincides with the visit of Florey and Heatley in July 1941 up to 1943 when significant quantities of the drug were first produced. This phase of the history of the antibiotic industry involves federal government sponsorship through the Office of Scientific Research, the War Production Administration, and the Northern Regional Research Laboratory of the Department of Agriculture. Private support was provided by several drug firms as well as hospitals and universities which became involved in the clinical phases of the program.

Government Interest in Penicillin.--In June 1941, the Committee on Medical Research was formed under the Office of Scientific Research and Development. (These are hereafter referred to as the CMR and the OSRD.) The function of this

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[13]Florey et al., Antibiotics, p. 639.

committee was to ". . . initiate and support scientific research on medical problems affecting the national defense."[14] By September 1941 this committee was convinced of the value of Florey's research and agreed to expedite the production of penicillin. In October, the first of a series of meetings was held between the committee and representatives of four pharmaceutical firms. The purpose of the meeting was to discuss the possibilities of a co-operative research program between Merck, Squibb, Pfizer, and Lederle Laboratories, a subsidiary of American Cyanamid, with the committee acting as a co-ordinating agent.[15]

In December a second meeting was held in which the Committee was able to secure an agreement from these four firms ". . . to put their research teams or a fraction of them on the problem. As a result we began to get a trickle of a supply of penicillin during the early months of 1942."[16] Further, the agreement provided that any research results or information would be turned over to the Committee for dissemination among the firms involved in the program. This was in accord with the Committee's goal of a maximum production of information on the potential of penicillin.

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[14]FTC, Report, op. cit., p. 34.

[15]U.S. Congress, Senate, Subcommittee of the Committee on Military Affairs, Hearings Before the Committee on S. 1297, 79th Cong., 1st Sess., 1945, Part 3, pp. 461-62; FTC, Report, op. cit., p. 36 and Appendix, pp. 321-26.

[16]FTC, Report, op. cit., p. 36.

Commercial Interest in Penicillin.--It appears that commercial interest in penicillin did not develop until the first meeting held between the CMR and the four drug firms in October. Up to 1940 we have no indication of commercial interest. Charles Thom, in 1945, noted that

> survey of laboratory correspondence during the period from 1933 to 1940 shows that requests for Fleming's organism came from a number of great laboratories engaged in bacteriological research, but not from the pharmaceutical manufacturers. 17

But Merck in its 1943 Annual Report stated that it had begun studies of penicillin in the fall of 1939.[18] And Pfizer in 1940 began the support of penicillin research at Columbia University as a result of the published reports of the Oxford group.[19] The effect of this early research on these firms' ability to later produce penicillin is of course tenuous. But it can be noted that in the period 1943-45, Merck and Pfizer built two of the largest three plants for penicillin production,[20] and that for the first four months of 1944 they were the largest producers in the market.[21] Thus there is the possibility that this early research

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[17]Statement of Charles Thom, quoted in FTC, Report op. cit., Appendix II, p. 317. It must be noted, however, that Merck in its 1943 Annual Report stated that it had begun studies of penicillin in the fall of 1939, but there is no evidence that anything came of this in the form of being in a position to begin production in the 1940-43 period. FTC, Report, op. cit., Appendix II, p. 317 and n. 64.

[18]FTC, Report, op. cit., Appendix II, p. 317 and n. 64.

[19]Florey et al., Antibiotics, op. cit., p. 650.

[20]See Table 2, p. 32.

[21]FTC, Report, op. cit., Appendix II, p. 331.

indicated the profit possibilities in penicillin production for Merck and Pfizer, and that this realization led in part to the decision to invest in penicillin capacity. But there is little doubt that government interest in penicillin production played a key role.

While government interest, as well as the early research by Merck and Pfizer, provided stimulants to penicillin production, the visit to the United States by Florey and Heatley had a disseminating influence. In search of a supplier of penicillin to their laboratory in England, these men visited both government and private laboratories in the United States and Canada. Florey is reported to have spoken with the representatives of the following firms: Merck, Squibb, Lederle, Lilly, Johnson and Johnson, Eastman Kodak, and Connaught Laboratories of Canada.[22] Of these firms, the latter three did not become involved in the penicillin program that later was to develop and three firms were reported to have expressed a serious interest in the problem. They were: Merck, Squibb, and Pfizer.[23] There is no evidence of how Pfizer came into contact with Florey as this firm was not included in his list. The most likely explanation is that contact was made through the Pfizer-supported research project at Columbia. The entry or interest of Squibb was based on a co-operative arrangement between Squibb and Merck to

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[22] Ibid., Appendix II, p. 315, n. 53.

[23] Florey et al., Antibiotics, op. cit., p. 650.

share research findings.[24]

Contributions of the Northern Regional Research Laboratory.--In addition to visiting commercial firms, Florey also visited the Department of Agriculture's Northern Regional Research Laboratory (hereafter referred to as NRRL). It was this laboratory that he was first directed to in July 1941, prior to his conferences with private laboratories.[25] And it was in this initial meeting that the solution to the problem of large scale production was first suggested.

The production problem that had plagued Fleming and which Florey brought to the United States for solution was one of technology. The problem can be divided into two parts; first, the inherent productivity of the particular strain of mold initially used (productivity here defined as the ability of the mold in question to grow or multiply within a given period of time), and second, the physical conditions in which the mold is contained for fermentation.

The magnitude of the production problem can be seen in a crude comparison of the yields at different periods of time. In the 1939 to 1943 period, to produce a million units of penicillin required about 210 liters of culture broth.[26] By 1945 the same quantity of penicillin could be produced with one-half a liter of broth, and by 1958, by one-quarter

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[24]A. N. Richards to J. C. Woodruff, Merck & Co., Inc., March 12, 1942, National Archives, RC 227, cited in FTC, Report, op. cit., Appendix II, p. 320.

[25]Florey et al., Antibiotics, p. 649.

[26]Fleming, op. cit., p. 37.

of a liter.[27] In addition, there was a corresponding decrease in the time required for the fermentation process.

The primary causes of the increase in the productivity of the manufacturing process were the development of improved mold strains and the so-called "deep fermentation" process. The NRRL was largely responsible for both of these improvements. It is of interest to note that in the first meeting between Florey and Dr. Coghill of the NRRL, the deep fermentation process was suggested by the latter.[28] This approach to the problem of large scale production was undoubtedly based on the work of the NRRL. Prior to Florey's visit in 1941, this laboratory had been engaged in research to develop a use for corn-steep liquor, a by-product of cornstarch manufacture. Along these lines of research the deep fermentation technique was used as an experimental method.

With the surface culture manufacturing process, penicillin grew on the surface of the medium, feeding on the nutrient material below. The physical conditions under which the penicillin mold came into contact with the nutrient material limited the size of the vessel that could be used, thereby breaking the production process up into as many steps as vessels used. This in turn required that each vessel be separately inoculated with the initial mold, checked periodically for contamination and growth levels, and harvested. On the other hand, the deep fermentation process allowed the

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[27]FTC, Report, p. 119.

[28]Florey et al., Antibiotics, p. 649.

growth of the penicillin within the culture medium with feeding taking place on the surrounding nutrient material. This meant that the size of fermentation vessels could be increased from one liter to tanks with capacity in the two to ten thousand gallon range. The effect was to replace the "small army of unskilled workers,"[29] with a few workers skilled in the operation of an automatic process.

This then was one major contribution of the NRRL. A second contribution was the examination of different types of molds in search of a higher producing strain. In co-operation with a research group at the University of Wisconsin, among others, a series of more productive strains were found and developed for commercial production.[30] A third contribution of the NRRL was the discovery that corn-steep liquor was an efficient culture medium.

The economic contributions of the work of the NRRL can be summarized rather broadly at this point. The application of the deep fermentation process to penicillin production, the discovery of the improved strains, and the utilization of corn-steep liquor as a nutrient medium, had the effect of shifting outward the production possibilities curve for penicillin production. Although there is no means by which the shift can be quantified, the magnitude of the shift would seem to be considerable in view of the increase in penicillin output that resulted from these developments.

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[29]Fleming, op. cit., p. 43.

[30]FTC, Report, pp. 347-51.

Patent Influence.--Following Florey's visit to the NRRL and commercial laboratories, two lines of reactions appeared. First, as noted above, the NRRL concentrated on the problem of large-scale penicillin production. As a result of this research, the Department of Agriculture became the holder of certain key patents on the production of penicillin by the deep fermentation method.[31] In a December 1941 meeting between the CMR, Pfizer, Squibb, Merck, and Lederle, copies of the patent application on the deep fermentation process were made available.[32] Two of these firms had extensive knowledge of the fermentation art. Pfizer, which produced citric acid by deep fermentation,[33] and Merck which had in 1938 established a fellowship for the study of citric acid production by this method.[34] Thus, at this point at least four drug producers had the benefit of the research by the Oxford group as well as the technical information of how to produce penicillin on a mass production basis, and two possessed previous experience in the technique. But it was not until June 1944, two and a half years later, that the supply of penicillin was sufficient to release the

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[31] Ibid., pp. 228-29. The Department of Agriculture followed a policy of licensing all qualified applicants on a royalty free basis which in the late 1940's was a factor in the large-scale entry which took place.

[32] Ibid., p. 327, n. 98 and p. 238. See also Government Patents Board, Chemical Products and Process Patents, Government Owned Inventions Available for License, Department of Commerce, Patent Abstract Series No. 2 (Washington: 1954), p. 29, where the patent on this process issued to Dr. Moyer, and assigned to the Department of Agriculture, is described.

[33] T. Mahoney, The Merchants of Life (New York: Harper, 1959), p. 239.

[34] FTC, Report, p. 332.

drug for limited sales to civilian hospitals.[35]

The hypothesis that tends to explain this lag between research findings and production is that significant patents either on penicillin itself or on its process of production were unavailable. Rather than devote research resources to the problem at hand, drug firms allocated their resources to attempts at synthetic production of penicillin where both product and process patents were available. The rationale of this position was provided by Merck. They reasoned that as in the case of vitamin B, where synthesis made the natural extraction process obsolete, that synthesis of penicillin would eradicate the investment in research and equipment on the fermentation process.[36] Evidently the drug producers were able to convince the CMR that the synthesis program offered a higher probability of success than the fermentation program. Of the 56 research contracts we have data on, nine were with drug firms and involved a synthesis approach. In addition, these nine contracts did not call for government payments to cover the costs of this research, although such payments were offered.[37] This self-financing would of course give the firm a better claim to any patents on the results of their research.

The patent issue forced a divergence of goals. The CMR's primary interest was in adequate production with minimum delays. To this end they attempted to set up lines of

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[35] Ibid., p. 331.

[36] Mahoney, op. cit., pp. 197-98.

[37] FTC, Report, pp. 47-49.

communication between the various research projects to share information on progress. The goal of the commercial laboratories was the production of patentable information which required secrecy. As late as the middle of 1943 the CMR was experiencing difficulties in co-ordinating the synthesis research programs and in having information pooled among the various firms.[38]

As a result of the delays in the penicillin research program the CMR made a study to determine which firms should continue the synthetic research program. Ten firms were selected and invited to enter into contractual arrangements with the OSRD.[39] The patent aspect of the contract provided:

> (i) there is provided a complete interchange of information through OSRD of information discovered by all OSRD contractors, (ii) the work being done by the commercial firms is financed by their own funds, and (iii) the OSRD is given the right to determine the disposition, among the organizations that make contributions through OSRD of valuable information or inventions, of all patents covering discoveries or inventions made under the contracts that are attributable to the interchange of information through OSRD. In addition the Government receives royalty free licenses for military . . . and national defense purposes under all patents resulting from work done by the OSRD contractors in the synthetic penicillin field . . . Also, OSRD has the right to require the OSRD contractors that ultimately become titleholders of the patents to license either designated organizations, whether or not they are

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[38]"Two of the seven companies are sharing information, viz: Merck and Squibb, I believe, by formal agreement. Pfizer, to some extent, shares with Merck and is contemplating sharing also with Squibb. Otherwise, there is no pooling." A. N. Richards to V. Bush, August 14, 1943, records of OSRD, NA, RG 227, quoted in FTC, Report, p. 341.

[39]Nine of the firms which signed contracts with the OSRD were Abbott Laboratories, Eli Lilly, Merck, Parke Davis, Pfizer, Shell Development Company, Squibb & Sons, Upjohn, and Winthrop Chemical. FTC, Report, p. 346.

contributors of inventions or relevant information upon the payment of reasonable royalties. 40

There is some evidence that the drug firms had little choice in whether to accept the OSRD's contract or not. The War Production Board was in a position on the advice of the OSRD to deny priorities on supplies and equipment. In addition to this threat the firms were informed that the OSRD had important information from University sources as well as from the English research programs that it was willing to share with the contracting firms.[41]

This contract provision relevant to the patent issue clearly indicates an attempt to eliminate the delays in the penicillin program and to prevent any possible abuse of the patent position if and when established. Thus, neither a legal or illegal monopoly in penicillin was to be allowed. Recovery of research costs then had to be through royalties or through the price of penicillin in sales to the government.

What is not explained here is why, with the patent issue settled, did these firms continue to finance this research program from their own funds rather than from public funds. The answer here may well be that if one firm followed this approach others would have to follow to maintain the same relative position in the determination of the allocation of patent rights. From the profit point of view, it would

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[40]Penicillin Contract Patent Provisions, read at a meeting of the Penicillin Producers Industry Advisory Committee, February 8, 1944. Records of the WPB, N.A., R.G. 227, quoted in FTC, Report, pp. 335-336.

[41]See the Richards letter addressed to nine firms as well as the Bush letter on the proposed contract in FTC, Report, pp. 341-42 and 343-44.

make no difference in the long run, as the cost of this research could be recovered in sales of penicillin to the government. In determining the price, undoubtedly, this element of cost would be considered.

The experience of the OSRD with the commercial firms suggests that the patent institution had the effect of allocating resources away from the more promising line of development. That is, from the deep fermentation process of production to an attempt at synthetic production. With the settlement of the patent issue by contract in early 1944 and the rapid progress made by the NRRL in the deep fermentation process, attention shifted to implementing this process which in a few months satisfied military demands.[42]

Patents and the Production of Knowledge.--The question raised at this point is, did participation in the synthetic penicillin research program result in greater productivity of knowledge for those firms under contract to the OSRD than for firms which concentrated on production? A crude test of this question is provided by the statistics on antibiotic patents held by commercial firms. Table 1 indicates the patent holdings of firms engaged in synthetic penicillin research and those not in the program for the years 1942 to 1956. Two heroic assumptions are involved here. First, that patent statistics accurately reflect research productivity, and second, that the knowledge gained in the synthetic research program was transferable to the

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[42] Ibid., p. 347.

discovery and production of improved antibiotics. In the light of these assumptions the data in Table 1 indicates that on the average the synthetic research program was not a significant producer of new knowledge. Here firms in the program produced on the average of 47 patents, while those not in the program produced 52. The tentative conclusion here is that the patent did not have any positive long-run effects to offset its short-run misallocation of research resources.

TABLE 1.--Antibiotic patents held by commercial firms 1942-1956

Numbers of Patents held by Firms in the OSRD Program		Numbers of Patents held by Firms not in OSRD Program	
Abbott	10	Lederle	60
Lilly	67	Bristol	50
Merck	111	Commercial Solvents	46
Squibb	40		
Parke Davis	42		
Pfizer	40		
Upjohn	20		
Total	330		158

Source: Federal Trade Commission, Economic Report on Antibiotic Manufacture (Washington, 1958), p. 235.

Further support for this conclusion is evident in the statistics of inventions of these firms between 1945 and 1959. (Invention is defined as the introduction of a new drug product either from the firm's own laboratory, or as a result of its financial support of outside research.) In these terms, on the average, the firms not in the program

had an average of four inventions in this fourteen year period. (Lederle leads the list with seven, and Bristol is credited with one. Commercial Solvents is not considered here for shortly after the war they left the industry.) The firms which participated in the program averaged 2.3 inventions.[43] This would tend to suggest that the firms which concentrated on penicillin production and ignored the question of patents were, in the long run, more inventive. This question is discussed further in Chapter VI.

COMMERCIAL PRODUCTION OF PENICILLIN

This phase of the history of the antibiotic industry can be dated from mid-1943 when the CMS decided that the synthetic research program would have to be subordinated to the actual production of penicillin by the deep fermentation process, to 1950 when Pfizer integrated forward into direct selling to the pharmaceutical trade. Within this period the industry experienced sharp increases in penicillin capacity, entry and price competition, the discovery and marketing of streptomycin, and a basic change in the structure of the industry as two of the major producers integrated forward.

Penicillin Production.--The research of the NRRL and that of various university laboratories indicated to the CMR that the deep fermentation process offered the best approach to the problem of production. In May of 1943, production

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[43] A fuller discussion of this question is presented in Chapter VI. For details of the record of inventions, see Table 20, p. 210.

plans were formulated with the co-operation of the War Production Board, (hereafter referred to as WPB), in the assignment of priorities for the procurement of materials. In August 1943, a meeting was held between the CMR and the WPB where it was agreed that the WPB would assume responsibility for

> . . . expanding the production of penicillin, determining the type of production by various producers, surface or deep fermentation, providing financing for producers where necessary, issuing necessary priorities for materials required by producers for plant construction and operation, making arrangements for the disclosure of necessary technical information relating to techniques of production on terms just to producers, and dealing in some just and effective manner with patent rights relating to methods and apparatus for production of penicillin by the present means . . . [44]

It was further agreed that the OSRD would continue its responsibility for the research on synthetic production and handle the details necessary for this project.

The major problem faced by the WPB was the selection of producers for inclusion in the production program. Of some 1200 firms classified as drug producers, more than 175 had expressed interest in penicillin production.[45] The WPB's criterion for selection was evidently the existence of production facilities which could be modified for penicllin rather than the construction of new facilities. Non-selection of a firm for participation meant only that it would not receive WPB assistance in securing materials. The eithteen firms listed in Table 2 were those selected by the WPB, together with the costs of these facilities.

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[44] FTC, Report, pp. 329-30. [45] Ibid., p. 42.

TABLE 2.--Cost of construction of penicillin facilities authorized by the WPB, and amounts authorized for rapid depreciation (1943-1945)

Firm	Total Cost	Public Share	Per cent Public Share	Rapid Amortization	Per cent Amortized
Abbott	$ 670,704	$ 197,497	29.9	$ 473,207	100.0
Lederle	4,147,292	784,528	18.9	899,178	26.7
Ben Venue	355,672	355,672	100.0	0	0
Bristol	2,410,000	2,410,000	100.0	0	0
Cherohee	210,000	0	0	0	0
Commercial Solvents	1,869,000	0	0	1,817,000	97.2
Cutter	850,000	850,000	100.0	0	0
Emerson & Dettlebeck	36,000	0	0	0	0
Heyden	3,000,000	3,000,000	100.0	0	0
Hoffmann La Roche	1,935,000	0	0	1,281,000	66.2
Lilly	710,000	0	0	548,079	71.1
Merck	5,749,000	0	0	276,000	4.8
Parke Davis	789,000	0	0	480,000	60.8
Pfizer	3,396,902	0	0	3,151,396	92.8
Schenley	1,175,174	0	0	1,175,174	100.0
Squibb	2,107,615	0	0	1,847,128	88.9
Sterling	157,000	0	0	80,000	51.0
Upjohn	324,128	0	0	269,590	83.2
Totals	$29,873,367	$7,577,697	25.4%	$12,325,752	55.3%

Source: Federal Trade Commission, Economic Report on Antibiotic Manufacture (Washington: 1958), pp. 54-55.

In addition three other firms were initially selected. They were Wyeth Laboratories (a division of American Home Products), Cheplin Biological Laboratories (purchased by Bristol during World War II), and the William H. Merrell Company, later the Vick Chemical Company. Of the twenty-one firms selected, three never became significant producers, the William H. Merrell

Company, Cherohee Laboratories, and Emerson and Dettleback. Only one firm appears to have entered the market without WPB assistance to become a significant producer. That was Sharp and Dohme, later merged with Merck.[46]

The production goal set by the WPB for 1944 was 300 billion units per month. By December of that year, 93 per cent of this goal had been met by eighteen firms.[47] The rapid increase in penicillin production coincided with the introduction of the deep fermentation process. But to reach this stage it was necessary to overcome a degree of reluctance on the part of the firms to invest in the necessary facilities.[48] In light of the patent oriented synthetic research program, this hesitance is not surprising. To devote scarce research personnel to a production research program would eliminate any chance of success in the synthetic program. If, on the other hand, a competitor was to succeed in producing a synthetic penicillin, past experience indicated that the entire cost of the research could be lost and the production facilities rendered obsolete.[49]

This impasse was broken by expanding the production program to include firms that had not been under contract to

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[46] Ibid., p. 331. [47] Ibid. [48] Ibid., p. 61

[49] Detail of the effect of synthetic production on the "natural" methods of production is provided by Mahoney, op. cit., Chaps. XI, XIII, and XVI.

the OSRD in the synthetic program,[50] and by pressure on those in the latter program to begin production.[51] To overcome the industry's aversion to risk, the government agreed to provide funds for plant construction and additions and to allow rapid amortization of private funds so used.[52] The firms which were financed with public funds used the surface fermentation technique. The only firm financed with private funds which used this technique appears to have been Merck. Lacking any information on the dates the various firms in Table 2 began the construction of large scale penicillin facilities, it is only possible to speculate on the reason for the selection of the surface fermentation technique. It would appear that when the WPB and the CMR decided in mid-1943 to concentrate on production, the surface technique was well developed through research conducted in England as well as being the usual method of production for laboratory and clinical studies. Thus, to develop some sources of supply it was necessary for the government to provide financial support to construct what in fact were obsolete plants. Other firms evidently preferred to delay plant construction until the deep fermentation technique was perfected. From

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[50] Firms brought into the production program over the objections of those in the synthetic program were Ben Venue, Cheplin Laboratories (purchased by Bristol in 1943), Cherohee Laboratories, Commercial Solvents, Hoffmann La Roche, Lederle, Reichel Laboratories, (purchased by American Home Products in December 1942), Schenley Laboratories, Sterling Drug, and William H. Merrell Co. In addition Sharp and Dhome entered without WPB assistance, FTC, Report, pp. 54-55.

[51] Ibid., p. 329. [52] Ibid., p. 53.

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the production records of firms that used the deep fermentation technique it is evident that by mid-1944 this technique was perfected.[53] What is lacking here to support this explanation are the dates when the publicly supported plants began operation.

The explanation for Merck's construction of a surface fermentation plant is that they believed the synthetic process would be shortly successful.[54] Rather than reassign research personnel to the production program, it was possible to enter the lucrative penicillin market by expanding the surface fermentation technique from a pilot plant to large scale production.

The implication of this discussion is that the CMR, aware of the NRRL's research on the deep fermentation technique, was faced with something of a dilemma. The snythetic research program carried on by the drug producers after two and a half years' work was not nearing a solution. Large-scale production of penicillin was becoming imperative as the war progressed. But by mid-1943, the companies were not in a position to undertake large-scale production using the more efficient deep fermentation method, having devoted their research to synthetic production. Thus the CMR and WPB were forced to authorize and finance construction of the less productive surface fermentation facilities. Here the issue of patents had an indirect effect of reducing productive

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[53] Ibid., p. 331.

[54] Mahoney, op. cit., pp. 197-98.

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Cost of Penicillin Capacity.--The effect of the deep fermentation process on capital costs can be indicated from the data in Table 2. For twelve of the eighteen firms in Table 2 it is possible to indicate which initially used the surface fermentation process and which used the deep process. In Table 3 the twelve firms are divided into these two

TABLE 3.--Investment costs and capacity of penicillin facilities 1944 (in millions of Oxford units)

Firm	Capacity	Investment Costs	Costs per Million Units
Firms Using Deep Fermentation Techniques			
Pfizer	100,000	$3,396,902	$ 33.97
Squibb	55,000	2,107,615	38.32
Commercial Solvents	50,000	1,869,000	37.38
Schenley	6,000	1,175,174	195.86
Firms Using Surface Fermentation Techniques			
Heyden	18,000	3,000,000	166.67
Merck	12,000	5,749,000	479.08
Bristol	7,000	2,410,000	344.29
Lederle	6,000	4,147,292	691.22
Abbott	2,000	670,704	335.35
Cutter	2,000	850,000	425.00
Ben Venue	2,000	335,672	167.50

Source: Capacity and investment figures from Federal Trade Commission, Economic Report on Antibiotic Manufacture (Washington: 1958), pp. 54-55 and 331.

[55]Much the same conclusion was reached by Richard Harris, "Annals of Legislation, The Real Voice," The New Yorker, March 14,21, 28, 1964. See especially p. 69 of the March 14th issue, ". . . the firms were too busy trying to corner patents on various processes in the production of penicillin to produce much of it, and the government began to press them to work together." Also see FTC, Report, pp. 37-38, on this point.

categories. Of the firms in the first category all except perhaps Squibb had prior experience with the deep fermentation process. Two of these firms--Schenley and Commercial Solvents entered the drug field from other industries. Firms in the second category, with the possible exception of Ben Venue, were drug producers prior to the war, and with the exception of Merck lacked prior experience in the deep fermentation process.

The difference in capital costs for the two production techniques is considerable. For firms in the first category the average cost per million units of capacity was $76.38, while for the second it was $372.73, or a difference of $296.35 per million units.[56]

Two conclusions are suggested by this data. First, the degree of importance of the NRRL's work in the development and application of the deep fermentation process to penicillin production emerges as significant. The second conclusion is more in the nature of a hypothesis. Here we have two groups of firms, the first with a definite competitive advantage over the second in the productivity and cost of producing penicillin. The first group of firms could be characterized as possessing a degree of market power, based on an absolute cost advantage, greater than that of the first group. The question here then is, which group of firms developed new drugs? If the first, then this would tend to

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[56]Interfirm differences in capital costs are undoubtedly due in part to the fact that some firms had plants or equipment that could be modified for penicillin production.

support the thesis that a degree of market power is necessary for invention and innovation. If the second, this would support the thesis that the forces of competition are a sufficient spur. This question is examined below.

MARKET STRUCTURE IN PENICILLIN

In the period between 1944 and 1950 the penicillin market structure can be characterized as highly competitive. The number of firms producing penicillin as well as the number of firms purchasing bulk supplies for sale under their own label resulted in a continuing decline in penicillin prices. The pressure on prices and profits was a force in the search for new drug products which could be protected by patents. Success in this area was followed by forward integration in an attempt to gain better control over the market.

Structure and Prices.--In February 1944 the government began purchasing penicillin from the producers.[57] The price established after consultation with the producers was $200.00 per million units.[58] It is unlikely that this price prevailed for long. At a price of $200 per million Oxford units, and with a conversion factor of 603.8 (or 603.8 million Oxford units per pound), a pound of penicillin would have been worth $120,760. In Table 4, 1944 unit value per pound averaged $13,212. Thus, it appears that initial penicillin prices declined sharply in 1944 as the costs of

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[57]Prior to this date what penicillin was produced in laboratory pilot plants was given to the CMR without charge for distribution in their clinical testing program.

[58]FTC, Report, p. 149.

production declined. But the limiting factor on price undoubtedly was the cost of production of the firms using the less efficient surface fermentation method.[59]

TABLE 4.--Production and sale of penicillin (1944-1950)

Year	Production in Pounds	Quantity in Pounds	Sale Value (000)	Unit Value Pounds	Number of Producers
1944	2,649	2,649	$35,000	$13,212	17
1945	12,345	11,746	46.462	3,955	16
1946	44,717	33,124	89,000	2,687	16
1947	69,605	61,387	87,102	1,419	15
1948	161,503	112,172	108,301	965	15
1949	248,924	197,983	87,458	442	16
1950	396,364	329,746	93,052	282	14

Note: The following factors were used for converting from Oxford Units to pounds: 1944-1947, 603.8 million Oxford Units per pound; 1948, 575.5 million Oxford Units per pound; 1949 and 1950, 554.8 million international units per pound.

Source: U.S. Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale, Second Series, various Reports.

In March of 1945 the WPB allowed the sale of penicillin through normal trade channels.[60] As a result a bulk market developed as packagers purchased penicillin from the manufacturers for resale under their own labels.[61] The earliest data on the number of packers begins with 1950.[62] Between 1950 and 1956 the number of firms at this stage in the distribution process grew from twenty-seven to forty-five. Table 4 indicates that the number of manufacturers declined

[59] Ibid., pp. 44-45.
[60] Ibid., p. 45.
[61] Ibid., p. 162.
[62] Ibid., p. 66.

from seventeen in 1944 to fourteen in 1950.[63] On a net basis it appears that from 1945 on, the number of sellers increased.

The data in Table 4 relative to the net unit value of penicillin is in accord with the Federal Trade Commission's conclusion that prices fell sharply in the 1945-50 period.[64] This then is a reflection of the improvements in technology and the pressure of competition.

New Drug Products.--[65]Between 1945 and 1950 three significantly new drugs were discovered and marketed. These were streptomycin, chlortetracycline, and chloramphenicol. Each of these drugs was marketed by a firm that had found the penicillin market unprofitable.

The first of these products was streptomycin, discovered at Rutgers University in 1944 and marketed by Merck in 1946. Merck was the firm that had bet on the synthetic penicillin program and when forced into production used the surface fermentation process. Chlortetracycline was discovered and marketed by Lederle in 1948. Lederle also had entered the penicillin market equipped with the surface fermentation technique and had clearly been forced out of the

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[63]Five firms left the penicillin market completely by 1950--Lederle, Ben Venue, Hoffmann La Roche, Sterling, and Sharp and Dhone, while two entered--Wyeth (a division of American Home Products) and the William H. Merrell Company. Two of the five that left the market used the surface fermentation process, while it is possible that the other three also used this process. However, on this point information is absent.

[64]FTC, Report, pp. 162-171.

[65]The subject is taken up in the broader context of the entire ethical drug industry in Chapter VI.

market by 1947. The third drug was chloramphenicol, discovered at Yale University and first marketed by Parke Davis in 1949. Parke Davis also appears to have selected the surface fermentation process but never became a significant producer and evidently left the market by December of 1944.

Less significant drugs were discovered and marketed during this period. Both Lilly and Squibb improved the basic penicillin drug. Merck discovered an improved version of streptomycin by 1949, and Pfizer found a competitive substitute to Lederle's chlortetracycline--oxytetracycline.

The significance of this record in answer to the question raised earlier is that the firms under the more intense competitive pressure were the ones that engaged in innovation. Of the firms who began production with the more efficient deep fermentation process, hence under less competitive pressure, only minor advances were forthcoming.

Forward Integration and Decline of the Bulk Market.--With the introduction of new drug products certain basic changes took place in the structure of the antibiotic market. In the case of penicillin, the basic drug was unpatentable and as a result unrestricted entry both in manufacture and in packaging took place. Prices in turn were driven to the competitive level. Certain firms such as Pfizer, Merck, Schenley, Commercial Solvents, Bristol, and Heyden specialized in manufacturing as they lacked the sales force necessary to contact the physician and build brand name allegiance. For these firms the bulk market was their primary source of

buyers. With this type of market structure, it was impossible for the manufacturer to set price.

With the discovery of streptomycin, Merck received the patent on this drug under the terms of its contract with Rutgers University. But here Merck was faced with a dilemma. To exploit its monopoly position required an extensive sales force which Merck lacked. To sell through the bulk market would repeat the penicillin experience. Merck solved this problem eventually by merging with Sharp and Dhome in 1952, but in 1946 Rutgers University forced the solution. Rutgers argued that the discovery of streptomycin was too important to await Merck's building of a sales force. They proposed that the patent be turned over to a non-profit organization at Rutgers, and that Merck take in return a non-exclusive license and $500,000 in royalty abatement.[66]

Eight producers, including Merck, were licensed to produce and sell streptomycin.[67] The market results were as anticipated. Entry at the packaging level took place and price was rapidly driven to the competitive level.[68]

In 1949 Merck discovered in its laboratory dihyrdrostreptomycin, a substitute for streptomycin. It had a clear claim on the patent which resulted, but again lacking a detail force to market the drug under its own label and in

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[66] FTC, Report, p. 229.

[67] In 1950 the producers of streptomycin were Lilly, Squibb, Pfizer, Merck, Schenley, and Heyden, the latter four selling primarily in the bulk market. See Table 1, Appendix, p.

[68] FTC, Report, pp. 178-182.

light of the substitutive relationship between the two drugs, Merck granted non-exclusive licenses to other manufacturers. The market experience was a repeat of the penicillin-streptomycin experience.[69]

In the case of Squibb and Lilly, both were able to modify the basic penicillin drug sufficiently to obtain patents. Both were fully integrated into packaging and selling. However, the value of these patent monopolies was severely restricted by the competitive relationship between these modifications and the basic penicillin drug as well as by the cross licensing which was necessary to settle the interference proceedings.[70] By 1950 some twelve firms produced potassium penicillin and thirteen firms produced procaine penicillin.[71] Included in these groups were several bulk suppliers. The prices of these penicillin salts closely followed the basic penicillin price structure.[72]

With the discovery of chlortetracycline by Lederle in 1948 the situation allowed the establishment of an exclusive patent monopoly position. Here was the first of the broad spectrum antibiotics, hence was not faced with effective competition from established drugs. In addition, Lederle possessed a large sales organization and a corporate name familiar to the medical community. Requests for domestic

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[69] Ibid., pp. 178-182 and 230.

[70] Ibid., pp. 237-240.

[71] See Table 1, Appendix, p.

[72] FTC, Report, p. 162.

licenses to produce or sell chlortetracycline were refused. As a result the price structure in the broad spectrum antibiotics market has been inflexible. The question of pricing in this market is discussed in detail in Chapter V.

Parke Davis, in its marketing of chloramphenicol under similar market conditions in 1949, followed Lederle's example as well as its price structure.

By 1950 Pfizer had discovered a substitute for Lederle's chlortetracycline. A patent application was filed and eventually granted. But in marketing its discovery, Pfizer faced the problem of how to exploit its market position with a sales force composed of eight detailmen. An advertising agency was hired to prepare the market while its discovery awaited Food and Drug administration clearance. With clearance received, the sales force concentrated its efforts on wholesalers, contacting them by telephone, and later concentrated on hospitals. The program was successful, judging from the fact that Pfizer captured about 24 per cent of the broad spectrum market by 1951.[73]

To complete the record at this point, by 1956 the firms that had depended upon the bulk market as a primary outlet for their output either left the market or integrated forward. Pfizer and Bristol accomplished this through internal growth although Bristol's scale of operation was considerably smaller. Merck merged with Sharp and Dhome as has been noted earlier. Schenley and Commercial Solvents left

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[73] Ibid., pp. 140-42.

the industry as did several smaller producers. Heyden's antibiotic facilities were purchased by Lederle's parent, American Cyanamid, during a patent dispute. In effect then, the basic structure of the antibiotic market changed from a competitive structure with the emphasis on price competition, to a monopolistic structure based on patents.

SUMMARY AND CONCLUSIONS

The discovery of penicillin by Fleming and subsequent development by Florey laid the foundation for one of the most important segments of the domestic ethical drug industry. On this foundation, the contribution of the NRRL in developing the deep fermentation process, and in the discovery of improved mold strains, and that of the OSRD in the co-ordination of research and financing of private plant construction, fabricated the basis of commercial production.

The issue of patents appears to have been a major force in the commercial firms' synthetic research programs. In following this line of investigation initially, rather than attempting to apply the contribution of the NRRL to large-scale production, the production of penicillin for military and civilian requirements was delayed. As early as December 1941, at least four firms--Pfizer, Squibb, Merck, and Lederle--had the technological information necessary to solve the problem of production. All except Lederle directed their research efforts to the synthetic approach under contract with the OSRD. (On the direction of Lederle's efforts,

information is absent except to the extent that Lederle did become a producer in mid-1944 using the surface fermentation technique, hence probably did some research.) A crude test of whether firms that entered the synthetic research program were in the long run more inventive than other firms suggests that they were less inventive. Thus in terms of both short run as well as long run effects, the patent appears to be deficient in directing scientific resources.

A second effect of the patent lies in its influence on the market variables. In the case of the improved versions of penicillin and in the case of the streptomycins, the patent was ineffective as a basis for monopoly. In the penicillins and in dihydrostreptomycin the availability of close substitutes sufficiently restricted the price which could be set, hence eliminating any monopoly gain. In the case of streptomycin direct access to the prescription and hospital market was not immediately available, hence the competitive bulk market could not be by-passed. In each of these situations, while the product was patented, the market results were competitive.

In the case of chlortetracycline and chloramphenicol, the bulk market could be eliminated as both Lederle and Parke Davis had direct access to consumer markets. The result here was exclusive domestic production and sale and inflexible prices. With the discovery of oxytetracycline by Pfizer, the elimination of the bulk market was recognized, and forward integration resulted.

Thus the tentative conclusion at this point is that the patent may provide the basis of monopoly power. But the patent in its own right is not sufficient. To be used as the basis of a monopoly position, certain structural characteristics of the market must be present.

To the question, "Which structural characteristic, competitive or monopolistic, is likely to result in product advancement?" the tentative answer is "competitive." Those firms which employed the surface fermentation process, at an absolute cost disadvantage relative to deep fermentation users, were the firms which first discovered or innovated new drug products.

CHAPTER II

THE TECHNOLOGY OF ANTIBIOTIC RESEARCH

In the preceding chapter it was argued that the antibiotic industry developed from the work of the Oxford group in England in combination with government support in this country through the OSR and the NRRL. Further, that with the key patent on the deep vat fermentation process held by the Department of Agriculture, entry took place at the manufacturing and distribution level, driving price towards the competitive level. The medical and commercial success of penicillin became a stimulant to further research in the antibiotic area.

In this chapter, the writer indicates the antibiotic drugs which followed penicillin and attempts to rank these drugs in order of importance. The purpose of this ranking is to examine the underlying research which led to these inventions. In particular the following questions are raised: (1) What was the contribution of basic and applied research to these inventions? (2) What in this flow of inventions was the key invention? (3) Which firms accounted for the more significant inventions and what was their competitive position in the penicillin market? (4) Were the inventors of these drugs leading members of the scientific community? (5) What in fact did the patent system reward in granting a degree of monopoly power to the inventing firm? In attempting to

answer these questions, the invention of the tetracyclines and chloramphenicol are examined in detail.

MAJOR ANTIBIOTIC DRUGS SINCE 1941

Any attempt to construct a list of antibiotic drugs that represents major advances in drug therapy faces the problem of a criterion for inclusion. Ideally the criterion ought to be one that considers a particular range of pathogenic microorganisms and the "drug of choice" (defined as the most popular among physicians), used to treat the resulting disease. With this type of criterion, an antibiotic drug accepted by the medical community as the "drug of choice" could then be included as representative of a major advance. There are two problems with such an approach. First, one would have to assume that the medical community is not persuaded to prescribe by advertising, thereby yielding transitory inclusions as in the case of chloramphenicol; and second, this does not completely solve the question of relative ranking.

There are, on the other hand, two general lists of major drugs. Both were submitted in the course of debate before the Kefauver subcommittee in its study of administered prices in the drug industry. The committee staff produced a listing of major drugs in its attempt to demonstrate that American drug producers were not discoverers of new drugs.[1]

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[1] U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, Part 19, 86th Cong., 2d Sess., 1960, pp. 10943-10945.

The selection of drugs for inclusion by the committee staff came under rather strong criticism in a statement read by Dr. Austin Smith, President of the Pharmaceutical Manufacturers Association. The major line of criticism offered by the Association was that the committee had in fact no criterion upon which to base drugs for selection. In support of this contention it was shown that the committee's list contained drugs that were not currently used medically and some that had never been so used. In addition, some drugs included were discovered in the sixteenth and seventeenth centuries. In rebuttal the Association had prepared its own list of major drugs discovered since 1923.[2] With certain modifications it is this list which provides the basis for the discussion which follows.

The major drug advances listed by the Association did not make use of the ideal criterion outlined earlier. Instead, the primary selector was 1959 sales volume. A secondary selector were drugs of low sales volume but important in the treatment of diseases that had a low incidence in the population. Exactly which drugs fell into this latter category was not provided by the Association.

Table 5 reproduces the Association's list of antibiotic drugs with the addition of penicillin and chlortetracycline. From this list it is possible to discuss each entry in an attempt to judge its significance as an advancement in drug therapy. For this purpose these drugs are divided into

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[2] Ibid., pp. 10840-10854.

two categories, narrow and broad spectrum.

TABLE 5.--Major antibiotic drugs in current use

Generic Name	Year	Discoverer	Developer
Penicillin	1928	Fleming	Florey, Merck, Squibb
Potassium Pennicillin	1945	Oxford Group	Squibb
Streptomycin	1946	Waksman	Merck, Squibb
Chloramphenicol	1949	Yale University	Parke Davis
Chlortetracycline	1949	Lederle	Lederle
Oxytetracycline	1950	Pfizer	Pfizer
Benzathine Penicillin G	1951	Wyeth	Wyeth
Erythromycin	1952	Lilly	Lilly
Tetracycline	1954	Lederle, Pfizer	Lederle, Pfizer, Bristol
Phenoxymethyl Penicillin	1955	Lilly	Lilly
Demethylchlortetracycline	1959	Lederle	Lederle

Source: U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, 86th Cong., 2d Sess., 1960, Part 19, pp. 10840-10841.

The Narrow Spectrum Antibiotics.--The first entry, penicillin, discovered by Fleming, requires little discussion to support its inclusion as a major advancement in drug therapy. For here is the drug that through a demonstration of its chemotherapeutic properties stimulated the search for other drugs with similar properties.

Potassium Penicillin G, developed in tablet form by Squibb, claims significance as the "first orally effective penicillin preparation."[3] Prior to this Squibb development, penicillin was administered intramuscularly or intravenously. The advantage claimed for the oral administration was that

[3]Ibid., Part 19, p. 10840.

absorption into the blood stream was slower, therefore sustained concentration rates in the blood were higher over a longer period. The disadvantage of this type of penicillin, as well as other oral forms, is that they are inactivated by gastric juices and intestinal bacteria. As a result the oral administration of Potassium Penicillin G would require a five-fold increase in dosage to yield the same blood levels as penicillin administered intramuscularly.[4] This would have been an increase in the recommended dosage from 1,600,000 units to 8,000,000 units per day.[5]

Using the 1947 price of penicillin of 30 cents per 100,000 units,[6] the intramuscular route would cost $4.80 per day, while the oral route would cost $24.00 per day. On this basis there is no cost advantage to be gained by substituting the oral penicillin for other forms.

The problem is where to rank Potassium Penicillin relative to other drug inventions. Clearly this penicillin form is a modification of the basic drug with a similar range of effectiveness against pathogenic microorganisms. Its medical disadvantage of requiring a five-fold increase in dosage levels argues for classifying this form of penicillin as a minor advance in antibiotic therapy.

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[4]Elsie E. Krug, Pharmacology in Nursing (St. Louis: The C. V. Mosby Co., 1963), pp. 139-40.

[5]Ibid., pp. 143-45.

[6]Federal Trade Commission, Economic Report on Antibiotic Manufacturer (Washington: Government Printing Office, 1958), p. 166.

Benzathine Penicillin G is an improved version of the basic penicillin compound, containing a different side chain. Its advantage lies in its slow rate of absorption, giving an effective blood level of from one to four weeks.[7]

On the basis of 1954 manufacturers' prices of Benzathine Penicillin G of $11.30 per 6 million units,[8] the cost of the recommended dosage of 2.4 million units[9] is $4.52. A comparative course of treatment for fourteen days with Procaine Penicillin G would require 4.2 million units.[10] At 1954 prices of 80 cents per 3 million units[11] the total cost would be $1.09.

In terms of relative ranking, Benzathine Penicillin, based on its prolonged action, would seem to fall between Potassium Penicillin and Penicillin. Thus, this penicillin form is classified as a major advance.

Erythromycin in the general case is a poor substitute for the penicillins. It has a slightly larger range of antibiotic activity than the penicillins but this is offset by the fact that resistant pathogenic strains develop rapidly with its use. In certain cases it may be used where the individual is sensitive to the penicillins.[12] The

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[7]Krug., op. cit., p. 145.

[8]FTC, Report, pp. 175-76.

[9]Krug, op. cit., p. 145.

[10]Ibid., p. 144.

[11]FTC, Report, p. 168.

[12]Krug, op. cit., p. 154.

inclusion of Erythromycin by the Association would seem then to be not on the basis of sales volume, but on the basis of importance in the treatment in penicillin-sensitive cases. However, given the rather low incidence of this condition, Erythromycin is deleted from the list of significant drug advances, and considered a minor drug advance.

The last of the penicillin drugs to consider is phenoxymethyl penicillin or penicillin V. The claim is made that this penicillin form is of higher potency than other oral forms. Using 1956 manufacturers' prices for penicillin V at $1.45 per gram and for procaine penicillin G at $.73 per gram,[13] yields costs per day are $.22 for procaine penicillin G and $.72 for penicillin V. Thus it would appear that penicillin V ought to be included as a minor drug advance on the basis of its somewhat greater potency.

The last of the narrow spectrum antibiotics is streptomycin, isolated by Selman Waksman in 1943. By 1946 it was fully developed as a chemotherapeutic agent and shown to have a wider range of activity than the penicillins. On the introduction of streptomycin to the medical profession it was thought that this drug was a general substitute for penicillin. However, it has a tendency towards toxicity which limits its use to those diseases for which it is highly effective, mainly tuberculosis.[14]

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[13] FTC, Report, p. 173 and p. 177.

[14] Krug, op. cit., pp. 152-53.

Streptomycin's claim as a major breakthrough in drug therapy is based on the fact that it revolutionized the treatment of tuberculosis, effectively bringing this disease under control. In addition its discovery confirmed the research path broken by the discovery and development of penicillin. That is, it demonstrated that the soil was a producer of microorganisms that were effective as antibiotics.

The Broad Spectrum Antibiotics.--The first broad spectrum drug to be discovered was chloramphenicol. This drug was first isolated in 1947 and marketed in 1949 by Parke Davis.[15] Chloramphenicol was found to be highly effective against typhus and typhoid fever, and initially thought to be an effective substitute for penicillin in the general treatment of disease. In 1951 sales reached a peak volume of $52 million.[16] However, in the following year the incidence of the side effects from chloramphenicol became generally known, cumulating in an American Medical Association press release warning physicians of these side effects. By October of 1952, Parke Davis' share of the broad spectrum market had fallen to 5% from a high in June of 38%.[17] Although it was later found that the incidence rate was 1.75 per 100,000 cases, this in effect eliminated the penicillin substitute claim. However it is today the "drug of

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[15]Mahoney, The Merchants of Life, pp. 66 and 68.

[16]Ibid., p. 68.

[17]Fortune Magazine, "Shock Treatment for Parke Davis," XXXVIII, 108.

choice" in the treatment of typhoid fever.[18]

Chloramphenicol, as in the case of streptomycin, demonstrated the productivity of the soil in producing antibiotic products. While not a pathbreaker in the sense that penicillin was, nor significant in sales volume in the prescription market, due to its toxic side effects, it appears that this drug would have to be judged as a major advance.

The tetracycline drugs, including oxytetracycline, tetracycline, demethyclortetracycline, and chlortetracycline can be considered as a group as they have quite similar chemical structures. All but the latter, chlortetracycline, were included in the list prepared for the Pharmaceutical Manufacturers Association. These four drugs have a similar range of effectiveness against pathogens and the same low range of side effects.[19] The range of effectiveness is greater than in the case of penicillin, and the incidence of side effects is lower than in the case of streptomycin or chloramphenicol. On these grounds the tetracyclines must be considered an advance in drug therapy. The problem is whether to rank them together or to choose the first to appear. The latter course is selected on the grounds that the tetracyclines following chlortetracycline were essentially substitutes for the original drug. Hence, chlortetracycline is ranked as a major breakthrough as the first effective broad spectrum antibiotic and its substitutes as minor advances.

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[18] Krug, op. cit., p. 155. [19] Ibid., pp. 148-51.

Table 6 summarizes the classification of the antibiotic drugs that have appeared up through 1959. Each of the drugs classified as major breakthrough or advance meets the initial criterion in that it is considered a "drug of choice," for particular diseases. The minor advances, on the other hand, appear to be effective substitutes for established drugs,[20] inasmuch as recovery rates would not appear to be affected by the non-development of the drugs in the minor category.

Table 6.--Ranking of major antibiotic drugs

Major Breakthrough	Major Advance	Minor Advance
Penicillin	Benzathine Penicillin	Potassium Penicillin
Streptomycin	Chloramphenicol	Penicillin V
Chlortetracycline		Oxytetracycline
		Erythromycin
		Tetracycline
		Demethychlortetracycline

RESEARCH TECHNOLOGY

The common thread in the discovery process of the major antibiotics, with the exception of penicillin, is the observation that pathogenic microorganisms, with few exceptions, do not survive in soil. The implication of this observation was that the soil must then produce a substance or substances antagonistic to these microorganisms. This then becomes one strand in the discovery and development of

[20] Ibid., pp. 139-57.

antibiotics. The second is the medical theory of the causes of diseases according to which a substance, normally toxic to the human system, could by controlling dosages, be used to combat disease. The "invention" was the bringing together of these two strands of knowledge, thereby bringing into existence substances and methods of treatment that were "new."

It has been argued that discovery or technical progress ". . . is an indivisible moving stream . . ."[21] which is a cumulation of progress in many fields of endeavor. This statement has particular application to the field of antibiotic research. Bacterial antagonism was first demonstrated by Pasteur and Joubert in 1877. In 1885 Cantani wrote:

> The known fact that certain bacteria can destroy the culture of other, even pathogenic, microbes if they come into contact with them in any way gave me the idea of exploring this procedure for the treatment of various infectious diseases. 22

Garre writing in 1887:

> Bacteriotherapy, which we already recognize as a prophylactic procedure in different inoculations, now no longer appears to be in the realm of dreams as a means of fighting already developed disease. 23

McLeod and Govenlock in 1921:

> Lastly it is remotely possible that such substances [inhibitory substances produced by the pneumococcus] may have therapeutic applications, since it may be that

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[21] John Jewkes, David Sawers, and Richard Stillerman, The Sources of Invention (New York, Macmillan Co., 1961), p. 12.

[22] Florey, et al., Antibiotics, II, p. 5.

[23] Ibid., p. 7.

> the pneumococcal products which kill staphylcocci and pneumococci and leaves streptococci much less affected may be more lethal to the former than it is to the tissue of the body. 24

In addition to this early work by medical bacteriologists, the plant and soil bacteriologists were also observing, experimenting and accumulating a store of literature on the existence of microorganisms in nature. The research in this area was comparable to that in the medical field—the control of disease in plants. It was from this field of knowledge that Waksman succeeded in isolating streptomycin and laid the research foundation that produced other antibiotics.

The modern beginnings of antibiotic research technology lay in the problem investigated by soil bacteriologists. In attempts to control diseases in plants it was necessary to determine the nature of the soil microbiological population and the interaction between different microorganisms. In this process of identifying and classifying microorganisms, it was observed that pathogenic organisms did not survive in soil. As early as 1914, one scientist had succeeded in isolating a substance from the soil that had antibiotic properties.[25] Porter, in a 1924 paper, described the inhibiting action of several bacteria. "One of the bacteria was investigated and when grown on a plate shown to produce

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[24] Ibid., p. 31.

[25] John Crofton, "Streptomycin," in Penicillin, Its Practical Applications, ed. Alexander Fleming (St. Louis: The C. V. Mosby Co., 1950), p. 400.

a diffusible substance which could inhibit the growth of fungi as far away as 2 cm."[26] Laboratory observations of the inhibiting nature of certain substances were extended in an attempt to control disease. Henery, writing in 1931, ". . . reported that the addition of bacteria, actinomycetes, and fungi isolated from the soil reduced the severity of foot-rot infection caused by H. sativum, and that fungi were more effective than actinomycetes and bacteria."[27] In 1932, Tims succeeded in isolating numerous actinomycetes from a sugar-cane field ". . . which were antagonistic to a Pythium parasitic on sugar-cane."[28] Nakhimovakaya, in 1937, found that ". . . in certain soils the actinomycetes were capable of exerting antagonistic action, but in others they were ineffective."[29]

At the Rutgers University Agricultural Experiment Station, a series of studies were undertaken beginning in 1915 to determine the occurance of actinomycetes in the soil and their effect on plant life.[30] These studies indicated the wide distribution of actinomycetes in the soil and their varying degree of effectiveness against bacteria. There was in the period up to 1939, little appreciation of the possible significance of these studies for chemotherapy. This was due in part to the unstable nature of these compounds,

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[26]Florey, et al., Antibiotics, p. 39.

[27]Ibid., p. 44. [28]Ibid., p. 53.

[29]Loc. cit.

[30]Selman Waksman, Neomycin (New Brunswick N.J.:Rutgers University Press, 1953), p. vii.

and in part to their highly toxic nature.[31]

In 1939, Waksman and others began a comprehensive research program at Rutgers University on the action of antibiotics.[32] Whether this research program was the result of Fleming's work in the early 30's or of private communication with members of the Oxford group, Waksman does not say. The impression he leaves is that the inception of the program was an independent decision based on prior work at the experiment station. In 1941 Florey's work was published and the result was an intensification of Waksman's research:

> The rapid progress that was being made, during the years 1941 to 1942, on the production, isolation, and utilization of penicillin soon convinced us that an outstanding chemotherapeutic substance is already available for combating disease caused by Gram-positive bacteria. Therefore, it was decided that the research activities be directed mainly towards a search for antibiotics active against Gram-negative bacteria, and later, also against acid-fast bacteria. As a result of the very first survey . . . it was established that such agents are being produced by actinomycetes and it appeared that little difficulty would be experienced in isolating them from the medium, provided the proper techniques for such isolation were developed. 33

Shortly after, Waksman isolated streptothricin, which had a typical antibiotic character. Testing in animals confirmed the laboratory observations. However, ". . . the animals that recovered from the infection through use of streptothricin later died because of certain latent toxicity of

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[31] Ibid., p. viii.

[32] Selman Waksman, "Production of Streptomycin and Other Antibiotics by Actinomycetes," eds. G. W. Irving and H. T. Horace, Antibiotics (Brooklyn: Chemical Publishing Co., 1949), p. 75.

[33] Ibid., p. 78.

this antibiotic."[34] This success, although limited, combined with the proved success of penicillin to further intensify the research effort. "It was now definitely only a question of continuous search before similar compounds with less toxic properties could be found. This led to the isolation, a year later, of streptomycin."[35]

The impression left by Waksman's statements is contrary to the stereotyped idea of the discovery process. The discovery of streptomycin was not a "flash of genius" where the solution occurred to the inventor where it had not occurred to others. Rather it was an idea, based on the work of many other investigators, that certain microorganisms possessed antibiotic properties. And, an iteratative approach or procedure characterizes this research. This then is one strand in the discovery of the antibiotic drugs.

The second strand necessary to both the discovery and development of antibiotic drugs was the acceptance by the medical community that a substance normally toxic to the body could be used to control disease. The great therapeutic success of penicillin leading to medical acceptance was a necessary condition to the discovery of other antibiotic drugs.

The research process developed by Waksman and others at Rutgers University was basically a procedure to screen soil samples. This procedure can be described or divided

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[34] Waksman, Neomycin, p. ix.

[35] Loc. cit.

into five steps.[36] The first step was the collection of soil samples from many different locations. From the literature on microbiology, it appears that the effective antibiotic organism is a fleeting substance whose existence depends upon several environmental factors being at an optimum simultaneously. Thus, given a suitable environment the particular microorganism will exist up to the point that one of the controlling factors itself changes. This required that many soil samples be collected in the hope that one would yield an effective antibiotic. In his search for streptomycin, it is said that Waksman examined some 10,000 soil samples before the one that yielded streptomycin was found.[37]

In the second stage the microorganism is separated from the soil sample and placed in a culture medium to induce growth. When a suitable quantity of the microorganism is present it enters the third stage where it is separated from the medium and exposed to predetermined types of bacteria. If it is observed that the microorganism under investigation destroys bacteria to which it is exposed, further investigation is warranted. As of 1955 some 3,000 to 4,000 microorganisms with antibiotic properties have

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[36]There is no evidence that this screening procedure was original with Waksman, although it would appear that certain techniques were developed in his laboratory. Speculation indicates that the screening procedure was an enlarged version of a small-scale laboratory procedure used in microbiology research for isolation and identification of microorganisms. For a more detailed description of the steps in this research process, see Hearings on Administered Prices . . ., Part 25, pp. 15303-15305.

[37]Jewkes, et al., The Source of Inventions, p. 374.

been isolated to enter the fourth stage.[38]

In the fourth stage the isolated substance is tested for toxicity on animals infected with specific pathogenic bacteria. The purpose here is to determine the size of the gap between the effective therapeutic dose and the lethal dose as well as determining the general pharmacological properties. Success in this fourth stage would place the drug in the hands of the physician for review and clinical testing. If the clinical testing program confirms the results obtained in animal testing the drug is ready for marketing in a technical sense. It has been estimated that on the average only two products a year survive the clinical stage to reach the market.[39]

From the simplified description of the research process two conclusions may be gained. First, it would not be valid to conclude that this technology is without its problems that must be solved on a technical level. There are of course many such problems, from the choice of culture mediums to techniques of separation, isolation, and identification. These sorts of problems must first be solved before the program can be turned over to others for routine operation. Here, then, was the nature of Waksman's contribution. In effect he invented a method of invention.[40]

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[38] FTC, Report, p. 113. [39] Loc. cit.

[40] This also seems to have been the case in hybrid corn. See Zvi Griliches, "Research Costs and Social Returns: Hybrid Corn and Related Innovations," Journal of Political Economy, LXVII (October 1958), pp. 419-31.

The second conclusion which follows is that the research technology invented by Waksman was susceptive to mass production operation. The screening process was standardized at several stages and capable of operation by individuals of limited skill and training. The tasks to be performed are largely repetitive and mechanical, even to step three--observing the antibiotic action of the isolated substance. It is then this sort of mass research which seems well-suited to commercial firms and which produced the majority of the advances, both major and minor, in the antibiotic drugs.

The question can be raised at this point whether Waksman's research was of a basic or applied nature. Kuznets would have us distinguish between these concepts on the basis of the workability of the discovery. That is, once it can be demonstrated that the discovery or invention works, what follows is applied research.[41] But in the case of Waksman's discovery, what is indicated by the term "work"? The answer to this question is complicated by the fact that here we have two products--the product streptomycin, and the research technology. An application of the Kuznets definition implies that both were in the area of applied research. For here it was Florey and the Oxford group which demonstrated that a microorganism found in the soil worked in the sense that it possessed the ability to control and

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[41]Simon Kuznets, "Inventive Activity: Problems of Definition and Measurement," in National Bureau of Economic Research, The Rate and Direction of Inventive Activity: Economic and Social Factors (Princeton: Princeton University Press, 1962), p. 34.

cure disease in man. It was this group that opened the medical door through which could pass streptomycin and its followers. Thus, by applying the Kuznets definition, Waksman's research effort was not inventive activity. But in view of the productivity of Waksman's technology this conclusion appears too restrictive.

Another approach to this problem is to distinguish between basic and applied research on the basis of the probability of success of the research project in question. If the success (here success is defined as a marketable result), of the project is highly uncertain then it is a type of basic research activity. On the other hand if success seems fairly certain, it is a type of applied research.[42]

Applying the probability rule to Waksman's research, the isolation of streptothricin, with all the properties of an acceptable antibiotic except for the problem of latent fatal toxicity, indicated that an acceptable drug would be forthcoming with a high degree of certainty.[43] Thus, as the research project progressed the probability of success increased and the project was converted from one in basic research to one in applied research.

The implication here is that basic research in some way makes a greater contribution to the growth of knowledge

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[42] Statement of David Novick, in Hearings on Administered Prices . . ., Part 19, pp. 10510-10523.

[43] See p. 61 where Waksman is quoted on this subject to the effect that it was only now a question of continuous search.

than does applied research, although it is recognized that there is a feedback relationship from applied to basic research.[44] Here we are clearly faced with two questions: first, how are the two activities to be differentiated, and second, why does basic research have a greater economic effect? The answer to the latter question is largely determined by the definition of basic research. If the National Science Foundation approach is used then basic research is an activity that seeks knowledge for its own sake without any view to practical application.[45] Basic research then is an activity which adds to the stock of knowledge and applied research performs the primary function of translating from this stock of knowledge to practical application in terms of new products and new processes. Or in somewhat different terms it is an activity which increases the range of investment opportunities available in the economy.

Applying this approach to the general research that produced penicillin and streptomycin illustrates the differences in the concepts. In the development of penicillin the research undertaken by Florey was critical. His major contributions in an economic sense were to show that production and extraction of the active substance from the

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[44]See for example Burton H. Klein, "The Decision Making Process in Development," in National Bureau of Economic Research, pp. 477-97. See also Richard R. Nelson, "The Simple Economics of Basic Scientific Research," Journal of Political Economy, LXVII (1959), pp. 297-306.

[45]National Science Foundation, Third Annual Report (Washington: 1953), pp. 38-39; and The President's Scientific Research Board, "The Nation's Medical Research," Science and Public Policy, V (Washington: U.S. Government Printing Office, 1957), p. 8.

Fleming broth was possible. Of equal importance was the clinical demonstration of the medical effectiveness of the drug. For the latter of these two contributions ensured that demand would be generated, while the former indicated that supply was at least within the realm of the possible. Again, both of these contributions increased the stock of knowledge, but each in a somewhat different sense. There was here an increase in the stock of technical knowledge available to the scientists, but there was also the knowledge created that here was an investment opportunity. It was this increased stock of knowledge from which the OSRD could draw to convince the commercial firms to undertake research looking to large-scale production. The research programs that resulted from OSRD pressure, was basically applied research as its goal was the solution of technical production problems necessary to exploit the investment opportunity presented.

In the same vein the development of the soil screening technique did not in itself produce investment opportunities. But it did produce the knowledge that the operation of this technology could isolate drugs of sufficient importance that investment in exploiting these drugs might be worth the effort. Thus the development of this technology was basic research while its operation was a question of applied research.

RESEARCH AND THE TETRACYCLINES

It has been argued that the research technology developed by Waksman was highly susceptible to mass production utilization. That is, it was a type of repetitious research that required minimum scientific skill for its operation. By definition it is a form of applied research, as the primary function was the isolation of substances with antibiotic properties.

The first of the tetracycline antibiotics to be isolated was chlortetracycline. The research that eventually led to this drug began in 1944 when Lederle Laboratories (a subsidiary of American Cyanamide Company) sought an improved product over penicillin. Two factors appear to account for the selection of this research project. First, it was in this period that reports on streptomycin confirmed the soil screening approach as a producer of antibiotic drugs.[46] An indication of this success was provided by Waksman's isolation of streptothricin in 1943. Second, Lederle's production of penicillin was, in this period, by surface fermentation which placed them at a competitive disadvantage relative to the deep fermentation producers. To remain competitive in the antibiotic market Lederle had two alternative courses of action. They could have invested in the necessary plant and equipment to become an efficient penicillin producer, or they could invest in the research

[46]Florey, et al., Antibiotics, p. 1297.

necessary to isolate an improved antibiotic drug. The first course of action, given the alternative, would not have appeared to be particularly profitable. There were no effective patent restrictions or other artificial barriers to entry, and with marked increases in productivity of penicillin facilities it would have appeared that the market would be well supplied. In addition, whatever research Lederle had undertaken on penicillin, it had not shared it with other firms through the OSRD.[47] Hence, they could expect no help from OSRD in receiving patent rights.[48] These considerations would seem to have served to press for the investment in antibiotic research.[49]

The research program initiated by Lederle was headed by a Dr. Duggar, a 72 year old retired professor from the University of Wisconsin. The research technology was one of soil screening where soil samples were sent to Lederle from all parts of the world by "explorers, Boy and Girl Scouts [and] oil men in foreign countries."[50] By 1947 Duggar had succeeded in isolating chlortetracycline which was first marketed in December 1948. The patent on this drug was

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[47] Ibid., pp. 783-84 where a list of restricted publications which were provided to British scientists through OSRD, is indicated.

[48] FTC, Report, pp. 48-49, where a list of these contractors is provided.

[49] This is not to argue that investment in antibiotic research was to the exclusion of other areas of applied research developed during World War II. But the availability of Waksman's method of inventing was undoubtedly an important variable in ranking antibiotic research high on the list of possible projects.

[50] Mahoney, The Merchants of Life, pp. 175-76.

issued to Duggar in September 1949 and assigned to the American Cyanamid Company.[51]

The evidence on the discovery of chlortetracycline seems consistent with the hypothesis that the research technology developed by Waksman could be operated in a rather mechanical manner by less skilled individuals. Why was Duggar selected to head this research project in spite of his age and his failure to publish work of importance in connection with antibiotic research? Florey, in his discussion of the discovery of chlortetracycline makes no reference to Duggar, nor does his extensive bibliography cite any of Duggar's publications.[52] The 1949 edition of American Men of Science fails to cite Duggar as the discoverer of chlortetracycline.[53] Duggar's qualifications would appear to have been a general familiarity with the process of screening soil samples in connection with his work as a microbiologist.

Given the research technology that produced chlortetracycline, was the result of sufficient importance to warrant patent protection? What was being rewarded indirectly was the research technology which was a matter of public knowledge. Prior to the discovery of streptomycin, patents on products such as chlortetracycline were not

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[51]FTC, Report, p. 231.

[52]Florey, et al., pp. 1532-1533; and bibliography beginning on p. 1579.

[53]Jacques Cattel (ed.), American Men of Science (8th ed.; Lancaster: 1949), p. 661.

issued on the grounds that these were products of nature, hence unpatentable. But, in the case of streptomycin, Merck argued successfully that the antibiotic product was transitory in nature and its isolation constituted an invention within the meaning of the patent statutes.[54] Applying the same argument to chlortetracycline one can only conclude that the product was patentable under the interpretation of existing patent statutes.

The related hypothetical question here is--would Lederle have embarked on this research project if the Patent Office had rejected Merck's argument? The problem here is the relative weights to give to the various factors in the decision. Lederle's competitive position in the penicillin market and the availability of the Waksman's screening process certainly seem of greater importance than the availability of patents. Generally, patents on drug products have been available to the industry all through its history, but it was not until after World War II that the industry became interested in the search for new drug products. Thus, there is a tendency to assign a relatively low value to the patent variable. If the Patent Office had rejected Merck's argument on streptomycin, it seems likely that Lederle would have still invested in the chlortetracycline project, but that its ranking relative to other proposed projects may have been somewhat lower. The implied reallocation of

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[54] F. Cacciapaglia, Jr., and H. B. Hockman, "The Proposed Drug Industry Antitrust Act--Patents, Pricing, and the Public," The George Washington Law Review, XXX (June 1962), 890.

research resources to other projects could have meant that the discovery of chlortetracycline, or some similar broad spectrum antibiotic, would have been delayed. But the loss here might have been compensated by the earlier discovery of some other drug of equal importance. To this sort of question there is no answer, but it is possible to conclude here that the patent apparently was of minor importance in the decision to invest in the chlortetracycline project.

The second of the tetracycline drugs to be discovered was oxytetracycline. The research program that led to this drug was begun in 1944 by the Charles Pfizer Company. This research project was initiated for reasons similar to that of Lederle with exception that Pfizer's competitive position relative to production technology was different in that they were a leading producer of penicillin by deep fermentation. Pfizer did face a highly competitive market and similar conditions were developing in the streptomycin market. Although streptomycin was patented, the patent was assigned to a non-profit institution at Rutgers University which by 1948 had granted licenses to eight producers.[55] One may add to this description of competitive conditions in the penicillin and streptomycin market the often quoted 1950 statement of Pfizer's President McKeen to the effect, "If you want to lose your shirt in a hurry, start making penicillin and streptomycin."[56]

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[55]FTC, Report, p. 229.

[56]Quoted in Mahoney, The Merchants of Life, p. 241, among others.

Between 1944 and 1949 the research program that led to oxytetracycline progressed at a leisurely pace.[57] But early in 1949 the research program was intensified by the exclusive and successful marketing of chlortetracycline by Lederle in December 1948,[58] and by Parke Davis' chloramphenicol in March 1949.[59] By November of 1949 Pfizer's efforts yielded a substance of sufficient interest to warrant a patent application on the process and product oxytetracycline. Such a patent was issued to a Dr. Sobin, Finlay, and Kane in March 1950 and assigned to Pfizer.[60]

The research technology utilized in the isolation of oxytetracycline was, as in the case of streptomycin and chlortetracycline, soil screening of samples received from many parts of the world. The isolation of this drug required the examination of some 100,000 soil samples by a team of eleven researchers.[61] With the development of oxytetracycline Pfizer abandoned its traditional policy of selling only to other pharmaceutical firms and entered the retail market with a $7.5 million advertising expenditure.[62]

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[57] Mahoney, op. cit., pp. 241-42.

[58] FTC, Report, p. 231.

[59] "Shock Treatment for Parke Davis," Fortune, September 1953, XLVIII, 108.

[60] FTC, Proposed Findings of Fact, Conclusions of Fact and Law, and Order to Cease and Desist, Docket No. 7221 before the Federal Trade Commission in the Matter of American Cyanamid, et al., June 1960, p. 11.

[61] Mahoney, op. cit., p. 242; also John Gunther, "Inside Pfizer," New York Times, March 23, 1958, sec. 10, p. 6.

[62] Mahoney, op. cit., p. 243.

The research efforts that produced oxytetracycline were similar to those which produced chlortetracycline. The three Pfizer researchers to whom the oxytetracycline patent was issued may be assumed to have been the major contributors to the research effort. Yet their prior contribution to antibiotic research was nil as measured by Florey's bibliography.[63] The American Men of Science lists only two of the three patent holders,[64] and neither is credited with discovering oxytetracycline.

Of the eleven members of the research team which worked on oxytetracycline only one member, Dr. G. O. Hobby is extensively noted by Florey with fifteen articles. It would appear that a good deal of Hobby's work was done while connected with Columbia University in a co-operative research project with Pfizer on penicillin.[65] One other member of this team is noted by Florey with two articles on techniques of assay of penicillin. Thus, of the eleven members of this research team, only one could be considered accomplished in antibiotic research, and his contribution to the isolation of oxytetracycline was apparently secondary to those in whose name the patent was issued.

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[63]Florey, et al., Antibiotics, pp. 1579-1662; according to Mahoney, The Merchants of Life, p. 242, the patent was issued to Sobin, Finlay, and Kane.

[64]Sobin is unlisted. Finley is listed as holding the M.A. degree and Kane with the B.S. American Men of Science, 9th ed., pp. 593 and 1002.

[65]Mahoney, op. cit., p. 239.

With the clinical and market success of oxytetracycline established, the next step was to establish its chemical structure with the objective of cheaper synthetic production. This was accomplished by R. B. woodward, who headed a Pfizer research team in the summer of 1952. Woodward was able to demonstrate the chemical structure not only of oxytetracycline but of chlortetracycline.[66] With the knowledge of the chemical structure of these drugs and with the knowledge that "slight alteration with such structures may strengthen or weaken a typical action,"[67] Conver, a member of Woodward's research team, was successful in removing the chlorine atom from chlortetracycline, thereby producing tetracycline.[68] After rather extensive litigation, a subject covered in Chapter III, a patent was issued to Conver in January 1955 and assigned to Pfizer.[69]

The choice of Woodward to head the Pfizer research team indicates the selection of an experienced antibiotic researcher. As measured by Florey's author index, Woodward, as a member of Harvard University's department of chemistry did extensive work on the synthesis and structure of peni-

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[66]Federal Trade Commission, Findings as to the Facts and Conclusions of Law, Docket No. 7211, before the Federal Trade Commission in the Matter of American Cyanamid Co., et al. (Washington: August 8, 1963), p. 7.

[67]Harry Beckman, The Year Book of Drug Therapy (Chicago: Year Book Publishers, 1961), p. 6.

[68]Federal Trade Commission, Initial Decision, Docket No. 7211. Before the Federal Trade Commission in the Matter of American Cyanamid Co., et al. (Washington: 1961), p. 13.

[69]FTC, Report, p. 253.

cillin. Applying the same standards to Conver, and to Minieri, Heyden's discovery of tetracycline, indicates that neither were publishers of significant antibiotic research.[70]

The type of research which led to tetracycline was essentially different from that which had produced streptomycin, chlor- and oxytetracycline in that it involved changing the chemical structure of chlortetracycline.[71] Three factors seem to account for the investment in learning the chemical structure of oxytetracycline. First, as previously noted, it was recognized that a slight modification in the chemical structure of a drug substance could lead to a different (improved) therapeutic effect. Second, knowledge of a substance's chemical structure was a prerequisite to any attempt at synthetic production. The earlier history of the industry indicates that synthetic production involves lower per unit costs.[72] A third factor which exerted an

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[70]Conver, in whose name the tetracycline patent was eventually issued is unlisted in The American Men of Science.

[71]However, it does appear that Heyden Chemical Company did produce tetracycline by fermentation in 1953, without knowledge of the chemical structure of oxytetracycline or chlortetracycline. Commercial production of tetracycline is by fermentation, but whether it is produced from the same strain used by Heyden is not clear. Regardless of the Heyden contribution, tetracycline was a product of a different type of research technology than that of soil screening. See for example: American Cyanamid Company, Proposed Findings of Fact, Conclusions of Law and Proposed Order, With Reasons in Support Thereof, Before the Federal Trade Commission in the Matter of American Cyanamid, et al., October 14, 1960, I, 16-17 and 54. A. Leon Higginbotham, Opinion of the Commission, in the Matter of American Cyanamid, et al., Docket No. 7211, August 1963, pp. 5, 9-10.

[72]Mahoney, op. cit., pp. 196-98.

influence was the fact that Pfizer's substitute for Lederle's chlortetracycline was unable to overcome Lederle's lead in the market.[73] In part this was undoubtedly due to the fact that Pfizer lacked in this period the extensive marketing facilities of Lederle. A possible fourth factor might have been the advertising value of the "discovery" of a new antibiotic. Again, there is no way to assign relative weights to these variables, but it would appear that this combination of factors would give a high rank to the investment in determining the chemical structure of oxytetracycline.

Was tetracycline sufficiently different from chlortetracycline and oxytetracycline to warrant patent protection?[74] From a technical point of view it can only be concluded that it was on the basis that it was a product with a somewhat different chemical structure. From an economic point of view, it was essentially a perfect substitute for chlortetracycline. The same range of pathogenic microorganisms were attacked and the side effects were similar. But the patent statutes recognize technical rather than economic differences, and tetracycline met the standard of the Patent Office.

The last of the tetracyclines, demethylclortetracycline, was isolated by Lederle in 1957. It is the product

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[73] Rough estimates of 1950 market shares for broad spectrum antibiotics indicates that Lederle accounted for about 70 per cent and Pfizer for about 10 per cent. Appendix, Table 1, p. 241.

[74] The patentability of tetracycline is discussed in Chapter III.

of a mutant strain of Streptomyces aureofaciens and is produced commercially by fermentation.[75] Beyond the fact that this drug is claimed to have increased therapeutic efficiency over the other tetracyclines, there appears to be no other published information on the research that led to the isolation of this drug.

CHLORAMPHENICOL

The isolation of chloramphenicol was the result of a research program similar to that which produced the majority of the other antibiotics. Paul Burkholder of Yale University succeeded in isolating this antibiotic from a soil sample obtained in Venezuela in 1947.[76] The program was initiated in 1943 when Parke Davis made a grant of $5,000 to Burkholder with instructions to find an antibiotic effective against six types of bacteria.[77] Considerable impetus was given to Parke Davis' testing and development of this drug in the late 40's by their competitive position in the antibiotic market. As one writer stated the case, "they missed the penicillin boom that made other firms rich and later built a streptomycin plant, but the market broke before it

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[75]Paul Folsom, Physicians' Desk Reference (16th ed.; Oradell, N.J.: Medical Economics, Inc., 1961), p. 636.

[76]Florey, et al., Antibiotics, p. 412.

[77]Mahoney, Merchants of Life, p. 66.

was finished."[78]

With the marketing of chloramphenicol in March 1949, sales success followed to the extent that Parke Davis had to turn to Pfizer and Monsanto Chemical for supplementary production. Production at this time was by fermentation. However Parke Davis' research was able to determine the chemical structure of this drug and chloramphenicol was the first antibiotic produced synthetically.[79]

The patent on chloramphenicol was issued in the name of four persons in October 1949 and assigned to Parke Davis.[80] Assuming that these four individuals were responsible for the major research on this drug, their previous antibiotic research as measured by Florey's bibliography reveals little significant published research. There is one joint article authored by the four, and one article by Bartz. Burkholder, the discoverer,[81] is listed with four.

The evidence on the isolation and development of chloramphenicol fits into the pattern of the other broad spectrum drugs. The research technology was one of soil screening initially operated in the mid-1940's by a scientist with previous research in the antibiotic area.

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[78] Fortune, op. cit., p. 109.

[79] Ibid.

[80] U.S. Patent Office, Official Gazette, DCXXVII, October 4, 1949, p. 229. The Gazette lists the following names as the patentees: Harry M. Crooks, Mildred C. Rebstock, John Controulis, and Quentin R. Bartz.

[81] American Men of Science, p. 342, lists Burkholder as the discoverer.

The effect of the successful development of this drug was to further confirm the soil screening process and along with Lederle's success with chlortetracycline, to intensify Pfizer's research program which led two years later to oxytetracycline.

CONCLUSIONS

Basic research has been defined as an activity that increases the stock of scientific knowledge, or alternatively as an activity where the probability of success is quite low. Applied research, in turn, has been defined as an activity which uses the stock of existing knowledge to create a marketable product, or alternatively, where the probability of success is to some degree greater. In addition, there exists a feedback relationship between applied research and the stock of knowledge in which the operation of the former activity can enlarge the size of the latter. This is not to argue that basic research cannot result directly in a marketable product, for with streptomycin this was clearly the case. Rather, it is to argue that the primary goals of the two activities differ.

Following the development of basic penicillin, ten antibiotic drugs followed through 1959. Two, on a "product importance criterion," were ranked as major breakthroughs. One, streptomycin, was the by-product of basic research, and the second, chlortetracycline, was the product of applied research. Similar results are observed in the case of

the major advances. Chloramphenicol resulting from basic research and benzathine penicillin a product of applied research. Of the six minor advances, all appear to have been the result of applied research. From this sort of evidence it must be concluded that applied research is capable of generating significant drug products although the probability of any one invention being significant appears relatively low.

In the case of the broad spectrum antibiotics, the key invention was found to be Waksman's soil screening process. It was the operation of this technique which generated two highly significant drug products--chloramphenicol and chlortetracycline--and two close substitutes--oxytetracycline and tetracycline. Tracing the discovery of these antibiotics from Burkholder to Conver, it was found that the qualifications of the inventors, as measured by their prior publication on antibiotics, declined. This lends further support to the importance of Waksman's technique and indirectly to the basic research which produced it.

Some attempt was made to isolate the variables responsible for the commercial investment in research beyond a mere statement that such research was profitable. Three variables were apparently important: (1) the existence of a proven research technology suitable for commercial utilization; (2) the market position of the innovating firms; (3) the patentability of research results. Each of the innovating firms, prior to their major effort in antibiotic

research, experienced a high degree of competition in the antibiotic market. Merck gambled on synthetic penicillin and along with Lederle entered the penicillin market with the high cost surface fermentation process. Parke Davis missed the antibiotic market entirely. Pfizer, a leading penicillin producer, was early faced with unrestricted entry and price competition. Later, with Lederle and Parke Davis marketing broad spectrum antibiotics, their future profitability and market position was threatened. Waksman's method of inventing new antibiotics provided a means of maintaining market positions through the isolation of more or equally effective drugs. The possibility of patents would avoid the unrestricted entry situation of the penicillin market, thereby giving a measure of protection to market positions.

What, in the final analysis did the patent system reward in granting patents on the majority of the antibiotic drugs? The reward was for the iterate operation of a research process. From a social point of view the important contribution was the research process. The commercial operation of this process produced private property rights which could be exploited for profit. Whether the society paid more than was necessary to elicit utilization of the process cannot be stated with any degree of certainty, but in a market characterized by oligolopy where one firm engages in the development process it would seem that others would be forced to follow.

CHAPTER III

THE TETRACYCLINE PATENT PROCEEDINGS

The analysis of market control in the tetracycline market through patents is divided into three parts. The first part, discussed in this chapter, considers the forces that determined the interrelationships of the major antibiotic producers and their efforts to secure a patent on the drug tetracycline. In the following chapter the domestic and foreign license agreements resulting from the tetracycline patent are discussed, and in Chapter V the pricing of antibiotics is analyzed.

By way of introduction the general relationship of the antibiotic to the overall drug market is briefly indicated, as is the market positions of the major producers. The question here is what were the characteristics of the antibiotic market that allowed the development of a degree of monopoly power through patents? With the isolation of tetracycline what were the alternative courses of action open to the firms in securing the patent? In the litigation and manoeuvring that ensued what was the overriding consideration? What was the reaction of two smaller firms in competition with the two largest firms for the patent on tetracycline?

In this chapter I will argue that under the assumption of initial noncollusive behavior that Lederle held a key position in Pfizer's attempt to patent and market tetracycline and could have prevented the product patent from issuing. But to do so would have exposed the market to unrestricted entry. Faced with a choice of conduct, Lederle suppressed the information which would have prevented the issue of the tetracycline patent and entered a collusive agreement with Pfizer to ensure the latter's securing this patent. In addition Lederle used its market power in conjunction with Pfizer in an attempt to prevent entry and monopolize the tetracycline market.

MARKET POSITIONS

The antibiotics are the largest segment of the drug market in terms of the value of shipments. In 1947, antibiotics accounted for 9.4% of the total drug market and by 1954 had increased to 16.9%.[1] By 1950, prior to the isolation of tetracycline, the three broad spectrum antibiotics accounted for some 38.5% of the antibiotic market. By 1956, this percentage increased to 54.7%, with tetracycline accounting for the largest share of the antibiotic market at 24.2%.[2] In absolute terms the broad spectrum market in 1950 involved

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[1] 1958 Census of Manufacturers, II, Industry Statistics, Part 1, General Survey and Major Groups 20 to 28 (Washington: U.S. Government Printing Office, 1961).

[2] See Tables 1 and 2, Appendix, p. 241 and p. 242.

sales at the manufacturer's level of $82 million. With the introduction of tetracycline this market by 1956 had increased to $148 million.[3]

The absolute size of the broad spectrum market and its relative profitability[4] made entry attractive. Thus, with the isolation of tetracycline in 1952, the largest segment of the antibiotic market was threatened with entry and with the strong possibility that price cutting would develop as in the case of penicillin and streptomycin.

The relative share of the antibiotic market held by the various firms is indicated in Table 7. These figures are not directly comparable as in the 1944 period only one antibiotic was produced--penicillin. In both 1950 and 1956 some eight to nine products are included with varying degrees of competitive relationships.[5]

Relative movements in market positions can be explained to a degree in the 1944-1950 period by the existence of product patents. In this period five patented drugs were introduced to the market and in all but one case the firm in question was able to increase its relative position. Lederle moved from seventh to first with chlortetracycline, Merck with the patent on dihydrostreptomycin moved from fourth to third. Lilly with the patent on procaine penicillin, and

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[3]See Tables 3 and 4, Appendix, p. 243 and p. 244.

[4]FTC, Report, pp. 211-12.

[5]Tables 1 and 2, Appendix, pp. 241-242 indicate for 1950 and 1956 market shares by products.

TABLE 7.--Market shares of antibiotic producers from own production

Firm	1944	1950		1956	
	Percentage	Percentage	Rank	Percentage	Rank
Pfizer	44.4	11.7	2	23.4	2
Commercial Solvents	18.2	2.5	11	0.4	11
Squibb	14.4	10.8	5	6.7	6
Merck	4.3	11.0	3	7.2	5
Heyden	2.9	2.8	9	(b)	
Reichel	2.3	(b)			
Lederle	2.2	26.6	1	28.1	1
Lilly	1.9	11.0	4	11.7	3
Abbott	1.8	2.7	10	1.1	10
Upjohn	1.4	0.7	15	4.4	8
Winthrop	1.4	(c)			
Cheplin	0.9	(c)			
Ben Venue	0.8	(c)			
Cutter	0.8	0.7	16	(c)	
Schenley	0.8	3.2	8	(c)	
Parke Davis	0.1	5.9	7	7.3	4
Bristol	(a)	6.0	6	4.3	9
Wyeth	(a)	1.8	12	5.0	7
Other	1.4	2.6		0.4	
Total	100.0	100.0		100.0	

(a) Entered the market after 1944
(b) Bought out by another firm
(c) Left the market

Sources: 1944 market shares are based on reported production for that year; 1950 and 1956 market shares are computed from manufacturer's own production. FTC, Report, p. 331 and pp. 94-95.

Parke Davis with patented chloramphenicol were able to increase their relative standings from eighth to fourth, and from sixteenth to seventh respectively. Pfizer holding the patent on

oxytetracycline was the exception slipping from first to second. In only one case was a firm able to improve its market position without a significant product patent. This was the case of Schenley which moved from fifteenth to eighth on the basis of its production and bulk sales of penicillin.

These relative movements reflect more than the patent question. In the base period certain plants were not operating at their rated capacities due to the newness of the fermentation technique and the resulting technical problems. In addition these changes reflect the different efficiencies of the firms involved, their advertising and research expenditures, as well as the fact that some firms found the market unprofitable and transferred their capital to other markets. However, allowing for the effect of these factors, four out of the top five producers between 1944 and 1950 had marketed patented drugs. Further, in two out of these four cases production and sale of the drug was carried on exclusively by the firm in question. Only Merck and Lilly licensed other producers to produce and sell dihydrostreptomycin and procaine penicillin. In the latter case only after extensive litigation.[6] Thus, while the effect of patents cannot be separated, the effect would appear to be significant.

Between 1950 and 1956 relative stability in market positions was achieved in spite of the introduction of tetracycline, a substitute drug for Lederle's chlortetracycline

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[6]FTC, Report, pp. 242-45.

and Pfizer's oxytetracycline.[7] One would be inclined to expect that with four firms isolating tetracycline within a year's time, where two of the four firms were bulk suppliers, that there would be some decline in concentration. However, the data on production indicates that the leading two producers in 1950 held 38.3% of the antibiotic market and 51.5% in 1956. In terms of sales, the leading two producers held 41.6% of the antibiotic market in both 1951 and 1960. However, in this nine-year period there was no change in the rankings of the leading four producers.[8] Of the eighteen product markets analyzed in the Arthur D. Little Report, only antibiotics shows this type of stability. Thus it would seem apropos to conclude that competitive forces were restrained in the antibiotic segment of the drug market in the face of the successful introduction of tetracycline.

To explain this observed stability in market shares, within the context of new product introduction and demand shifts, is a task of the discussion of the tetracycline patent.[9] Before turning to this topic it is useful to

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[7]Of the five firms selling tetracycline, Upjohn was able to increase its market position from fifteenth in 1950 to eighth in 1956, however this cannot be attributed directly to tetracycline. The data on production refers to sales from the firm's own facilities, but Upjohn was licensed only to sell tetracycline and not to produce it.

[8]Arthur D. Little, Inc., A Report on the Aspects of Concentration and Product Obsolescence in the Pharmaceutical Industry in the United States (Cambridge: Arthur D. Little, Inc., 1961), p. 12.

[9]See, for example, Michael Gort, "Analysis of Stability and Change in Market Shares," Journal of Political Economy, LXXI (February 1963), pp. 51-61, where it was found that industry growth through demand changes contributes to instability in market shares. This was not the case with tetracycline.

indicate certain other conditions that made cartelization of the tetracycline market possible. Up to this point two conditions have been indicated. First, the antibiotic market, and in particular the broad spectrum segment of this market, was characterized by fewness of producers, thereby reducing the number of agreements necessary between firms. Second, the absolute size of the broad spectrum market and the rewards available from a monopoly position in this market, were sufficient to make an effort at cartelization worthwhile. In addition to these conditions, there are three other major factors and two minor ones that influenced the behavior of the firms in question in their attempt to monopolize the tetracycline market.

First, it can be indicated from Chapter I that the narrow spectrum market, with many producer and sellers, was relatively competitive and characterized by declining profit margins. On the other hand in the broad spectrum market where production and sale were generally monopolized through patents and nonlicensing, profit margins were, in general, deemed adequate by the firms involved. The lesson of failure to agree was certainly not lost on the firms involved in the tetracycline agreement.

A second major factor favorable to a cartel scheme was the belief that the demand for drugs in general was inelastic so that price competition would have the sole effect of reducing total revenues. Here the demand for antibiotic drugs is largely a function of the incidence of disease susceptible to treatment by a particular antibiotic drug and the

knowledge of the physician of the range and activity of available substitutes.[10] This argument is acceptable for a static world, but expenditures to inform and influence the medical community did have the effect of shifting the demand for antibiotic drugs.[11] Thus the industry believed that demand was extremely elastic to selling expenditures. The point here is not a question of the shape and slope of supply and demand curves, but only that if firms believed that price competition would reduce total revenues in the short run this was sufficient to favor any scheme that would tend to eliminate this form of competition.

A third major factor which favored a private settlement of the tetracycline dispute as opposed to a court settlement was the legal climate relative to patent questions before the courts. As a general proposition, companies are rather hesitant to bring their patent disputes before the courts in light of judicial rulings on these questions.[12] In such litigation the court consistently reviews the findings of the Patent Office as well as looking beyond the patent issue to the question of misuse.

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[10] FTC, Report, pp. 152-54.

[11] See Table 5, Appendix, p. 245, for output data of medical grade antibiotics of a broad spectrum character.

[12] For example see, Robert Levine, "The Shrunken Patent Domain in the Expanded Anti-trust Universe," Journal of the Patent Office Society, XXXIV, No. 6, 1952, pp. 436-47; Benton Baker, "Patent Rights and the Anti-trust Laws," JPOS, XXXIV, No. 9, 1952, pp. 687-89; Karl B. Lutz, "Are the Courts Carrying out Constitutional Public Policy on Patents," JPOS, XXXIV, No. 10, 1952, pp. 766-91.

As an example of a somewhat extreme view there is the opinion of Judge Thurman Arnold where it was said

> if we apply the fundamental principles of the patent law to the actual facts of the complex modern technology of corporate research laboratories. These principles are (1) that a discovery which is the result of step-by-step experimentation does not rise to the level of invention; (2) that invention must rise above the level of accomplishment of the ordinary skilled technicians engaged in the art; (3) that the patent law must be so administered as to promote science and the useful arts. 13

Or on the question of influence of experimentation in Minnesota Mining and Mfg. Co. v. Coe, where the Court held:

> But a showing of great industry in experimental research is not in itself sufficient to constitute invention, when the product therefore differs from a prior art only in degree, the result--no matter how useful it may be--is merely one step forward in a gradual process of experimentation. 14

In Naamlooze Vernootshafs: W. A. Sholtens Chemische Fabrieken v. Coe:

> Experimentation may well have been necessary to determine this. But, . . . that progress in the chemical art is reached largely through experimentation, . . . it does not follow that every new and useful result accomplished by experiment is patentable. 15

These views are not quoted to express settled law on the question of industrial research, but to indicate the risk of judicial review. It was concluded that the discovery of chlortetracycline and oxytetracycline was the result of a step-by-step research technology essentially

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[13] Potts v. Coe, 145 F, 2nd 28 (1944).

[14] Minnesota Mining and Mfg. Co. v. Coe, 99 F 2nd 989 (1938).

[15] Naamlooze Vernootshafs: W. A. Sholtens Chemische Fabrieken v. Coe, 132 F, 2nd 575 (1943).

developed by Waksman. To subject this discovery process to judicial review would have run an unnecessary risk that could be avoided through interfirm agreement.

There were two other conditions present in the pre-tetracycline market that favored agreement. There was first, the general interrelationships of the chemical firms where agreements to license competitors was the usual case.[16] Second, there is the indication that the costs of production of antibiotic drugs by fermentation were similar among firms thereby eliminating the problem of profit pooling.[17]

Under these conditions, the simultaneous discovery of tetracycline foreshadow interfirm conflict over the patent. How this conflict was resolved for the private benefit of the group is the subject of the following section.

THE TETRACYCLINE PATENT

In 1950, prior to the introduction of tetracycline, the three broad spectrum antibiotics represented approximately 26% of total output of all antibiotics and 38.5% of the total value at the manufacturer's level. Lederle, with chlortetracycline held 26.6% of the total antibiotic market and 69.1% of the broad spectrum market. Pfizer, with oxytetracycline held 11.7% of the total antibiotic and 12.2% of the broad spectrum market. Parke Davis, with

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[16] See, for example, George W. Stocking and Myron W. Watkins, Cartels in Action (New York: The Twentieth Century Fund, 1947), Chap. IX.

[17] FTC, Report, pp. 11-12.

chloramphenicol, held 5.9% of the total antibiotic market and 15.3% of the broad spectrum market. In the case of Lederle and Parke Davis, one product was the total contribution to the antibiotic market. Pfizer on the other hand produced all but the two specialties of Lederle and Parke Davis.

Lederle's chlortetracycline was the first of the broad spectrum antibiotics to be marketed in 1948, followed by Parke Davis' chloramphenicol in 1949, and Pfizer's oxytetracycline in 1950. By 1951, following what has been termed a "blitz advertising campaign"[18] by Pfizer in its marketing of oxytetracycline, this entry accounted for some 25% of the broad spectrum market, while chlortetracycline fell to some 48% and chloramphenicol increased to 27%.[19] Up to 1952, these three drugs evidently were near perfect substitutes in that they were effective against the same range of microorganisms. But in 1952 the problem of the side effects of chloramphenicol restricted its use.[20] The following discussion then is largely restricted to the tetracyclines.

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[18] FTC, Report, p. 140.

[19] Mahoney, The Merchants of Life, p. 244.

[20] "Shock Treatment for Parke Davis," Fortune, XLVIII (1953), 108. The dangerous nature of the side effects of chloramphenicol made this drug an imperfect substitute for chlortetracycline and oxytetracycline in the general treatment of infection. Production fell from 136,676 pounds in 1952 to 4,892 in 1953, however there was no change in Parke Davis' list price on this drug.

Resuming the narrative of the tetracycline patent from Chapter II, where Woodward of Pfizer had succeeded in determining the chemical structure of both oxytetracycline and chlortetracycline and Conover in turn had succeeded in producing tetracycline by a modification of the chemical structure of chlortetracycline. This work resulted in two articles published in the Journal of American Chemistry. The first appearing in the October 1952 issue described the common chemical structure of the tetracyclines. (This article is hereafter referred to as the structure article.) In the September 1953 issue the second article appeared which described the production process of producing tetracycline. (This article is hereafter referred to as the production article.) In the same issue a similar article appeared written by Lederle's research staff.[21]

The publication of the structure article appeared as a threat to Lederle's market dominance with chlortetracycline. For with the knowledge of the chemical structure the implication was that Pfizer was in the process of attempting to modify the structure in an effort to develop a new broad spectrum antibiotic. As a result Lederle resumed research in this area that had been abandoned in 1948.[22] By the end

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[21]Federal Trade Commission, Opinion of the Commission, before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7211, August 1963, pp.9-10, hereafter cited as Opinion of the Commission.

[22]John T. Kelton, Respondent American Cyanamid Company's Proposed Findings of Fact, Conclusions of Law and Proposed Order, with Reasons in Support thereof, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7211, October 1960, I, 15-16, hereafter cited as Cyanamid's Proposed Findings.

of 1952 Booth of Lederle succeeded in producing tetracycline by the same technique as Conover at Pfizer had used. In the course of this work Booth learned that tetracycline was co-produced in the fermentation process that produced chlortetracycline.[23]

The point that emerges here is that with the co-production of tetracycline with chlortetracycline, Pfizer could not, without infringing the Lederle patent on chlortetracycline, produce the end product tetracycline.[24] Thus, Lederle was in an excellent position from which to protect its market against Pfizer's unrestricted encroachment. Before this issue could be settled, potential competition appeared in the form of two other firms that claimed to have discovered tetracycline.

The most potentially dangerous was the Heyden Chemical Company. In May of 1953, Minieri of Heyden produced a then unidentified antibiotic by direct fermentation. (That is, without first producing chlortetracycline.)[25] Thus, Heyden, in producing tetracycline, would not per se infringe the Lederle patent. What made Heyden an even greater threat was that they were primarily a bulk supplier of antibiotics to other firms.

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[23] Ibid., p. 16.

[24] Pfizer's initial patent application was in fact rejected on these grounds. See Opinion of the Commission, p. 9.

[25] Opinion of the Commission, p. 10; Cyanamid's Proposed Findings, pp. 16-17.

The fourth firm to claim tetracycline, and the one that proved the most difficult to deal with from the Pfizer-Lederle point of view, was Bristol. Prior to 1950, Bristol had employed the soil screening process in search of an antibiotic to compete with the broad spectrums and to offset declining profit margins in the narrow spectrum market. By September 1953, Bristol scientists had succeeded in isolating a substance with antibiotic properties but had not engaged in clinical testing. With the publication of the production article, Bristol produced tetracycline by the method described and compared the resulting product with their earlier product. Comparative tests indicated that these were the same products, thus Bristol filed its claim to discovery. But, as their "discovery" took place after Heyden's, and the product had not been clinically tested, hence not reduced to practice, it placed them at a disadvantage vis a vis Heyden.[26]

The relative bargaining positions of these four firms prior to the proceedings before the Patent Office can be summarized at this point. Lederle's position relative to Pfizer appears to have been the stronger of the two. Pfizer, in its production of tetracycline, had to first produce chlortetracycline which was patented by Lederle. Thus Pfizer would have to secure a license from Lederle with the

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[26]Allen T. Klots, et al., Bristol's Proposed Findings of Fact, Conclusions of Law and Answers to the Government's Contentions, Before the Federal Trade Commission, In the matter of American Cyanamid Company et al., Docket No. 7211, October 1960, I, 12-13; hereafter cited as Bristol's Proposed Findings.

latter able to control the terms of the license. Open competition between these two firms was not a likely alternative, but in such a contest, Lederle's hold of some 50% of the broad spectrum market as opposed to Pfizer's 25%, would provide sufficient resources to engage in such a conflict. In terms of absolute size, American Cyanamid was roughly three times larger than Pfizer as measured by sales or assets.

Pfizer's alternatives at this point were to reach an understanding with Lederle in securing a license, or to produce chlortetracycline, thereby infringing the Lederle patent and press the matter into the courts. Pfizer's only conceivable argument here would have been that chlortetracycline was unpatentable in that its discovery did not rise to the level of invention. Selection of this latter alternative was of course highly unlikely but its existence undoubtedly provided some force to Pfizer's bargaining for a license. As matters developed, a third alternative appeared which strengthened the Pfizer position. If Pfizer could secure the product patent on tetracycline, by convincing the Patent Office that co-production did not in fact occur, it would be free of the Lederle patent control on chlortetracycline. This would of course require the co-operation of Lederle in not contesting the co-production issue. Speculation on Lederle's position under this alternative would indicate that it was to their advantage to license Pfizer to produce chlortetracycline and to co-operate with Pfizer in securing the product patent on tetracycline. In this way potential

competitors would be faced with two patent barriers--on the end product tetracycline, and on the intermediate product chlortetracycline. Not to co-operate with Pfizer might have meant that a product patent would not be issued and that market control could only be achieved through the chlortetracycline patent. This was a less preferred position for two other firms claimed to have produced tetracycline by direct fermentation--a process that apparently did not infringe the chlortetracycline patent. Thus, co-operation became the preferred position instead of allowing the entry of Bristol or Heyden.

The Lederle-Pfizer bargaining positions, relative to Bristol and Heyden, presented certain problems. Both the Lederle and Pfizer patent applications claimed the product tetracycline and its method of production by deschlorination of chlortetracycline. Heyden and Bristol made similar claims but based on direct fermentation. The Heyden application was filed on September 28, 1953; while the Bristol application was filed on October 19, 1953. Fifteen days after the Heyden application was filed, Lederle filed the Martin-Bohonos application, and on November 12, 1953, Pfizer was in the Patent Office with an application similar to Lederle's in that both claimed tetracycline by fermentation.[27]

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[27]Federal Trade Commission, Findings As to the Facts and Conclusions of Law, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7211, August 1963, pp. 8-11. Hereafter cited as FTC, Findings.

The Lederle fermentation application resulted from their purchase of the antibiotic facilities of Heyden Chemical Co. Heyden announced its discovery of tetracycline on October 1, 1953 and on November 4th the purchase agreement was jointly announced. Thus it would appear that Lederle had immediate access to Heyden's research on tetracycline, (assuming that negotiations were initiated immediately following Heyden's public statement on the 1st of October), to have been able to file its fermentation application by the 12th of that month.

The Pfizer fermentation patent application is somewhat more difficult to explain as it seems unlikely that their independent research could have discovered the strain of microorganism responsible for the direct production of tetracycline in such a short period of time.[28] Two alternative explanations can be offered. First, in a later development in the contest for the tetracycline patent, Pfizer was found guilty in the New York Courts of employing a John G.

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[28] A search of the briefs and proposed findings of the respondents Pfizer and Lederle turn up no statements to the effect that they conducted research seeking to produce tetracycline by fermentation. This is not unexpected as both Pfizer and Lederle defended their cross-licensing arrangement in tetracycline with the argument that in the absence of such an agreement a blocking situation would have resulted and the public would have been denied the benefits of this discovery. If Pfizer could have produced tetracycline by direct fermentation it would not have required a license from Lederle. Arthur G. Connolly, Pfizer's Answering Brief, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7221, April 1962, Part 2, p. 9.

Broady to tap the telephone lines of Bristol and Squibb.[29] It is possible that through this procedure the strain of microorganism used by Bristol was learned. There is, however, no evidence that such tactics were employed at this stage in the contest. A second alternative is that Pfizer and Lederle were at this stage engaged in a co-operative effort to exclude competition from the tetracycline market and to insure that Pfizer received the patent on this drug. Under this hypothesis Lederle may have made the Heyden research available to Pfizer so that they could enter a claim of direct fermentation, thereby strengthening their case. Again there is no direct evidence that in fact such a co-operative program was engaged in at this stage.

With the elimination of Heyden only Bristol was left to be dealt with. Although other firms had expressed an interest in marketing tetracycline, none were in a position to undertake production in the light of the patent question.[30] Bristol's bargaining position relative to that of the Lederle-Pfizer, appeared to have been a poor one. Its fermentation patent application and date of isolation were preceded by the Heyden application now under the control

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[29]Allen T. Klots, et al., Bristol's Answering Brief, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7221, April 1962, Appendix pp. 1-12.

[30]Federal Trade Commission, Proposed Findings of Fact, Conclusions of Fact and Law and Order to Cease and Desist, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., June 1960, pp. 66-68; hereafter cited as FTC, Proposed Findings.

of Lederle. In absolute terms its size relative to Lederle or Pfizer was considerably smaller. Primarily a bulk supplier without a large sales force, an antibiotic house specializing in the relatively unprofitable narrow spectrum market, its ability to compete with its larger rivals must have appeared limited indeed. Under the assumption that Pfizer and Lederle were engaged in a co-operative program to insure that Pfizer received whatever patent might issue on tetracycline, Bristol was not included. Rather the decision was made to eliminate this source of competition first through the patent office and if this failed through the courts. But here full consideration was evidently not given to the determination of Bristol to enter the broad spectrum market, nor to the aid they would receive from other firms also determined to break into this profitable market.

PATENT OFFICE ACTIONS AND REACTIONS

This section is concerned with: (1) how the tetracycline patent was secured by overcoming the patent examiners' rejection based on the issue of co-production; (2) how Bristol was able to force its way into the market by threatening to prove that tetracycline was unpatentable over chlortetracycline.

The first patent application acted upon by the Patent Office was the Conover-Pfizer application filed on October 23, 1952. This application was rejected on July 23,

1953, on the grounds that tetracycline was not patentable in the light of the Duggar-Lederle patent on chlortetracycline. In addition, the patent examiner argued that because the chemical structure of oxytetracycline and chlortetracycline were similar, the discovery of tetracycline was obvious, hence its isolation did not rise to the level of invention within the meaning of the patent statutes. On October 20 Pfizer amended its application to argue that at the time of Conover's discovery the chemical structure of tetracycline was not in fact known.[31] This was sufficient to overcome the patent examiner's initial objections and the Pfizer application was readmitted for examination.

The second patent application to reach the Patent Office was the Morton-Lederle application filed on March 16, 1953. With the readmittance of the Pfizer application an interference was declared on December 28, 1953. The interference was anticipated, for in November two meetings were held between the presidents of Lederle and Pfizer in which an agreement was worked out to protect their respective positions in the broad spectrum market regardless of which firm

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[31] The FTC contended that this statement to the patent examiner was a misrepresentation of the facts as Woodward's work on the structure question was complete when Conover made his discovery. What Pfizer says it meant by this statement was that the chemical structure was at the time of Conover's work not public knowledge, but internal information that was part of its research input. Arthur G. Connolly, Pfizer's Brief in Support of Its Tetracycline Patent, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7211, October 1960, p. 12, hereafter cited as Pfizer's Brief.

secured the patent on tetracycline.[32]

The basic positions of the two firms in working out this agreement appear to be that Lederle was willing to concede priority of discovery to Pfizer, in light of Pfizer's earlier discovery date and the fact that Lederle had abandoned its work in this area. On the other hand Pfizer could not produce its basic input material, chlortetracycline, without a license from Lederle. At this time Lederle was shifting its fermentation capacity into tetracycline production, thereby securing a lead in the market over Pfizer. It was then essential that Pfizer, who had no experience in chlortetracycline production, secure an agreement with Lederle to prevent them from building a commanding lead in the market. In a sense a blocking situation resulted on the assumption that tetracycline was in fact patentable. And on the additional assumption that direct fermentation was not a possible alternative that would not infringe the Duggar-Lederle patent. There are two possible views on the question of the reasons for the meetings between Lederle and Pfizer. The companies involved claim that agreement was in fact necessary to prevent a blocking situation from developing.[34] On the other hand the government claims that the primary purpose of the meetings and resulting agreement was to monopolize the market by excluding competition. This was

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[32]FTC, Findings, p. 12.

[33]Cyanamid's Proposed Findings, pp. 20-22.

[34]Ibid., p. 24.

based on the fact that at the time of the meetings in November 1953, there had been two rejections of patent applications on the product tetracycline and its method of production. There was the rejection of the Pfizer application on the grounds of lack of novelty over the Duggar-Lederle patent, previously noted; and in addition there was a rejection of the Minieri-Lederle application on October 29, 1953, on the grounds of inherent co-production.[35] Thus, Lederle was in a position to support the Patent Office arguments for rejection, thereby denying the patent to Pfizer. Here, then, the blocking situation could only develop on the assumption of the patentability of tetracycline, and this assumption was not supported by previous Patent Office actions. And, of course, it was the blocking situation, or its possibility, that justified the meeting and subsequent agreement.

In addition, Lederle acted to eliminate by purchase, the only known competitor, besides Pfizer, for the tetracycline patent. Further support for the government contention is provided by the fact that Lederle was instrumental in Pfizer's entry into the tetracycline market. Part of the agreement provided that Lederle licensed Pfizer to make chlortetracycline, furnished them with the necessary technical information, and supplied bulk chlortetracycline for conversion to tetracycline.[36] Thus it would appear that

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[35] FTC, Proposed Findings, pp. 41, 45.

[36] Cyanamid's Proposed Findings, I, 23-24; FTC, Proposed Findings, pp. 70-73.

Pfizer greatly strengthened its market position in spite of the apparent weakness of its bargaining position. The weight of evidence indicates that the purpose of these meetings was the monopolization of the tetracycline market.[37]

As a result of the agreement, Lederle, after an exchange of relevant information with Pfizer, conceded priority of invention to Pfizer, thereby terminating the interference proceedings. However, on March 2, 1954, a second interference was declaired between the Pfizer-Conover and the Bristol-Heinemann applications.

Bristol's initial patent application had been filed in October 1953, claiming tetracycline and its method of production by fermentation. This application was rejected first on the grounds of inherent co-production, and second, on the grounds that the publication of the structure article constituted a statutory bar to the Bristol application.[38] However, even before the Patent Office rejection, Bristol evidently was unsure of its ability to secure the patent, due undoubtedly to the publication of the structure article a year before the filing of the application, and due to the

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[37] In addition, the agreement provided that the two parties would exchange information to determine priority of invention and that the company lacking priority would aid the other in securing the patent. There was the usual cross-licensing arrangement and the royalty rate on chlortetracycline was set at 2-1/2% of Pfizer's net sales of tetracycline, and at 2-1/2% on net sales of tetracycline by Lederle if Pfizer secured the patent. Thus in effect, royalty payments netted out in the case of equal market sharing. Cyanamid's Proposed Findings, I, 23-24.

[38] Bristol's Proposed Findings, I, 12-14; and FTC, Opinion of the Commission, p. 11.

fact that the fermentation work that led to tetracycline was part of an earlier abandoned experiment.[39] In November 1953, the president of Bristol contacted Lederle to work out a cross-licensing agreement. In this meeting Lederle was informed that Bristol's fermentation process did not infringe the Lederle-Duggar patent on chlortetracycline. Bristol was offered a license for its own label, but this was rejected as Bristol required at least two bulk customers to reach an efficient volume of production. Bristol's own sales force was insufficient in size to achieve adequate volume.[40]

The appearance of Bristol on the scene, with a production process that claimed not to infringe the Lederle-Duggar patent, must have given some degree of acceleration to the Lederle-Pfizer negotiations. But of even greater importance, it increased the need to secure some form of patent protection to exclude the entry of Bristol and whatever bulk customer they would bring into the market. To admit only Bristol with its small sales force would not have disturbed

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[39]FTC, Opinion of the Commission, p. 11. However, on this latter point, the research process appears to be one in which the collection and isolation of the microorganisms in soil samples proceeds at a faster rate than does the animal testing thereby building up a backlog of microorganisms for testing. This sort of phenomenon may be a result of the level of training required in different phases of the research technology where in the latter or clinical phases greater skills are required. Thus, with the publication of the structure article, Bristol searched its backlog of microorganisms to expedite the testing of those that had the characteristics of tetracycline. Thus, it is possible that the question of abandonment was not controling, leaving only the questions of statutory bar and inherent co-production.

[40]FTC, Findings, p. 11; Bristol's Proposed Findings, II, 186; Squibb's sales force was estimated at 700 to 750, while Upjohn's was estimated at some 1,000. Bristol's sales force was but some 50 salesmen.

the market positions of Lederle or Pfizer. But to admit Bristol and its bulk customers Squibb and Upjohn would have threatened that position. In this regard, Lederle, in purchasing Heyden's antibiotic facilities, also acquired the Minieri patent application for tetracycline by fermentation. Thus, Lederle held a patent application competitive to Bristol's and in light of the date of this application, relative to the publication of the structure article, Bristol's bargaining position must have appeared weak. But here Bristol, as the events of the case developed, did have leverage to force admittance for itself on its own terms. It did know from its own patent application rejections that the Patent Office considered co-production of tetracycline with chlortetracycline a bar to the issuance of the patent on tetracycline. Thus, Bristol was in a position to open the market to unrestricted entry.

With the settlement of the first interference between Lederle and Pfizer, Bristol reacted by amending its application to claim the salts of tetracycline. This action, as has been noted, led to the second interference being declaired. In this interference the patent examiner made what amounted to a tentative determination that the salts of tetracycline were patentable. Lederle was admitted to this interference in spite of the fact that it already conceded priority to Pfizer. In effect Lederle's arguments in these proceedings attempted to dissolve the proceedings thereby eliminating the Bristol claim. Success here would have meant an earlier

issuance of the patent, hence an earlier date on which Lederle would have to begin royalty payments. This action, it was contended, indicated that Lederle was in opposition to its own interests and thus engaged in a conspiracy with Pfizer to exclude Bristol, the only competitor.[41] Bristol entered the market in May 1954, under its own label; concluding an agreement with Squibb and Upjohn in September to supply them with bulk tetracycline.[42] The second interference proceedings were terminated in November 1954, with the ruling that tetracycline was not patentable on the grounds of co-production.

Before discussing how this ruling was reversed by Pfizer it is well to note the behavior of Bristol in demonstrating that it would consider the interests of Lederle and Pfizer if granted a license on its terms. In later Patent Office proceedings Bristol was in a position to prove from its own laboratory experiments that, in fact, tetracycline was co-produced with chlortetracycline thereby supporting the patent examiner's argument for rejection of the tetracycline patent application. Bristol did not make this information available to the patent examiner until it appeared that Lederle and Pfizer were determined to exclude Bristol from the market.[43]

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[41] FTC, Findings, p. 17.

[42] FTC, Opinion of the Commission, p. 13.

[43] It must be noted here that such action was also in the best interest of Bristol. To have informed the Patent Office that in effect tetracycline was unpatentable would have opened the market to unrestricted entry and also destroyed Bristol's leverage in forcing a license from Pfizer.

In addition, Bristol was faced with the problem of controlling the selling prices of its bulk customers. With its entry under the Bristol label the wholesale price was set above the prices established by Lederle and Pfizer.[44] In its price agreement with its two bulk customers, Squibb and Upjohn, it set a price which "would have permitted the purchaser no profit on the initial order if the final products were sold at prevailing market prices."[45] The agreed price was $1 million for the first 1,000 kilograms, with subsequent orders priced at $500 per kilogram, with reductions below this price to follow as Bristol's costs of production declined. The market price at this time was $5.10 to the retailer for a bottle of 16, 250 milligram capsules.[46] On a per gram basis this amounted to $1.275. The bulk cost of the initial order was $1.00 per gram, leaving some $.275 cents to cover the costs of packaging, waste, and the distributor's margin. (Subsequent prices left a margin of $.73 per gram.) The initial price of bulk tetracycline was set at $1,000 per kilogram to allow Bristol to recover its research and development costs. But in addition this price to the bulk customers made price cutting on their part an unattractive proposition as it would involve certain losses. Thus, upon entry, Bristol by its own pricing in the wholesale market, the price charged its bulk customers,[47] and its

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[44] Bristol's Proposed Findings, II, 169.

[45] Ibid., p. 167. [46] FTC, Report, p. 192.

[47] Bristol in its sublicense foreign agreements on tetracycline exerted control over the prices charged by the licensee. See Chapter IV below.

actions in the Patent Office proceedings, indicated that it would act in the best interests of the group if licensed.

The position of Bristol's bulk customers can be noted at this point. Given the potential value of the tetracycline market Squibb and Upjohn considered entry an attractive possibility. To this end they were willing to support the Bristol bargaining position under the assumption that a patent would issue and Bristol would secure a license. (The alternative assumption being that a patent would not issue and they could enter on their own terms.) It appears that they did not question Bristol's ability to force entry. To this end Upjohn and Squibb agreed to "indemnify Bristol against all damages and losses which Bristol might incur as a result of infringement. . . ."[48] The patent that could be infringed at this point was the Duggar-Lederle patent on chlortetracycline. But to produce tetracycline Bristol did not first have to produce chlortetracycline, hence any infringement suit on this patent would have to involve Bristol's use of a strain of microorganism identified by the Duggar patent. There was at this point no patent on tetracycline hence no infringement action. If such was the case the question arises of why should Upjohn and Squibb agree to this provision beyond the possibility that it was something Bristol demanded in the agreement? One possible answer is that it

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[48]Gerhard A. Gesell, et al., Brief and Proposed Findings and Conclusions of the Upjohn Company, Before the Federal Trade Commission, In the matter of American Cyanamid Company et al., Docket No. 7211, October 1960, p. 71; hereafter cited as Upjohn's Brief.

placed Lederle and Pfizer on notice that Bristol had the financial support of two firms with adequate resources to support a prolonged legal contest. This would have eliminated one weapon available to Lederle and Pfizer in driving Bristol out of the market.

PFIZER SECURES THE TETRACYCLINE PATENT

Returning to Pfizer's actions to reverse the patent examiner's action in the second interference, the examiner ruled that the salts of tetracycline were not patentable separate from the basic product (thereby eliminating the Bristol application). That the microorganism used to produce tetracycline by fermentation was of the same species as disclosed by the Lederle-Duggar patent (thereby eliminating the Minier-Heyden-Lederle application). And that tetracycline was co-produced with chlortetracycline hence "a purer form of an old product is not inventive. . . ." (thereby eliminating the Pfizer-Conover application). These rejections left the Lederle-Duggar patent controlling which gave some measure of protection to the Lederle-Pfizer market positions. But it also meant that the patent barrier on the final product was potentially eliminated. The resulting scale of entry could overwhelm the legal defense based on the intermediate product patent.[49] Thus Pfizer decided to continue its attempts to secure the product patent.

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[49]Following the FTC decision that Pfizer had secured the tetracycline patent through "unfair" means several smaller firms entered the market only to be driven out by Pfizer's determination to utilize the courts to protect its monopoly.

Pfizer, after receiving notice of the rejection of its patent application, began a series of experiments to determine the exact amount of tetracycline co-produced with chlortetracycline. A week later this work was ordered discontinued on the advice of Pfizer's patent attorney.[50] Nevertheless this work was continued but the results were recorded separately from the regular records kept of scientific experiments. The results showed that in the production of chlortetracycline according to the Lederle-Duggar and Niedercorn patents (the latter an improvement patent in the production of chlortetracycline), from 5-10% of the resulting product was tetracycline.[51] Thus Pfizer, in its own laboratory, was aware of the correctness of the patent examiner's position in rejecting the Pfizer application.

The experiment did, however, yield two bits of information that Pfizer later found useful. First, it was found that the broths prepared according to the Niedercorn patent were low in antibiotic content. Second, it was found that the recovery process described in the Duggar and Pidacks patents (the latter an improvement patent in the production of chlortetracycline held by Lederle) destroyed most of the tetracycline present.[52]

A conference was held between the patent examiner and the Pfizer patent attorney in December 1954. At this

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[50] FTC, Findings, p. 23. [51] Ibid., p. 24.

[52] FTC, Proposed Findings, p. 168 citing a Pfizer report from a Dr. Bogert who conducted this experiment.

meeting it was argued that the examiner had no reasonable basis upon which to speculate that tetracycline was co-produced with chlortetracycline. The patent examiner took the position

> that he would withdraw his objection if Pfizer could demonstrate that tetracycline could not be recovered in clearly identifiable form from fermentation broths produced strictly in accordance with the Duggar and Niedercorn disclosures, using the strain S. aureofaciens NRRL-2209 which had been deposited by Cyanamid with the Northern Regional Research Laboratory as part of its disclosure requirements in receiving the Duggar patent.[53]

To support its position before the Patent Office Pfizer set out to prove that co-production did not take place. After obtaining the required micro-organism sample, a culture medium was selected from the Niedercorn patent, the same that had proved earlier to be a poor producer of tetracycline, and one from the Duggar patent which also proved to be a producer of low potency broth. They were represented to the patent examiner as being average producing mediums from these patents.[54] In addition, Pfizer stated that the mediums were prepared strictly in accord with the disclosures in question. In fact the record contains evidence that such was not the case.[55]

The two broths were subject to recovery processes in

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[53] FTC, Opinion of the Commission, p. 18. [54] Ibid., p.19.

[55] Ibid., pp. 19-20. The Niedercorn disclosure stated that the best yields were obtained in a medium having a pH of 6.4 to 7 during the 48-hour fermentation period. Tanner, who conducted the experiment, inoculated the medium when the pH had a value of 8.1. Six and a half hours later the pH was still 8.1 and no growth of the microorganism had taken place. The medium was then adjusted downward.

an attempt to determine whether tetracycline was present and in what proportions. The three recovery procedures used were the type designed for commercial recovery of tetracycline from broths with higher potency than that of the test broths.[56] From this Pfizer was able to conclude that "this product was tested in a manner that he [Bogert] knows is capable of detecting even a small proportion of tetracycline in the presence of chlortetracycline and showed only chlortetracycline."[57] Thus the one individual Pfizer had to convince of its argument was so convinced and the tetracycline patent was issued to Pfizer January 11, 1955.

The issue of fraud in securing the patent revolves on the issue of what the patent examiner was in fact interested in relative to the co-production question. Pfizer argued that the grounds for the initial rejection of its application was that tetracycline had been in public sale more than a year prior to its filing of the patent application, and that tetracycline was but a purer form of an old product--chlortetracycline. What the patent examiner was attempting to establish, according to Pfizer, was whether tetracycline was co-produced to the extent that the therapeutic activity of chlortetracycline was due to the presence of tetracycline. That is, if chlortetracycline contained 50% tetracycline, to separate out tetracycline for a separate patent would fail as there would have been no advancement over the prior art. From this Pfizer argues that the examiner was not interested in

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[56] Ibid., p. 20. [57] Ibid., p. 21.

"useless trace amounts which cannot be separated from the broth by methods now recommended for recovery of new antibiotics."[58] Thus, according to Pfizer the 5-10% tetracycline found in its own experiments and later confirmed by other, was a useless trace amount.[59]

Pfizer in one of its interviews with the patent examiner stated that he could assume that up to 10% tetracycline was co-produced. It was further argued that even if tetracycline was co-produced, this was accidental and unrecognized production of an inefficient amount which did not negate the novelty of Pfizer's invention. Thus, as a matter of law, there was no basis for rejection on this issue of co-production.[60] But the patent examiner could not rule on the basis of an unsupported assumption. This was the very information he sought from Pfizer and which was withheld. Further it can only be concluded that as a matter of law the issue of co-production was basic to the examiner's decision.[61]

The issue here is what information the examiner

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[58] Pfizer's Brief, p. 63.

[59] While Pfizer, for its purposes, claimed that this percentage of tetracycline was insignificant and accidental, Lederle based its suit against Bristol for infringement of its Duggar patent on just this point. FTC, Proposed Findings, pp. 304-08. Bristol argued that as a matter of law there are two separate and unrelated facts and that the government was not justified in drawing any inference from one to the other of these facts. Bristol's Proposed Findings, I, 135-36.

[60] FTC, Opinion of the Commission, pp. 44-45, citing an FTC exhibit relative to Pfizer's argument of the application of the patent code.

[61] FTC, Findings, pp. 14-15.

wanted from the Pfizer experiments. The Commission, based on the statements of the examiner, found that he was interested in any presence of tetracycline, and that Pfizer interpreted this to mean any recoverable quantities.[62] The implication here is that Pfizer interpreted "any" to mean "recoverable quantities" because its earlier experiments had shown that it could set the experiment up in a manner in which tetracycline could not be recovered from the resulting broth. Thus Pfizer, by withholding from the patent examiner the facts that the broth was not representative of the prior disclosures, and that the recovery methods used were designed for broths of higher potency, misled the patent examiner in issuing the tetracycline patent.[63] Pfizer's answers to these points were largely premised on what it assumed the examiner was concerned with on the issue of co-production. The assumption being that his interest was in recoverable quantities sufficient to affect the therapeutic quality of chlortetracycline. In Pfizer's view only such significant quantities could in any way affect the outcome of the examiner's decision. From this assumption it then followed that what was withheld was not material to the decision as 10 per cent tetracycline present in chlortetracycline could not affect the therapeutic qualities of the latter, hence the discovery

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[62] Ibid., pp. 18-19, 20-21; FTC, Opinion of the Commission, pp. 46-47.

[63] FTC, Opinion of the Commission, pp. 54-57.

of tetracycline did rise to the level of invention.[64] But the question here is whether Pfizer's assumption was warranted in view of the several statements of the examiner. Given the importance of the tetracycline patent to Pfizer, as well as to Lederle, in preventing a repetition of the penicillin-streptomycin experience, the assumption was convenient.

The question that arises at this point is what would have been the patent examiner's ruling if he had known the proportion of tetracycline co-produced in the Duggar patent? In view of the examiner's rejections the question becomes one of how much co-production of tetracycline was necessary for rejection. Or on Pfizer's grounds, what part of the therapeutic activity was in fact due to the presence of tetracycline? We can, of course, only speculate on this issue as the Patent Office, following its usual policy, did not allow the examiner who handled the tetracycline application to testify. Nor did the Commission find it necessary to settle the issue directly.[66]

In the Commission decision there is the distinct implication that the patent would not have been issued in the absence of misrepresentation. If the patent examiner had the same information from the experiments as Pfizer, he would have followed his original decision in rejecting the tetracycline application.

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[64] Pfizer's Brief, pp. 21-23, 62-66, 37-39.

[65] FTC, Opinion of the Commission, p. 23, n. 7.

[66] Ibid., p. 2.

BRISTOL SECURES A TETRACYCLINE LICENSE

In the proceedings before the Patent Office Bristol was in a position to prevent any patent from issuing by making known the results of certain of its experiments which confirmed the fact that co-production took place.[67] But here it was in Bristol's best interests not to do so. By withholding this information it increased the probability that Pfizer would secure the patent. With the patent issued, Bristol was in a position to force a license from Pfizer on the basis that it could show in court that tetracycline was co-produced with chlortetracycline thereby having the patent declaired invalid.

As noted earlier, during the second interference proceedings Bristol entered the market under its own label and supplied tetracycline in bulk form to Squibb and Upjohn. Both Lederle and Pfizer recognized that to force Bristol out of the market through Pfizer's securing the product patent on tetracycline was too slow. The alternative course of action was then adopted in which Lederle harrassed Bristol with an infringement suit based on its Duggar patent, claiming that in the production of tetracycline by fermentation, chlortetracycline was produced in amounts of 2 to 4 per

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[67] FTC Proposed Findings, p. 285. This withholding of information according to the Commission made Bristol a party to the misrepresentation practiced before the Patent Office by Pfizer. However, from a legal point of view there appears to be no requirement that such information be made available on a voluntary basis.

cent.[68] On December 9, 1954, Pfizer received notice that its tetracycline application had been allowed. In mid-December Lederle settled its suit against Bristol by granting a license to produce chlortetracycline in the production of tetracycline in exchange for royalties of 5 per cent of the net sale value of Bristol's tetracycline.[69] But on January 11, 1955, Pfizer sued Bristol for infringing its tetracycline patent.

On the basis of these facts the government built a conspiracy case against Lederle and Pfizer to exclude competition from the market. The theory was advanced that the settlement between Lederle and Bristol was to avoid suspicion from having two of the largest firms in the industry attack a smaller competitor at the same time. The suit was settled when Lederle knew that Pfizer was to receive the patent. While there was no direct evidence that this information was given to Lederle, such an inference was drawn from the earlier cross-licensing agreement, and from the fact that in the

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[68] Lederle's suit also had the effect of serving notice on Bristol's customers that they were open to suit as contributory infringers, which with alternative source of supply available at the same price would have had the desired effect of "slowing Bristol down." For a review of the tactics used in these types of patent cases see, Joseph Borkin, "The Patent Infringement Suit--Ordeal by Trial," The Chicago Law Review, XVii, 1950, 634-652.

[69] Lederle and Bristol claim that the reason for settlement was that Bristol allowed Lederle to examine its production culture and found that the strain was "so closely related as to be . . . [the] . . . legal equivalent . . ." of one claimed in the Duggar patent. Cyanamid's Proposed Findings, I, 48; also Bristol's Proposed Findings, I, n.,136.

second interference Lederle acted to exclude Bristol but not its other competitor Pfizer.[70]

In this sequence of events Bristol may have recognized that the reason for Lederle's offer of a license was due to Pfizer's securing the tetracycline patent.[71] On January 3, 1955, Bristol filed with the patent examiner an affidavit to the effect that tetracycline was isolated from old samples of commercial chlortetracycline.[72] According to Bristol this was an attempt to delay the issuance of the patent thereby providing them with more time in which to build their financial position to contest an infringement suit. But in spite of this information the patent was issued to Pfizer on January 11th. Here either the examiner did not see Bristol's affidavit or, if he did, found it opposed by Pfizer's statement of its experimental results and accepted the latter.[73] Thus Bristol acted too late to prevent Pfizer from securing the patent on tetracycline.

The Pfizer infringement suit was settled informally on December 14, 1955, with Bristol taking a license from

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[70]FTC, Proposed Findings, pp. 100-16, 304-10.

[71]An alternative hypothesis is that with a license to produce chlortetracycline with tetracycline, Bristol attempted to insure its entry in the market by preventing Pfizer from securing the patent on tetracycline thereby freeing itself from patent restraints from this quarter.

[72]Bristol's Proposed Findings, pp. 20-23.

[73]The Commission's finding on this point is that Bristol's affidavit "did not put the patent examiner on notice of inherent production in the prior art, even if it can be assumed that the examiner saw the affidavit before the Conover patent issued." FTC, Findings, p. 34.

Pfizer and agreeing to pay a royalty of 3-1/2%. The reason for the settlement is a matter of major dispute between the parties to this case. Bristol and Pfizer argue that the settlement was forced by the Broady conviction for illegal wire tapping. The resulting adverse publicity that would result in Bristol's injecting this matter was sufficient to cause a settlement.[74] The government contends that the pre-trial examination of Pfizer's records and personnel by Bristol convinced Pfizer that the matter of fraud in securing the patent would be proven. To allow the case to come to trial would have meant in all probability the loss of the tetracycline patent which would place the burden of control on the Duggar-Lederle patent. As Bristol already had a license under this patent, along with Squibb and Upjohn, there was nothing to be gained by judicial review of Pfizer's tetracycline patent or the methods used to secure this patent.[75]

SUMMARY AND CONCLUSIONS

The claim to the discovery of tetracycline by two of the industry's dominant producers posed a threat to their respective market positions. Lederle under its Duggar patent was in a position to block Pfizer on the grounds that: (1) Pfizer had to first produce chlortetracycline to produce

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[74] Bristol's Proposed Findings, I, 27-29; Arthur G. Connolly, Pfizer's Answering Brief, Part 2: In Support of the Hearing Examiner's Conclusions that Pfizer was not a Party to any Conspiracy, Before the Federal Trade Commission, In the Matter of American Cyanamid Company, et al., Docket No. 7211, April 1962, pp. 23-24.

[75] FTC, Proposed Findings, pp. 318-26.

the end product tetracycline; and (2) that in the production of chlortetracycline, tetracycline was co-produced hence the latter product was unpatentable over the former. But with the appearance of Heyden and Bristol claiming the tetracycline patent by direct fermentation, both of Lederle's arguments involved risk. For, to deny Pfizer the patent on these grounds could have meant that tetracycline was unpatentable, thereby leading to free entry, or that if patentable but with a direct fermentation method of production, that its Duggar patent could not be used to force a license from the patentee. Rather than assume these risks the evidence of the case lends credence to the theory that Lederle entered a conspiracy with Pfizer to monopolize an important segment of the broad spectrum market. Here can be cited Lederle's purchase of Heyden's narrow spectrum antibiotic facilities in a distressed market, its infringement suit against Bristol and the conditions under which it was settled, the sale of bulk tetracycline to Pfizer to prevent Lederle from building a sales lead, its silence on the issue of co-production, and in the second interference proceedings the attempt to eliminate Bristol but not Pfizer from the proceedings.

Thus Lederle could have blocked Pfizer's entry, but nly by assuming the risk of competition. The alternative urse of action was to insure that Pfizer secured the patent ereby establishing a duopoly in tetracycline. This required e elimination of competitors on Lederle's part, and for zer to design its experiment on co-production in such a

way that the results were favorable to its case. This latter action gave Bristol the necessary leverage to force a license from Pfizer for itself, Squibb and Upjohn. This avoided judicial review of the tetracycline patent as well as possible review of the whole antibiotic patent structure.

In the formation of this conspiracy the patent became the legal instrument by which competition could be suppressed. But, in addition, the underlying market forces as well as the recent history of the industry, played significant roles. Lederle and Pfizer were the leading producers in the industry. Pfizer's position built on the narrow spectrum drugs and oxytetracycline, Lederle's exclusively on chlortetracycline. To maintain these positions the patent on tetracycline was essential. The entry of bulk suppliers such as Heyden and Bristol had in the narrow spectrum market resulted in price competition. Their elimination or suppression was necessary. The unfavorable legal climate on patent issues required that the tetracycline dispute be settled privately with court action a last resort. An additional lesson taught by the postwar antibiotic market was the importance of patent control to maintain market position. Only Schenley was able to make significant changes in its position without a major product patent between 1944 and 1950. These lessons, in combination with conditions of fewness in the broad spectrum market as well as the relative value of this market, were contributing factors that led to the tetracycline conspiracy.

The abuse of the patent system that was necessary in

securing the patent on tetracycline leads to the question of the effectiveness of this office in protecting the public interest. There is the fact that Pfizer had to convince but one individual who blocked the formation of a monopoly in an important antibiotic drug. The examiner was forced to rely on the self-serving experiment conducted by Pfizer to test his assumption of co-production. Lacking an independent laboratory to conduct such tests his resources to discover the truth of conflicting patent applications seem meager at best. Evidently the theory here is that the interference procedure is an adversary proceeding in which the parties are assumed to be in competition for the patent. But there is in these proceedings nothing to prevent the formation of a conspiracy against the examiner. Nor, as in the case of Bristol, is there anything to be gained by a competitor in making evidence available to the examiner which would prevent the issuance of the patent. On the contrary, there is more to gain by remaining silent and using such information to force admittance to the market through a licensing arrangement.

CHAPTER IV

THE TETRACYCLINE LICENSES

As a device to monopolize a market the patent and license agreement provide an unsurpassed legal instrument. The patent has the effect of carving out an area of exception from the general antitrust laws giving the holder the right to exclude competition in the product or process, or to admit competitors under the terms of a license. The restraining factor is that the license may not have the effect of extending the monopoly beyond that which is available to the licensor under the terms of his patent.[1] But to draw the line between actions that lie within the scope of the patent monopoly and those that lie beyond present formidable difficulties. In the analysis of the domestic and foreign license agreements relating to tetracycline the problem is to decide whether a particular restrictive clause had as its main objective a lawful business purpose or an attempt to suppress competition beyond the scope of the patent grant.

In the analysis of the domestic license agreements the main question is, do the terms of these agreements support the hypothesis that a five firm conspiracy existed in

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[1]Attorney General's Report of the National Committee to Study the Antitrust Laws (Washington: Government Printing Office, 1955), Chap. V.

the manufacture and sale of tetracycline? In the case of the foreign agreements was there an attempt to form or maintain a world cartel in antibiotic drugs? In the domestic market one would expect the licenses to contain covenants that controlled such market variables as price, output, markets, and future technical advances. Finding such restrictions would then tend to support the hypothesis of a conspiracy based on the patent license agreement.

DOMESTIC LICENSE AGREEMENTS

With the issuance of the patent on tetracycline to Pfizer, the cross-licensing agreement with Lederle became effective. These two firms legally controlled the production and sale of this drug--Pfizer through its Conover product patent and Lederle through its Duggar product and Niedercorn process patents.

Pfizer-Lederle License Agreements.--The two documents executed by Pfizer and Lederle settling their patent interference appear innocuous in isolation. Lederle, under its Duggar and Niedercorn patents, held a legal monopoly on the method of production and sale of chlortetracycline. Pfizer received a non-exclusive license to produce chlortetracycline as an input material to manufacture tetracycline by dechlorenation. Lederle in turn received a non-exclusive license to manufacture and sell tetracycline under the Conover patent. As noted earlier, it was agreed that technical information would be provided to Pfizer in producing chlortetracycline and in addition that such information was to be made available

to each in the future thereby sharing any technology advances.

It was provided that each firm could sublicense one firm in each foreign country where the licensor or its subsidiary did itself not manufacture the licensed products. Royalties were to be computed as a percentage on the basis of the net sales value of the licensed products. The net sales value was defined as the gross billing price less certain deductions for discounts to wholesalers, transportation charges, etc. This computation was based on the prices in each country where sales took place.

In essence, these license agreements did not extend the monopoly position of either firm. Pfizer could not, of course, sell chlortetracycline under its license from Lederle, but both were free to compete with tetracycline in the various therapeutic markets as well as in the agricultural markets.[2] Thus, in the absence of an expressed or implied agreement not to compete in terms of these market variables, these agreements appear to have as their major objective lawful business purposes.

Bristol-Lederle License Agreement.--The Lederle infringement suit against Bristol was settled with Bristol taking a license under the Duggar patent. Bristol received a non-exclusive license to produce up to 6 per cent chlortetracycline in its fermentation process for the production of

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[2]The markets here are defined as (1) therapeutic, which is further subdivided into human and veternary; (2) non-therapeutic, which is subdivided into feed supplement, food preservation, and crop spraying.

tetracycline. In return Bristol agreed to pay royalties of 5 per cent based on the net sales value of its tetracycline. In addition Bristol agreed that its fermentation process infringed the Duggar patent by using a strain of microorganism claimed in this patent. The strain involved was unidentified, being a "specied Streptomyces aureofaciens [as naturally occurring and/or as spontaneous or induced mutants], or sufficiently closely related thereto as to be its legal equivalent, to produce in the fermenter an antibiotic substance containing tetracycline . . ."[3] Thus, Bristol's fermentation process came under control of the Duggar patent.

The terms of the license did not allow Bristol to manufacture chlortetracycline in isolated form or for conversion to tetracycline nor into any other substance. This in effect prevented any further modification of the basic tetracycline molecule which required chlortetracycline as a starting material. This in combination with the statement in the license which allowed Bristol only to practice its "Present Operation" (defined as its fermentation process),[4] insured that a competitive drug would not be developed by Bristol unincumbent by patent restrictions. To escape the Cyanamid patent monopoly by developing a new and competitive drug, Bristol would have to be able to prove that chlortetracycline was not involved either as a starting material or as a co-

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[3]U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, Part 26, Appendix B, 86th Cong. 2d Sess., 1960, p. 15357.

[4]Ibid., p. 15360.

produced intermediate or final product. In addition the microorganism used would have to be sufficiently removed from the species defined in the Duggar patent so as not to infringe this patent. Having taken a license under this patent Bristol could not, of course, attack its validity.

An additional effect of this clause was the restriction of Bristol to a particular technique in producing tetracycline. Thus, in the event the deschlorenation process proved more efficient than the fermentation process, Bristol was denied the use of this process. There is no evidence available on this point, but if such was the case it meant that Bristol would be a high cost procucer as opposed to either Lederle or Pfizer who practiced the deschlorination process.

The definition of the licensed patents under which Bristol could operate did not extend to non-therapeutic products. Thus, Bristol could not, for example, enter the animal nutrition markets in competition with Lederle or Pfizer.[5]

Bristol had the right to grant sublicenses in those countries where it or its subsidiary did not practice the licensed invention. In addition, one German firm could grant a sublicense to its subsidiaries under a Bristol sublicense. Pursuing this point here, rather than in the section on foreign licenses, Bristol had sublicensed Farbwerke Hoechst of Germany to manufacture and sell tetracycline to the drug trade

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[5] Ibid., p. 15358.

only. Hoechst in turn had the right to sublicense Farbenfabriken Bayer who in turn had the right to sublicense any firm or firms of its choice to sell tetracycline to the drug trade but not in bulk in Germany or Austria.[6] While Hoechst apparently could sell tetracycline to its sublicenses at prices determined independently of Bristol, there is a clause which states that Hoechst must report invoice prices on sales, in addition to the net sales value upon which royalties were to be computed, and that Bristol had the right to itself check on the information supplied.[7] The implication of this price reporting system is that there existed at least an implied agreement on the prices Hoechst would charge. Further, that Hoechst could, through the sublicensing system, control the prices charged by its licensees. But neither Hoechst nor Bayer sold tetracycline in Germany, although it would appear from the Bristol license that their manufacturing plants were located in Germany. Only Lederle and Pfizer are listed as sellers in the German Market as of 1959. In the Austrian market six sellers are listed--Lederle, Pfizer, Hoechst, and Bayer--with identical prices of $6.02, Lepetit,[8] with a price of $6.36 and Biochemie, a sublicensee of Lederle, with a price of $5.90.[9]

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[6] Ibid., p. 15483. [7] Ibid., p. 15488.

[8] Lepetit, an Italian-based firm, was a sublicensee of Pfizer.

[9] Ibid. Part 24, pp. 13742-13743. Biochemie was a sublicensee of Lederle which purchased its tetracycline in bulk from Lederle of England, but evidently retained the right to set its own price.

Thus it appears that Hoechst received special consideration in the Lederle-Bristol license agreement with the understanding that they would leave their domestic market to Lederle and Pfizer. This point is developed further in the section on foreign license agreements.

Pfizer-Bristol License Agreement.--Under the terms of this agreement Bristol was licensed to sell tetracycline to the drug trade under its own label and in bulk only to Squibb and Upjohn. This effect was accomplished in the royalty provision of the license. For sales within the United States royalties were set at 3-1/2 per cent of the net sales value of therapeutic tetracycline sold by Bristol, "its subsidiaries and affiliates, and two existing bulk customers, and their respective subsidiaries and affiliates, to the Drug Trade . . ."[10] The term "drug trade" was defined to include retail drug stores, wholesalers selling to these outlets, hospitals, and veterinarians. Therapeutic tetracycline was defined to mean a product sold to the drug trade thereby eliminating the agricultural markets as well as bulk sales to packers other than Upjohn and Squibb. The royalty clause did contain a provision covering sales of non-therapeutic tetracycline in world markets, but this was meaningless as the process license from Lederle excluded Bristol from practicing the licensed invention in any but the therapeutic market.[11]

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[10] Ibid., Part 26, p. 15400. [11] Ibid., p. 15358.

An additional provision of the royalty section was that if Bristol or its two bulk customers sold tetracycline to their respective subsidiaries or affiliates in foreign countries the royalty liability was to be based on the net sales value prevailing on sales within the United States. There are two ways in which this clause can be interpreted. First, it could recognize variations in drug prices due to local governments setting relatively low prices as in certain of the South American countries, or, as in the case of Japan, where a degree of price control is exerted by the government through the trading companies. In addition, this provision would make the check of the royalty liability easier to compute as only one price need be used. Thus this clause can be viewed as a means of maximizing the royalty income on the assumption that prices in the United States were equal to or higher than prices prevailing in foreign markets. But for the seventeen countries for which price data is available, eleven show prices higher than in the United States.[12]

A second view of this royalty provision was that it discouraged price cutting in foreign markets and encouraged setting prices higher in these markets using the United States price as a base. To set or maintain higher prices, neglecting demand elasticities, would have no effect on the royalty liability, only increasing total revenues. This view requires in turn the assumption that some form of price agreement prevailed with respect to the price in the United States

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[12] Ibid., Part 24, pp. 13742-13743.

market. Otherwise this clause would operate to encourage price cutting in the domestic market thereby lowering the total world-wide royalty liability. The following chapter discusses the question of domestic prices in detail, but it can be noted here that price cutting on tetracycline did not occur.

The provisions for reporting royalty liability do not appear to reveal price information on individual sales. There is here, however, the indication that if Bristol sold to other than its two bulk customers, a different report would be due. That is, if Bristol sold to a different bulk customer or to a firm outside the drug trade as defined, it had to secure a report from the buyer of his inventory position and his use and resale of tetracycline, passing this information on to Pfizer. The only purpose this report would serve appears to be that it insures that Pfizer would know of such sales. Thus if there existed an implied agreement not to sell to such third parties, this would serve as a check on such activities.

Pfizer-Squibb and Upjohn License Agreements.--The license agreements between Pfizer, Squibb, and Upjohn were essentially the same hence these agreements will be considered together.

Squibb and Upjohn recieved a non-exclusive license from Pfizer to sell only therapeutic tetracycline to the drug trade. Both terms were defined as in the Pfizer license to Bristol to exclude non-therapeutic markets, and to prevent

bulk sales to other firms.[13]

In the case of sales of tetracycline within the United States, royalties were set at 3-1/2% of the net sales price. For sales in world markets royalties were based on the selling price of therapeutic tetracycline in the United States.[14]

These license agreements also contained a provision that neither Upjohn nor Squibb could terminate the license for a period of five years, or until 1961. This same provision appeared in the Pfizer license to Bristol, while in the case of the Cyanamid-Bristol license the period reached to 1966.[15] The usual provisions for termination calls for a period of 90 days following written notice to the licensor. The effect of this provision would prevent the licensed parties from terminating the license and then attacking the validity of the patent. Thus, even if the three licensed parties knew that the patent was obtained through fraud, as charged by the FTC, they would be powerless to use such information for a five year period.

Both Upjohn and Squibb argue that the license from Pfizer served a necessary business purpose. That is, by having a license to sell tetracycline they were not bound to purchase this drug from Bristol, or any of the existing producers. Upjohn argues that by having a license to sell, it

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[13] Ibid., Part 26, pp. 15427 and 15414.

[14] Ibid., Part 26, pp. 15429 and 15416.

[15] Ibid., Part 26, pp. 15372, 15411, 15422 and 15435.

could buy bulk tetracycline from unlicensed manufacturers and sell in any therapeutic market without infringing the Conover patent. It could, for instance, buy tetracycline from an Italian producer, where patent protection is not afforded to drug products, and import this tetracycline into the United States. Thus, the license had the effect of protecting Upjohn from prices set by the domestic producer on bulk tetracycline.[16]

Squibb presents essentially the same arguments as Upjohn, but adds that the license it took from Pfizer did not "apply, nor was it intended to apply, to any tetracycline purchased by Squibb from Bristol."[17] Thus, Squibb contends that it was free to resell bulk tetracycline purchased from Bristol as well as free to sell in any market. The fact that such sales never took place was simply a matter of commercial policy. In such resales Squibb would charge a bulk price which would include some measure of profit thereby resulting in a higher bulk price than charged by Bristol. Thus "Squibb would have to charge a bulk price which would effectively preclude a bulk purchase relationship with any other company."[18] But this argument assumes that Bristol could compete with

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[16]Gerhard A. Gesell, Brief and Proposed Findings and Conclusions of the Upjohn Company, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, October 1960, pp. 133-39.

[17]Allen F. Maulsby, Proposed Findings and Related Papers of Respondent Olin Mathieson Chemical Corporation, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, October 1960, p.84.

[18]Squibb's Proposed Findings, p. 87.

Squibb on such bulk sales. The terms of Bristol's license limited them to sales under their own label and to their two existing bulk customers. Thus Bristol could not become a competitor of Squibb in the bulk market. Squibb argues further that the license from Pfizer became effective only if Bristol did not supply bulk tetracycline. In this event Squibb was free to purchase tetracycline from any source--licensed or unlicensed--for resale to the drug trade without infringing the Pfizer patent. But in spite of the fact that cheaper unlicensed sources of tetracycline were available from foreign producers, Squibb never made such purchases.[19]

If the reason offered by the respondents for the license from Pfizer to Upjohn and Squibb is rejected, the alternative explanation is that Pfizer insisted upon this license for purposes of controlling the activities of these firms.[20] The legal principle involved here is that under the Pfizer-Bristol license arrangement alone, once Bristol sold bulk tetracycline to Squibb or Upjohn, no legal control could be exerted over the resale of the product.[21] By a separate

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[19] Hearings, op. cit., Part 24, p. 13791, Allen F. Maulsby, Answering Brief of Respondent Squibb, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, April 1962, p. 44.

[20] Federal Trade Commission, Appeal Brief, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, January 1962, p. 41.

[21] Boston Stores Company v. American Gramophone, 246 U.S. 8, 1917, set out the principle that once a patented article is sold the patentee has exhausted his right to control the terms of sale under his patent. See also, Adams v. Burk, 84 U.S. (17 Wall) 453, (1873); Cream Top Bottle Corp. v. Bailes, et al., 62 F 2d 714, 717 (10th Cir. 1933); Keeler v. Standard

license between Pfizer, Squibb, and Upjohn their sales could be legally limited to therapeutic tetracycline, thereby preventing entry into the agricultural market. And the definition of the licensed product in terms of sales to the drug trade became operative, thereby eliminating further bulk sales.

Conclusions on the Domestic License Agreements.--The problem here is what conclusions can be drawn from evidence of these license agreements first to the question of conspiracy, and second, in the absence of a conspiracy, to the extension of market power beyond the scope of the patent grant.

Relevant to the first part of this question it is clear that there was a limitation on competition in the non-therapeutic markets on the part of Lederle and Pfizer. The license agreements executed by these firms preserved these markets for their exclusive exploitation. It is also clear that the restrictions on bulk sales were designed to prevent entry from this quarter. The Pfizer licensing of Squibb and Upjohn can be viewed as business strategy designed to maintain market control within the existing patent structure. But these actions, isolated from the issue of how the patent was obtained, do not appear sufficient to support the hypothesis that a conspiracy existed. That is, in answer to the second part of the question, these licenses did not extend the monopoly power allowable under the basic patent grant.

Folding Bed, 157 U.S. 659 (1894), cited in Federal Trade Commission, Appeal Brief, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, January 1962, p. 41.

If, on the other hand, these licenses are examined in light of how the patent was obtained there is support for the hypothesis that these firms did conspire to ensure the issuance of the patent. Here the most damaging piece of evidence is the provision not to contest the validity of the Pfizer patent for a period of years. An examination of license agreements presented in the Hearings indicates, as noted previously, that the usual provision was for a 90-day notification upon which the license could be terminated. Thus the licensees were prevented from terminating their respective licenses and attacking the Pfizer patent on the grounds that certain facts had been withheld in securing the tetracycline patent. The implication here is that each of the licensees was aware of the reason for this provision and as such became part of the conspiracy to limit competition in tetracycline to the five firms involved.

A second supporting piece of evidence is the method by which royalties were computed. The use of the domestic price to compute the royalty liability for foreign sales appears as a force leading to price cutting in the domestic market. The fact that price competition did not develop leaves the impression that an explicit or implicit agreement existed to maintain domestic prices. In addition, the fact that neither Squibb or Upjohn legally required a license from Pfizer to sell tetracycline purchased from Bristol can be interpreted as a written agreement not to enter the agricultural markets nor to allow further entry through bulk sales to packers.

FOREIGN LICENSE AGREEMENTS

One approach to the study of the foreign license agreements is to attempt to quantify the restrictions in these contracts with the purpose of explaining why certain features appear in one group of licenses and not in others. This would involve a detailed study of foreign patent laws as well as the market conditions that existed in each country that the license operated. In addition, where the domestic producers were established abroad through foreign subsidiaries the degree of corporate control existing between licensee and licensor would have to be known. Lacking this sort of information, an alternative approach is to examine these agreements for consistency with the hypothesis that there was an attempt to maintain or form a world cartel in antibiotics.

If a world cartel existed or was to be formed with the tetracycline patent what sort of variables would be expected to be brought under control? The first requirement is control over the domestic market which was effective through the domestic license agreements. In the foreign agreements we would expect some means of controlling either price or market shares. This could be accomplished by alloting certain countries to specific firms or their sublicensees. One would expect to see some provision calling for the exchange of any future technical information that might be developed by the licensee or licensor.

License Provisions.--The Kefauver Hearings on drug prices contain twenty-nine license agreements between the three domestic producers and foreign firms.[22] Certain of the licenses are what might be called master agreements relating to chlortetracycline or general intent to license contracts, to which have been added tetracycline.

There are certain common provisions of these licenses. All contain restrictions relative to the geographic area in which the licensed product may be produced and/or sold. All call for royalty payments in one form or another, although the methods of computing royalty liabilities differ. Provisions relating to the reporting and payment of royalties are common with minor differences.

The first question here then is whether foreign prices can be set by the domestic licensor. Direct evidence on this point may be contained in the royalty rate charged the licensee, or a clause giving the licensor the right to determine such prices. On the latter point no such clauses appear and on the former point the royalty rates have been deleted by the Subcommittee.[23] Indirect evidence of price setting may be assumed where the license provides that the licensor has

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[22] Hearings, op. cit., Part 26, pp. 15458, Part 25, pp. 14226-15277.

[23] In a few cases there appears to be a difference in the royalty rate depending upon the country in which the drug is sold. For example, in the case of Pfizer's license to the Italian firm of Ledoga provides for a separate royalty rate for Argentina. (Ibid., Part 25, p. 15229.) But Ledoga does not appear as a seller in this market. (Ibid. Part 24, p. 15742.) A high royalty rate by Pfizer may have preserved the Argentine market for Lederle's exclusive supply.

the right to approve the price schedule of the licensee. Suspicion of a price agreement occurs where the licensor has the right to check invoice prices or to cancel the license without cause.

Table 8 indicates that in the case of Bristol with ten foreign license agreements, the licensee was

TABLE 8.--Summary of Restrictive clauses in foreign licenses

Firm	Number of Licenses	Price Restrictions	Bulk Sale Restrictions	Reporting Restrictions
Bristol	10	10	10	10
Lederle	8	4	8	2
Pfizer	1	0	1	0

required to report the invoice price. Where the license also contained an exclusive supply clause, the resale price had to be approved by Bristol. In the case of Lederle with eight usable foreign license agreements, four called for the report of the net invoice price. Where a supply contract was included the licensee evidently could set the resale price. In the case of Pfizer, with one foreign license agreement, no requirement appears to report the invoice price.

A second question is whether the licensees may sell in bulk to firms outside the patent licensing system. Evidence of the existence of this particular restriction is where the licensed product is defined to include only sales to the drug trade, or in finished form, or where expressly prohibited. Suspicion of such restrictions arise in cases where the

licensor may require reports in sufficient detail so as to be able to determine to whom the product was sold.

In each of the nineteen licenses analyzed the product or the market is defined in a way to prevent bulk sales to unauthorized firms. This restriction takes the form of outright statements to the effect that such sales cannot be made, or statements that they may be made on the approval of the licensor.

The third question is whether the reporting system incorporated in the license is the sort expected in a cartel arrangement. That is, does the licensor have the right to check on invoice prices, on quantities sold, on the form sold, or be informed of the identity of the buyer? In addition, does the licensor have the right to approve the form in which the product is sold--the package, its size, and contents?

In the case of Bristol the reporting clause could be interpreted as consistent with a cartel reporting scheme, but only two of Lederle's licenses could support this interpretation.

The evidence then on the existence of a world cartel is mixed. In general the restrictive nature of the Bristol licenses supports such a conclusion while those of Lederle and Pfizer do not.

Prices in Foreign Markets.--A further test of the hypothesis of a world cartel is provided by an examination of market prices. If such an organization existed one would expect that within particular markets selling prices would be

the same. In the seventeen foreign markets for which the Subcommittee provided price data, in sixteen cases more than one seller appears. In only five of these markets are prices the same. In three of these markets with similar prices--Australia, Germany, and Mexico--competition is between a combination of the five domestic firms. But in three markets--Canada, England, and Venezuela--where similar conditions prevail, prices differ. In six markets where the domestic firms face competition from one or more of their licensees, prices differ. Thus, if similar prices are taken as evidence of a cartel, the evidence of differences in these prices is not consistent with this hypothesis.

From the more restrictive nature of the Bristol licenses, as well as its behavior in the patent phase of the case, one would not expect Bristol or its licensees to be aggressive price cutters. The data on world market prices bears this out. Lederle appears to be the price leader in these markets.[24] In nine markets where Bristol or one of its licensees appears as a competitor to Lederle, in only two of these markets--India and Japan--is there a failure to follow Lederle's price.

As noted earlier, in the case of Germany only Pfizer and Lederle were listed as sellers in this market although two of Bristol's licensees--Hoechst and Bayer--were licensed for this market. In addition to Germany five other markets

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[24] Ibid., Part 24, p. 13753. Neither Pfizer or Bristol indicated any price policy in foreign markets.

contain licensed firms who are not listed as sellers. These are Austria, Brazil, France, Italy, and England. In two cases--Germany and England--Pfizer and Lederle appear as exclusive sellers although at least one other firm was licensed for each of these markets.

The tentative conclusion that is drawn from these rather mixed results is that a world cartel arrangement is not in existence. This is not surprising in the light of the problems that such an arrangement would face. For example, in a country such as Italy tetracycline can be produced and sold without fear of an infringement suit as patent protection does not exist. Strains of the microorganism used in the production of antibiotics can be obtained from a United States culture collection. As part of our disclosure requirements the Patent Office requires that such strains be deposited in this collection which is available to interested parties.[25] From the domestic Italian market it is but a step to export markets.[26] In any country which does not permit product patents, or where the product is not patented, the product may be sold without infringement. Even where product patents are allowed as in certain of the South American countries, imports of the

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[25] Leonard J. Robbins, "Patents for Microbiological Transformation--An International Problem," Journal of the Patent Office Society, XLII, 1960, 830-48.

[26] In the Italian market the largest number of sellers appears at sixteen. The closest second is France with six. Of the sixteen, only four can be identified as licensees with the implication that the balance are technical infringers.

patented product are not considered grounds for infringement.[27] In Europe the patentee in enforcing a drug patent faces a court that is inclined to view with hostility his claim for enforcement.[28] As a result it is often cheaper to license in the hope of maintaining some degree of control.

An additional problem faced in any attempt to organize world markets is that certain countries impose price controls directly, or indirectly through national health plans. Argentina provides an example of the former type of control while England of the latter.

While it is concluded that a world cartel did not exist at least up to 1960, the behavior of Bristol in world markets is consistent with its behavior in the domestic market. Here we find rather close control of its licensees and a failure to challenge the price leader in these world markets.

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[27] Leonard J. Robbins, Pharmaceutical Patents in Foreign Countries," Journal of the Patent Office Society, XXXVII, 1955, 271-88.

[28] See Robbins, ibid., p. 280; and Robbins, op. cit., p. 842, where producers in Italy "have invaded export markets in other countries where they can only be challenged by the costly and presently uncertain procedure of individual infringement suits." See also R. Spencer and L. Chereau, "France Allows Drug Patents, But on Products, Before Only Processes," Journal of the Patent Office Society, XLII, 1960, pp. and Robert E. Woodhams, "A Comparative Study of Patent Laws in the Americas and the International Effects Thereof," Journal of the Patent Office Society, XXXI, 1949, pp. 726-42.

CHAPTER V

PRICING OF ANTIBIOTIC DRUGS

The price history of the narrow and broad spectrum drugs presents a situation in which different market structures led to differences in the behavior of prices. With the narrow spectrum antibiotics entry was generally unrestricted leading to price flexibility on the down side as the technological processes were improved. With the introduction of the first of the broad spectrums, chlortetracycline, price initially decreased with entry of competitive substitutes such as chloramphenicol and oxytetracycline, but reached a level that was unchanged with the marketing of tetracycline.

One purpose of this chapter is to explain the behavior of price in the broad spectrum market. What were the major differences in the narrow and broad spectrum markets? Was price leadership the result of explicit or implicit agreement? What are the price policies of the various antibiotic producers and how are new drugs priced relative to established drugs?

The first section of this chapter considers the question of the price policy of several of the antibiotic sellers. The firms generally state specific profit goals and these are examined as to actual results and to their effect on price determination. An attempt is made to explain

both price and market shares with the Cournot model as new antibiotic drugs are introduced.

The next section is concerned with the price history of the narrow and broad spectrum antibiotics. Here the structure of these markets is analyzed for the effect on price.

The third section returns to the Federal Trade Commission charge of collusive price fixing. The different decisions of the Hearing Examiner and the full Commission are discussed.

Finally, an estimate is presented of the element of monopoly revenue earned in the production and sale of tetracycline. The following chapter examines in part the question of whether this element of monopoly had the effect of increasing the rate of technological progress in the industry.

Price Policy.--Lederle as the dominant producer in the broad spectrum market may be characterized as the price leader.[1] This role was largely undertaken by default, for with the introduction of chlortetracycline in late 1948, Lederle had to set some price relative to the narrow spectrum drugs. Later, with the development of close substitutes for chlortetracycline, they were, with one exception, introduced at the prevailing price of chlortetracycline.[2] Of the four price changes observed in the prescription market, Lederle

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[1] See Tables 1 and 2, Appendix, pp. 241-42 for Lederle market shares.

[2] The one exception was Pfizer's oxytetracycline introduced at a price above tetracycline. However, Pfizer experienced a degree of resistance to its price and was forced to match the Lederle price.

instituted three with Pfizer taking the lead in the other case.[3]

Of the six major broad spectrum antibiotic sellers, three--Lederle, Parke Davis, and Upjohn--stated a definite pricing policy, in either the Hearings or in replies to the Federal Trade Commission's charge of violation of section 5 of the Federal Trade Commission Act. The Upjohn statement is more a rule of thumb than a defined policy. They indicated that under normal conditions (normal being perhaps defined as non-competitive) they expected price to be three times manufacturing costs.[4] Lederle stated that its policy was to price so its "overall profit [after federal income taxes, was] 12 to 15 per cent on net sales of all drugs."[5] Parke Davis stated that its target was approximately 15 per cent on net sales after taxes.[6] Bristol stated that they could not set a target profit rate because of their inability to predict sales with sufficient degree of accuracy.[7]

The emphasis in these statements is upon an overall target rate. The ability of the four broad spectrum anti-

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[3]U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, Part 24, 86th Cong., 2d Sess., 1960, p. 13663.

[4]Gerhard A. Gesell, Brief and Proposed Findings and Conclusions of the Upjohn Company, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, October 1960, pp. 67-77, hereafter cited as Upjohn's Proposed Findings.

[5]Hearings, op. cit., Part 24, pp. 13639 and 13628.

[6]Ibid., p. 13960.

[7]Ibid., p. 13827.

biotic producers in achieving their stated percentage returns is indicated in Table 9. Lederle has in this period

TABLE 9.--Net profits after taxes as a percentage of sales for four broad spectrum antibiotic producers (1948-1959)

Year	Lederle*	Bristol	Pfizer**	Parke Davis	Average
1948	6.7	11.0	20.1	13.0	12.7
1949	13.9	1.4	16.5	14.3	11.5
1950	19.4	11.3	16.3	16.9	16.0
1951	13.8	11.7	12.2	14.9	13.2
1952	11.6	4.1	10.6	12.9	9.8
1953	12.7	(3.7)	11.1	3.5	5.9
1954	13.7	4.2	10.5	9.5	9.5
1955	14.1	7.0	9.4	11.6	10.5
1956	14.6	5.6	10.2	13.2	10.9
1957	17.5	7.2	11.1	17.2	13.3
1958	16.0	11.8	10.8	16.3	13.7
1959	17.7	8.4	9.8	16.2	13.0

*The Lederle data were reported separate from American Cyanamid.

**The Pfizer data is consolidated to include its foreign operations. Source: U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Hearings on Administered Prices in the Drug Industry, Part 24, 86th Cong., 2d Sess., 1960, pp. 13673 and 13959.

been able to achieve its stated minimum goal in all but two years, and has been able to exceed its maximum goal in four years. Parke Davis has achieved its goal in only four years, in three of the four cases in the last three years--1957-59. If it is assumed that Pfizer's target approximates that of its competitors at 12 per cent, based on their consolidated

data this level has been achieved in four of the twelve years. Bristol on the other hand exhibits the greatest amount of variability which perhaps accounts for their statement that such targets cannot be set.

The data in Table 9 is, as noted, for overall company drug operations. As each of the companies is a multiproduct producer and seller, they face varying degrees of competition by other drug products. Table 10 presents data showing the

TABLE 10.--Net operating profits as percentage of sales before taxes and by products (1950-1956)

Year	Penicillin	Streptomycin*	Broad Spectrum**
1950	21.4%	18.7%	52.1%
1951	22.9	21.3	50.1
1952	(13.0)	0.1	43.7
1953	(1.0)	(4.7)	43.4
1954	(7.4)	(20.9)	37.4
1955	(17.2)	(37.4)	35.1
1956	(5.6)	(41.4)	36.8

* Includes streptomycin, dihydrostreptomycin, and streptoduocin.

** Included chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol. Source: Federal Trade Commission, Economic Report on Antibiotic Manufacture, 1958, pp. 211-12.

average net operating profit before taxes of three antibiotic drugs. Here any policy of target return pricing would have to take into consideration that the target could not be achieved in all products due to the competitive nature of certain markets. Where the target cannot be achieved on a particular product this means that in less competitive markets

price must be higher to achieve the overall rate of return desired. Here then may be the familiar case of market power used to subsidize less profitable operations in competitive markets where a transfer of resources is indicated.[8]

By classifying Lederle as the price leader in the broad spectrum market implies, of course, that its competitors assume a role of following its lead. In general this acceptance of a followership role results from Lederle's competitors' view of the nature of the market. This argument, in brief, is that the market for broad spectrum antibiotics is inelastic with respect to price, hence any price cutting in general would not expand the market at the expense of competitive products, and that price cuts by any one firm alone would be self-defeating as such information would be immediately reported, with price matching the result.[9] Thus, the policy of the price followers is one of accepting the price established by Lederle. The only implication at this point is that

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[8]The reasons advanced for the continued production of *unprofitable* products are (1) desire to sell a full line of products, (2) reluctance to withdraw a drug needed by the public, and (3) an expectation of increased sales through market penetration. Federal Trade Commission, Economic Report on Antibiotic Manufacturs (Washington: Government Printing Office, 1958), p. 213.

[9]Allen T. Klots, Bristol's Proposed Findings of Fact, Conclusions of Law and Answers to the Government's Contentions, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, October 1960, II, pp. 153-54, 157-59 and 161; Gerhard A. Gesell, Answering Brief of the Upjohn Company (same case citation), pp. 23-30; Arthur G. Connolly, Pfizer's Answering Brief (same case citation), Part 2, pp. 29-30; Allen F. Maulsby, Proposed Findings and Related Papers of Respondent Olin Mathieson Chemical Corporation (same case citation), pp. 118-23; See Hearings, op. cit., Part 24, pp. 13980-13982 for Parke Davis' similar views of the nature of the market.

the pricing pattern established by Lederle was acceptable to the other participants, operating in a typical oligolopistic market. The question of conscious parallel action is discussed in a later section.

Pricing of Broad Spectrum Drugs.--The pricing of certain of the broad spectrum drugs provides an opportunity to test the hypothesis of target pricing as opposed to a policy of charging what the market will bear. In particular, in the pricing of chlortetracycline, where Lederle held a patent monopoly, if the monopoly price was set this implies that it was the market structure that was important, rather than a consideration of the firm's overall target profit. On the other hand to set a price significantly lower than the monopoly price could indicate an application of target pricing.

As previously noted, in the selection of the price of chlortetracycline in late 1948, Lederle had a degree of discretion in its choice of a price. According to company statements the major factors considered in the pricing decision were the prevailing prices of the narrow spectrum antibiotics, their overall income objectives, the element of obsolescense, and the level of research expenses.[10] To this list of factors considered should be added Lederle's selling expenses which in this period were, in all probability, at

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[10] Ralstone R. Irvine, Respondent American Cyanamid Company's Proposed Finding of Fact, Conclusions of Law and Proposed Order, With Reasons in Support Thereof, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, October 1960, II, p.96, hereafter cited as Cyanamid's Proposed Findings.

least equal to its research expenses.[11] In a sense the situation facing Lederle in pricing chlortetracycline was similar to that faced by other companies in the pricing of a basically new product where the emphasis is upon the demand side of the market.[12]

There are two basic approaches or frameworks in which the pricing process can be explained. This decision-making process can be set in terms of internal budgetary procedures, or in terms of some sort of oligolopy model. But here the selection of an oligolopy model depends upon what assumptions one is willing to accept. Thus, the budgetary framework is used to discuss the determinants of price, as stated by Lederle, to see what assumptions seem justified for model selection purposes.

The budgetary view of the pricing process assumes that what is important is future cash flows. The product to be priced taken in isolation, gives rise to costs that are translated into cash outflows, while the combination of price and volume is translated into cash inflows. Within this framework profit maximization takes the form of maximizing the net difference between these two flows.

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[11] FTC, Economic Report, p. 209; and U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Report on Administered Prices in the Drug Industry, 87th Cong., 1st Sess., 1961, pp. 31, 156-90. Hereafter cited as Report.

[12] For the case of DuPont's pricing of cellophane and nylon see, A.D.H. Kaplan, Joel B. Dirlam, and Robert Lanzillotti, Pricing in Big Business (Washington: The Brookings Institute, 1958), pp. 254-56, and 96-108.

The element of obsolescence in the drug industry means essentially that there is a limit in time in which a product will be a substantial producer of revenue relative to its costs. Here one of two events generally takes place. First, a competitor may develop a close substitute or the drug in question may not prove as efficient as initially thought in its development.

The effect of obsolescence is to place a limit on the planning period of the firm relative to its pricing and research efforts. One firm estimates that five years is the limit in which it can expect a new drug product to be a significant revenue producer before competition drives price to "unprofitable" levels or a better product is developed.[13] What this seems to mean is that on the average every five years the research effort must be able to turn out a significant new product. The influence here on pricing is that the combination of price and volume must be sufficient to support the research effort over the five dry years as well as meeting the other expenses of the firm. But here the selling efforts of the firm may be able to offset the inroads of competition.

The advertising expenditures associated with the marketing of a new drug are generally substantial.[14] The purpose of this activity appears to be twofold. First, there

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[13] Hearings, Part 24, p. 13650.

[14] Report, Chap. IX.

is an attempt to gain rapid acceptance of the drug by the medical community thereby establishing the brand name as the therapeutic name. Success in this area has the effect of informing the medical community of the benefits of the drug and insures sales volume in the prescription market. An insurance feature is based upon instilling the habit of brand name prescription writing by the physician in combination with the fact that in many states the druggist cannot by law substitute a different brand although the two may be identical compounds.[15]

The second purpose of advertising is to protect the firm from competitors' introduction of close substitutes. Until recently, on the average, some 300 so-called "new drugs" were marketed each year.[16] In fact only a few could be classified as a new drug in that they were a marked improvement over existing drugs, or effective against a previously untreatable disease. The overall effect has been to increase the proportion of the firm's resources spent on advertising. In 1950 this activity absorbed 12.9 per cent of the firm's sales dollar, [17] and by 1959 this had increased to 25.0 per cent.[18]

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[15] Report, pp. 235-44.

[16] Hearings, Part 21, p. 11628; Harry Beckman, The Year Book of Drug Therapy (Chicago: Year Book Publishers, 1960), p. 22.

[17] FTC, Economic Report, p. 209.

[18] Report, p. 31.

In terms of the firm's pricing of a new drug the price set must generate sufficient future revenues to cover the expected costs of advertising as well as other expected future costs. If the industry is spending more on this activity the innovator will be forced to increase his rate of spending to insure the adequate dissemination of information. The effect then is to increase the price that is set.

The third factor to influence the pricing decision is the current and future level of research expenditures. For the major antibiotic producers these expenditures expressed as a percentage of sales increased from 4.4% in 1950 to 6.7% in 1956.[19] A twenty-two firm average in 1959 indicated that for drug operations 7.3% of the sales dollar was spent for research.[20]

The size of current research budgets seems to be determined by past decisions, relative to what diseases will be investigated and the level at which these projects will be operated. Decisions relative to the areas to be investigated are based, to a substantial degree, on the firm's area of specialization. For example, one firm interviewed stated that it considered itself an antibiotic producer equipped with the specialized plant and knowledge relative to fermentation technology. As a result, project proposals were formulated by the research staff based on an antibiotic approach. These proposals were then reviewed by management with a view

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[19] FTC, Economic Report, p. 209.

[20] Hearings, Report, p. 31.

to the potential size of the market based on the incidence of the disease in question and available methods of treatment. This was followed by an estimate of the expected costs of the project and the chance of success. The acceptance of projects was said to be largely a matter of art in which the research director makes a best guess of what will pay off. If a particular area appears promising parallel projects are accepted until one stands out as likely to succeed. At this point efforts are concentrated on the one approach with a corresponding reallocation of resources. New projects are accepted with reference to the level at which current projects are expected to absorb funds and the overall research budget. The latter figure seems to be determined by a historic consideration of past research spending relative to sales and whether this ratio has produced successful results. If, as in the case of a second firm interviewed, success did not follow, then a substantial increase in the research spending was authorized, but with the idea of later bringing this figure back into line with something approaching the industry average. The basic goal in allocating funds to research is, of course, commercial success.[21]

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[21]See, for example, the statement of Dr. A. Dole Console, former Medical Director of Squibb--"In drug research as practiced by the industry, commercial success is the primary goal," in U.S. Congress, Senate, Hearings on a Bill to Amend and Supplement the Antitrust Laws with Respect to the Manufacture and Distribution of Drugs, and for Other Purposes, Part 3, 87th Cong., 2d Sess., 1962, p. 1424. Hereafter cited as Hearings on S. 1552.

From the budgetary point of view the future level of research expenditures becomes a cash outflow to be covered in part by the pricing decision of a new drug. But again such decisions cannot be made in isolation. Here it would appear necessary to consider the actions of competitors in terms of their discovering significant new products as well as their ability to market minor product modifications for their value in advertising. An example of the influence of the former action is provided by the activities of at least one antibiotic producer interviewed. With the success of streptomycin in 1947 the soil screening technique was a proven isolating method. It was generally known in the industry that several firms were heavily committed to the use of this technique in the search for new antibiotics. The reaction by one firm was to operate this technique so as to produce a backlog of microorganism for investigation of their antibiotic characteristics. Through this process, if a competitor was successful in isolating a significant antibiotic, there was a good chance that an identical antibiotic producing microorganism would be found in the backlog. In the patent interference that would follow the chances of settlement with a license were considered excellent. The effect here may be to produce competitive research, but how general this is within the industry cannot be stated.

Some support for the reaction of research expenditures to competitor's success in marketing a new drug is provided in Bristol's reaction to the Lederle-Pfizer success

with the tetracyclines. In 1951 Bristol spend 7.1 per cent of its sales revenue on research. In 1952 with the isolation of tetracycline the level of research spending increased to 13.4 per cent. Thus a competitor's success may have the effect of increasing the level of research spending with the view of forcing a sharing of the market under a license arrangement.

An additional influence on the level of research spending involves the element of newness and its value in advertising. Here there exists a force to spend for research in the form of product modifications. If a successful new drug can be changed sufficiently to avoid a charge of direct patent infringement but maintain the same therapeutic efficiency, a share of the market may be gained. But these competitive reactions are in all probability random and enter the budget as contingency elements. If the event occurs the research budget can be increased and/or other projects temporarily curtailed in an attempt to maintain the firm's competitive position.

These various factors enter the budgetary analysis along with the other costs that can be expected to be incurred over time. The exact way in which they enter cannot be stated as in the final analysis pricing is largely a matter of art rather than a strict science. But the budgetary approach does provide the firms an estimate of the lower limit of the price charged for the new drug.

A Duopoly Model.--At this point it is possible to select a duolopy model to describe the pricing of broad

spectrum antibiotics. Here features of the Cournot and Fellner models are used to explain market price and shares.

In the Fellner model the lower limit of the price range is determined by traditional cost function, while the upper limit is determined by the intersection of marginal cost and revenue where the firm is a monopolist.[22] But where rivals exist and cannot be driven from the market the demand curve facing the firm depends upon rivals' reaction to the initial price selected. Setting a price near the monopoly end of the price range does not allow rivals to capture what they think is a sufficient share of the market, thereby leading to price cutting. Setting a price near the zero profit end of the price range means that some profit is lost and the leader's position as interpreter of market conditions is endangered. In the final analysis the price selected must be acceptable to all parties given their view of rival's strength.

In terms of the pricing of chlortetracycline per se, Lederle did not initially face the problem of a rival's reaction. While the price structure of the narrow spectrum antibiotics had its influence upon the selection of a price for chlortetracycline, the gap in the chain of substitutability was sufficiently great so that the effect was undoubtedly minor. But Lederle must have been aware that Parke Davis was in the process of developing a broad spectrum antibiotic, so that its monopoly position in the broad spectrum

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[22] William Fellner, Competition Among the Few (New York: Augustus M. Kelley, 1960 ed.), p. 33.

market was limited. From Lederle's point of view the conservative assumption would have been that Parke Davis' chloramphenicol was of equal therapeutic effectiveness thereby implying an equal sharing of the market, less the advantage of Lederle's earlier lead in marketing. Thus while Lederle could initially select the monopoly price, with the entry of Parke Davis a lower price was necessary to prevent the possibility of price competition. The assumption here is that while the market demand curve is inelastic, it is not perfectly so. In addition, in certain markets, such as in sales to government agencies, demand is probably less inelastic as purchases in foreign countries are an available alternative to domestic suppliers. The effect of a lower price with entry would be to increase total market sales allowing the second firm to reach an acceptable volume and maintaining the sales volume of the first firm. Under dynamic conditions, where the effectiveness of advertising is admitted, the demand curve shifts outward allowing both firms to gain an increased share of the expanding market without engaging in price competition.

The problem now becomes one of estimating the monopoly price and the cost price. If it is assumed that penicillin was the only substitute for chlortetracycline, although sufficiently limited to have but a minor influence,[23]

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[23]Both penicillin and chlortetracycline are effective against gram positive bacteria, but only chlortetracycline is effective against both gram positive and negative bacteria. In addition where the exact bacteria causing the infection cannot be identified chlortetracycline would be the drug of

then the utility theory of drug therapy provides some clue to drug pricing.

The utility theory of drug pricing states simply that if a new drug is five times more effective in curing a particular infection than the drug currently in use, then the ratio of their prices ought to be five to one also.[24] With reference to the therapeutic effectiveness of chlortetracycline over penicillin, no medical authority is available to substantiate any such determination. In light of the problems involved in attempting to quantify this sort of question, the lack of such statements from the medical community is not unexpected. But in the area of the selling of drugs such restraints evidently do not operate. From a memo from Pfizer's medical department to its sales force we have an estimate that chloramphenicol is from 7 to 34 times more effective than penicillin against certain types of bacteria.[25] Assuming the same relations between chlortetracycline and penicillin a comparison of the price ratios of these drugs between 1949 and 1952 results in data consistent with the utility theory. In Table 11 significance is attached to the price ratio in 1948 when the price on chlortetracycline was selected, as well as the five year average of the price ratios of 31.

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choice. This is especially important in the prescription market where the physician often does not have access to the laboratory equipment to identify the bacteria, hence prescribes the more inclusive chlortetracycline.

[24] Hearings, Part 24, pp. 13639-13642.

[25] Hearings on S. 1552, Part 7, p. 3366.

TABLE 11.--Computed prices of chlortetracycline and procaine penicillin on a per day dosage basis

Year	Chlortetracycline	Procaine Penicillin	Ratio
1948	6.25	.26	24
1949	4.17	.11	38
1950	2.50	.09	28
1951	2.12	.09	24
1952	2.12	.05	42

Source: Federal Trade Commission, Economic Report on Antibiotic Manufacture, 1958, pp. 168 and 192.

In October 1948, two months prior to the marketing of chlortetracycline, procaine penicillin was listed at $13.34, or $.26 converted to a cost per day basis to the consumer. Applying the factor of 31 to the price of penicillin would indicate an initial price of chlortetracycline of $8.06 on a per day basis. This price is taken as the upper limit or monopoly price. An estimate of the lower limit or cost price is $1.00.[26]

[26]This estimate is derived from data presented by the Kefauver Committee relative to Bristol's production costs for tetracycline. Here they estimated that the production costs, defined as the cost of bulk tetracycline, capsules, finishing, packaging and royalties, at $3.91 for 100, 250 mgs capsules, or on a per day dosage basis of 4 capsules at $0.16. Hearings, art 24, p. 13876. Taking this figure as the cost of goods old, the expenses of selling, research, administration, and rofit, can be estimated from financial ratios for broad ectrum antibiotics. In 1956 the following ratios applied; search 7 per cent; administration, 7 per cent; and profit fore federal income taxes, 37 per cent. FTC, Economic port, p. 211. Assuming that these ratios apply in the case tetracycline adds some .40 to the Committee's cost figure r a total cost of $.63. This difference between this figure

The actual price set by Lederle was $6.25. This price can be interpreted as an offer price to Parke Davis on the assumption of equal product efficiency resulting in a degree of market sharing. This in turn implies the use of an undifferentiated duopoly model which can be extended to include more than two participants. The Cournot model is sufficient to explain the observed price and market shares which resulted.

The Cournot model in its simplest form assumes zero costs of production and a failure of the participants to recognize the element of mutual interdependence. With reference to Figure 1, a monopolist would produce an output equal to OD charging the monopoly price of DP, with total profits equal to ODPC. In this case 1/2 the competitive output OK is produced. If a second firm enters the market on the assumption that the other firm's output is constant, the best it can do is sell an output equal to DE, charging a price of EP', with total profits equal to DEP'F. The first firm by assuming that the second's output will be constant can increase its profits now equal to ODFB by reducing its output to 1/2 OK less DE. This sort of reaction continues until an equilibrium is reached, at which point each producer contributes 1/2 to the total output and each maximizes profits.[27] But at the point where output is reduced to

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and the estimated lower limit on price is accounted for by decreased production costs between 1956 and 1949.

[27]Edward H. Chamberlin, The Theory of Monopolistic Competition (Cambridge: Harvard University Press, 1962), 8th ed. Chap. III.

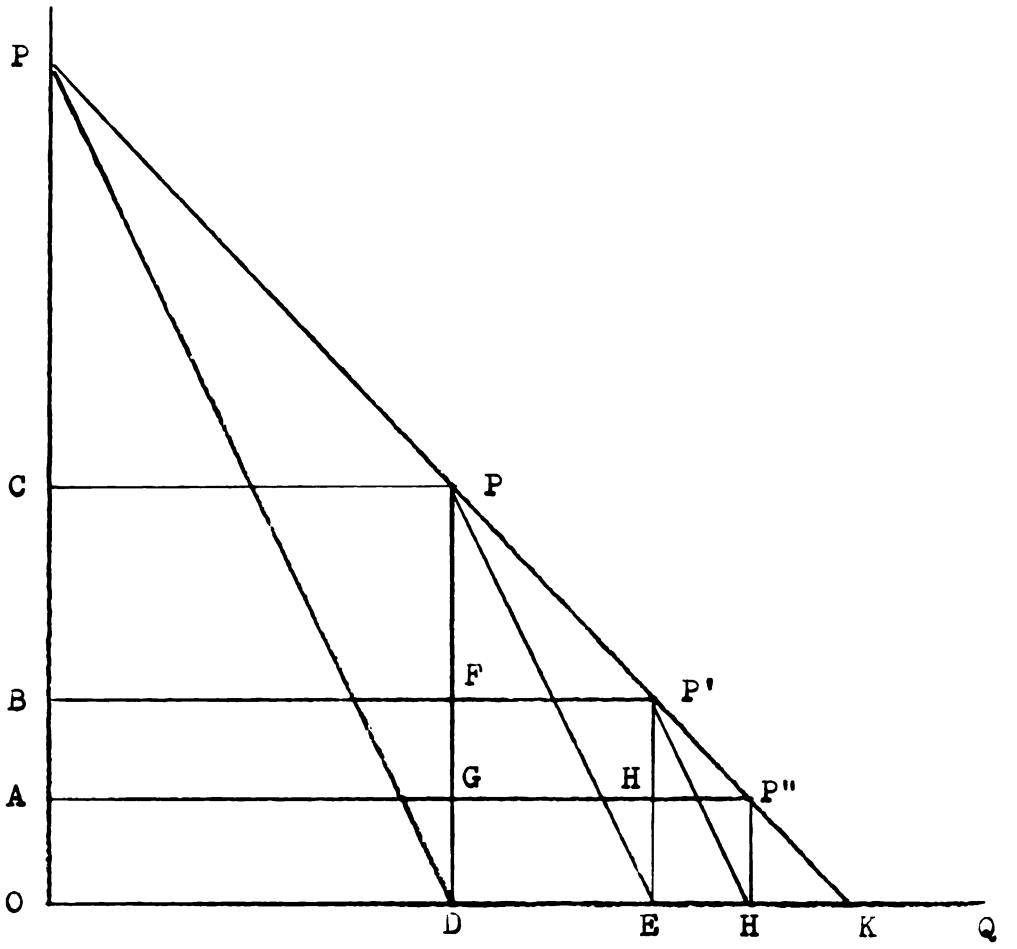


Figure 1

increase separate profits the Fellner concept of qualified joint industry profit maximization can be introduced.[28] That is, the price remains at P' and the first firm's output is not reduced in an effort to maximize its individual profits. This is because "the potentiality of . . . warfare always exists,"[29] and the market is dynamic in terms of shifting cost and demand curves. In addition, the market share which

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[28]Fellner, op. cit., Chap. VI.

[29]Ibid., p. 177.

results from the failure to move in the direction of the Cournot solution is favorable to the first firm in the face of incomplete information relative to its marginal cost and revenue curve. Lacking such information the share of the market resulting from a price decision in the context of rivals' reactions may be a first approximation to profit maximization. But the ability of the first firm to impose a market share on its rival depends upon Fellner's factor (a) through (d).

The data relevant to prices and price changes and the participants view of rival's market position can be injected into this model in an attempt to explain these observations.

The monopoly price has been estimated at $8.06 while the actual price was $6.25. It has been argued that this was an offer price prior to Parke Davis' entry on the assumption of equal therapeutic efficiency and mutually offsetting sales efforts. But with the entry of Parke Davis, Lederle cut the price of chlortetracycline to $4.67. The interpretation of this cut in price is that the initial Lederle offer price was rejected by Parke Davis as it had found a cheaper synthetic method of producing chloramphenicol, hence the balance of strength in a future contest between these participants shifted somewhat in favor of Parke Davis.[30]

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[30]Lederle seems to have adopted the assumption of equal costs of production of chlortetracycline and chloramphenicol based on a fermentation production process. Realization of the incorrect nature of this assumption required new estimates of what Parke Davis would settle for in terms of its share of the market.

In terms of the model the monopoly price is DP, while the initial price set by Lederle fell short of DP. With the realization that Parke Davis could produce chloramphenicol cheaper than chlortetracycline a new price was set at P' and accepted by Parke Davis. The results expected from the Cournot model are that the monopolist will maximize profits, pricing where marginal revenue is zero and one half the competitive output is produced. With the entry of the second firm, on the assumption that the first firm's output is constant, in the Cournot solution the second firm can maximize profits initially by producing one half of the first firm's output. In terms of Figure 1 this corresponds to DE at a price of P'. The initial solution indicates that 3/4 of the competitive output is produced, corresponding to OE, with the first firm selling 2/3 of the amount supplied, corresponding to OD, and the second firm selling 1/3, corresponding to DE. In addition, in this initial solution, the second firm's price is 1/2 the monopoly price.

If the game is stopped at this point because of the dynamic character of the market, the expected values are reasonably approximated by the observed values. In 1949, the one year a clear-cut case of duopoly existed in the broad spectrum market, the duopoly price of $4.17 was about 48 per cent of the monopoly price of $8.06, and the market shares in this year were 69 per cent for Lederle and 31 per cent for Parke Davis.[31]

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[31]See Table 6, Appendix, page 246 for market shares.

The fact that Parke Davis accepted the Lederle price offer by entering the market at this price implies the existence of a quasi-agreement not to compete in this variable. Here Fellner's factor's (a) through (d) appear to have exerted some influence on these decisions.

The first of the factors is the consequence of "faring too well" at the expense of rivals or of society in general. The latter invites institutional interference on behalf of the public interest, while the former invites some form of retaliation. This would seem especially pertinent in the drug industry where the products are vital to the health of the population and where moderate forms of socialization of medicine are currently taking hold. Relative to rivals it will be recalled that Parke Davis had not "fared" well in the antibiotic market up to this point. Lederle became one of the first firms to enter the penicillin market while Parke Davis never became a significant producer. Later Parke Davis built a streptomycin plant but this plant was never placed in production due to the development of price competition in this drug. For Lederle to attempt to hinder Parke Davis' entry could have been viewed by rivals as inequitable. As the various drug firms have built interrelationships based on patents and cross licensing agreements, Lederle's behavior towards a rival could have denied it access to future patented knowledge. Thus it would seem that Lederle was under some pressure to reach an accommodation with Parke Davis.

The second of Fellner's factors is the political consequences of a failure to reach an agreement, resulting in

destructive price cutting. Such behavior in turn can lead to public regulation of the industry. By reaching an agreement the private interests of the parties are protected. This was exactly the situation in the dispute over the patent on tetracycline. This issue could have been settled through the courts, but with the danger that all participants would be worse off if the court ruled that tetracycline was not patentable over chlortetracycline. Thus a private solution was reached and interests thereby suitably protected.

The third factor is the ability of the parties to take and inflict losses in the absence of an agreement. This develops from the fact that there are alternative solutions that divide the gains from the agreement which result in different positions of strength. The ability to engage in this sort of warfare "depends on wealth in general and on liquid wealth in particular . . ."[32] But perhaps of greater importance the willingness to engage in such conduct implies failure of the price leader to adequately consider the consequence of his action according to factor (a). In the situation under consideration, the failure of Lederle to set a price satisfactory to Parke Davis would have brought factor (c) under consideration as an alternative course of action. In absolute terms Lederle, if considered a part of its parent, was about twice the size of Parke Davis as measured by sales or assets. If this is taken as an index of relative liquid wealth available to the parties Lederle's ability to impose

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[32]Fellner, op. cit., p. 27.

a solution would seem clear.

The final factor listed by Fellner is the element of "toughness in the sense of unwillingness to yield in a range in which the other party is expected to yield if one fails to do so."[33] This produces cutthroat competition developing from the incorrect appraisal by each firm of its competitor's position or its willingness to engage in such activities. In attempting to judge Parke Davis' view of this element the evidence is contradictory. Industry opinion of Parke Davis was, up until 1952, that they avoided risk whenever possible, and were an unaggressive competitor. Yet Parke Davis was also known in the industry as a price cutter, except in the broad spectrum market. In view of its cheaper synthetic production of chloramphenicol it can only be concluded that the price established by Lederle was within the range acceptable to Parke Davis. Thus Lederle avoided the problem of a failure to agree.

The argument may be summarized briefly at this point. Lederle in its pricing of chlortetracycline initially determined the monopoly price with reference to the competition offered by penicillin according to the utility theory. The actual market price selected was in the nature of an offer price based on the realization that Parke Davis was about to enter the market with a competitive drug. With its cheaper method of production Parke Davis rejected the initial offer and Lederle responded with an acceptable price. While the

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[33] Ibid., p. 28.

initial solution is a disequilibrium according to the Cournot model, the dynamic character of the market and the mutual acceptance of the resulting price and market shares, indicates a stable solution.

An Oligopoly Model.--With the entry of Pfizer in the broad spectrum market the basic Cournot model can be used again to explain the price and market shares which resulted.

With the entry of a third firm into the stable disequilibrium postulated, the best it can hope for is to supply EH at a price of P". If the price leader foresees this entry it will select price P" thereby forestalling the appearance of price competition. Price P" is 50 per cent of the duopoly price and the indicated market shares are 57, 29, and 14 per cent of the total market OH. Table 12 summarizes the results

TABLE 12.--Comparison of expected and actual market shares and prices (1949-1953)

	Duopoly		Oligopoly				
	1949		1950		1951	1952	1953
	Expected	Actual	Expected	Actual	Actual	Actual	Actual
Price	$4.03	$4.17	$2.01	$2.50	$2.12	$2.12	$2.12
Market Shares							
Lederle	.66	.69	.57	.50	.51	.37	.51
Parke Davis	.33	.31	.29	.33	.30	.33	.10
Pfizer			.14	.17	.18	.30	.38

Sources: Observed market shares--Table 5, Appendix p. 245, Price, Hearings, Part 24, p. 13663 converted to a per day cost basis.

of both the duopoly and oligopoly expectations from the model and the actual results observed. One finds that in regard to price the actual prices observed were greater than the expected. This, of course, follows from the model where it has been assumed the production costs are zero. Injection of a linear horizontial average cost curve half way between OA on Figure 1, corresponding to a per unit cost of $1.00, means that the percentage reduction in price from the monopoly price is 47.7% where the observed reduction is 48.3%. In addition there are minor changes in the expected market shares. However, these results depend upon the elasticity of the market demand curve that one is willing to assume. But except for 1950, where the entry of Pfizer led to some degree of testing buyer reaction to price,[34] the expected and actual results are in reasonable agreement.

In regard to market shares there is again reasonable agreement between expected and observed in three of the five years under consideration. This may be increased to four out of five if 1953 is reclassified as a situation of duopoly. In this year, as noted, the side effects of Parke Davis' chloramphenicol were noted in the medical profession, and in addition, in November of that year tetracycline was introduced by Lederle, which in effect changed the product emphasis in

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[34] Pfizer in introducing oxytetracycline, priced it slightly higher than chlortetracycline or chloramphenicol, reportedly to make the impression that it was a superior product. Buyer resistance was met and the price was reduced to that of its two competitors. Cyanamid's Proposed Findings, II, 134-35.

the broad spectrum market. If on the other hand these two events had not taken place two interpretations of sequence possibilities are possible. First, it is possible that an approximately equal division of the market may have continued. This is explained on the basis that the quasi-agreement did not include all variables, in particular sales expenditures. Second, it is possible that Pfizer's increasing share of the broad spectrum market, and Lederle's declining share, were a sufficient spur to renewed research efforts. This question is deferred to the following chapter.

The apparent conclusions from this analysis are that Lederle, in its role as price leader in the broad spectrum market, selected price with the onset of entry so as to prevent price competition and thereby maximize joint industry profits. The nature of the agreement was essentially to compete in terms of non-price variables. The modified version of the Cournot model does a reasonable job, ex ant of predicting both the magnitude of price changes and resulting market shares up to 1953 when the essential character of the market underwent a considerable degree of change. In addition the model does provide a crude estimate of the loss in output due to conditions of fewness. Under conditions of free entry the industry output would have been in the order of OK (Figure 1), but actual output was OH or some 87% of the competitive output less whatever adjustment would have to be made for the introduction of costs of production. Thus the loss in output is estimated at between 12 and 15%.

Target Return Pricing.--Earlier in this chapter the question was raised whether the pricing of chlortetracycline was a reflection of target return pricing or a reflection of some other policy. A tentative answer indicates that the policy was one of maximizating joint industry profits. That is, the initial price selected reflected Lederle's view of market conditions in the light of Parke Davis' immediate entry. Data from Table 10, adjusted for federal income taxes, indicates that margins in the broad spectrum market were in 1950-51 about double the stated goals. The implication here is that these desired goals are useful for review purposes but that for pricing purposes the utility theory provides a useful first approximation.

Pricing History.--In presenting the price history of the narrow and broad spectrum antibiotics an attempt is made to judge whether the results have been acceptable from a social point of view. In making such a judgment the price behavior of the narrow spectrum market is used as a criterion with which to compare the results in the broad spectrum market. The assumption here is that the narrow spectrum market was competitive in the sense that price tended to reflect costs of production. The differences in the competitive elements between these two markets are discussed in terms of the number of firms, the existence of a bulk market, and the use of patents.

If competition is to be measured by the numbers of firms producing any one drug, or grouping of drugs on the basis of the degree of substitutability, then by definition,

the narrow spectrum market is the more competitive of the two. Table 13 presents data showing the numbers of firms producing and selling selected antibiotic drugs.

TABLE 13.--Number of firms producing and selling selected antibiotic drugs, 1960

Antibiotic	Producers	Sellers
Penicillin	7	20
Streptomycin	5	6
Dihydrostreptomycin	5	7
Tetracycline	3	5
Oxytetracycline	1	1
Chlortetracycline	1	1
Chloramphenicol	1	1

Source: U.S. Congress, Senate, Report 448, Subcommittee on Antitrust and Monopoly, 1961, p. 67; U.S.Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale, 1962; Physicians' Desk Reference, 1962 Edition.

The data in Table 13 with regard to the numbers of sellers is at best only an approximation. For example, in the case of penicillin, the count of sellers is taken from the Physicians' Desk Reference. There is no assurance that the coverage of sellers is complete. But in terms of numbers alone and on a product basis, the penicillin market is perhaps the most competitive.

The second major difference observed between the narrow and broad spectrum markets is the existence of a bulk market in the former market. The general policy of narrow spectrum producers has been "to sell part of their production in bulk to outside packagers who compete with the manufacturer

in the marketing of medicinal products containing antibiotics."[35] Table 14 provides some indication of the growth in numbers of packagers compared to manufacturers.

TABLE 14.--Numbers of antibiotic producers and packagers

Year	Producers	Packagers
1950	14	27
1951	13	26
1952	12	29
1953	12	33
1954	11	30
1955	10	37
1956	9	45

Source: Packagers--Federal Trade Commission, Economic Report, 1958, p. 66; Producers--U.S. Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale, various issues.

In this period while the number of producers of antibiotics declined, the number of packagers increased, purchasing their input materials through the bulk market. However, while numbers of packagers increased, the composition of this population changed to a considerable extent, leading the Federal Trade Commission to conclude in its study that entry at the packaging level was relatively easy.

By 1961, the number of narrow spectrum producers had declined to eight, while only nineteen non-producing firms

[35] FTC, Economic Report, p. 66.

[36] Ibid. Of the 27 firms engaged in packaging in 1950, seventeen had left the industry by 1956. Of the 45 firms listed in 1956, 35 had entered the industry after 1950.

can be identified.[37] This decline in the number of packagers can be attributed to several factors. First, in the growing broad spectrum market a bulk market did not develop. Second, the forward integration of Pfizer and Merck in the prescription market increased the degree of competition faced by the packagers. And third, an increased emphasis upon selling activities by the larger firms.

The third major differences in these markets was the use of patents to exclude competition. While streptomycin and dyhydrostreptomycin were patented, non-restrictive licenses were granted. This was not the result of benevolence on the part of Merck, the holder of the patent on dihydrostreptomycin, but rather an outgrowth of the fact that the patent on streptomycin was held by a non-profit foundation at Rutgers University which did grant unrestrictive licenses.[38] As the two products were close substitutes Merck had little choice but to follow the policy established by the Foundation. As a result a bulk market developed with open price quotations in these two drugs.

In the case of penicillin, while the basic drug was never patented, certain of its salts were so protected. In general, licenses were granted under these patents either as a matter of company policy developing in a similar vein to the Merck case, or as a result of settlement of patent inter-

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[37] Physicians' Desk Reference (6th ed.; Oradell, N.J.: Medical Economics, Inc., 1961) pp. 207-09.

[38] FTC, Economic Report, pp. 229-30.

ference proceedings.[39]

In the case of the narrow spectrum antibiotics the existence of the bulk market reduced the control the patentee could exercise over the sale of the product. This follows from the principle that the first sale of the patented product exhausts the patent monopoly. With the isolation of the broad spectrum antibiotics the decision not to sell in the bulk market increased the degree of control that could be exercised by virtue of the patent.

Thus to assume that the narrow spectrum market was sufficiently competitive to serve as a criterion with which to judge the pricing results in the broad spectrum market, seems reasonably supported by conditions in the former market.

In presenting price data there is the problem that the same product will sell in different markets at different prices. Table 15 seeks to avoid this problem by comparing rates of change in the realized price over all markets. For the three narrow spectrum drugs their average decline was on the order of 20 per cent per year, while for the one broad spectrum drug included in the sample the average rate of decrease was 8 per cent per year. Comparing rate of decrease over the first five years for which data is available on the basis that technological change is more prevalent in this early period, yields similar results. The average yearly change for the narrow spectrum drugs is 28 per cent, while

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[39] Ibid., pp. 237-45.

for the broad spectrum it is again 8 per cent.

TABLE 15.--Percentage changes in the average price received for four antibiotic drugs (1946-1961)

Year	Penicillin	Streptomycin	Dihydro-streptomycin	Tetracycline
1946	.47			
1947	.38			
1948	n.a.	.53		
1949	.35	.53		
1950	.36	.41	.37	
1951	*.03	*.05	*.05	
1952	.43	.30	.25	
1953	.43	.13	.27	
1954	*.01	.30	.18	
1955	.20	.29	.28	
1956	*.08	.27	.14	
1957	*.03	*.05	*.02	.07
1958	*.12	.13	.12	*.01
1959	.05	.37	.26	.05
1960	.11	.00	.18	.22
1961	.19	.18	.17	.08
Yearly Average	.18	.24	.18	.08

Source: Computed from U.S. Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale, various issues.

* Indicated increase.

It appears that the price decreases in the narrow spectrum drugs reflect increased productivity of the fermentation process through the isolation of more potent microorganisms and improvements in the culture medium.[40] As each

[40] Ibid., pp. 111-14, 119-22.

of the narrow spectrum drugs declined rapidly in price soon after their introduction due to reductions in costs, one would expect similar reductions in the costs of producing tetracycline. (The data on the realized price of tetracycline overstates the actual movement of price as this price is determined by dividing the revenue from the drug by the total output produced. With new drugs there is a tendency for the firms to give free samples to the physician in an effort to familiarize him with the product. With established products such as penicillin and streptomycin this is not necessary.) Thus it appears that prices of the broad spectrum antibiotics in the various markets were less felxible than in the narrow spectrum markets.

Price Structure.-- The channels of distribution in the antibiotic industry generally run from manufacturer to wholesaler, who in turn sells to druggists and local hospitals; from manufacturer to government agencies; and from manufacturer to bulk buyers. These channels do not establish hard and fast separation of customers. For example, a manufacturer may sell direct to a large hospital on a bid or list price basis, or a wholesaler may bid on sales to government agencies. In general, three broad customer classes may be identified. First, there is the prescription market composed of wholesalers and druggists where the consumer buys on a prescription basis. Second, there is the hospital market which is composed of hospitals subclassified on the basis of source of income. There are hospitals supported by city, county, or state

funds referred to as CCS hospitals. Hospitals supported by private sources of revenue are referred to as NPA hospitals, and finally hospitals supported by federal funds such as the Veteran's Administration and military hospitals. In the latter case purchasing is through the Military Medical Supply Agency on a bid basis. Third, there is the bulk market through which packagers obtain drug supplies either in bulk or in unlabeled dosage form for resale in the prescription and hospital markets.[41]

Each of these markets gives rise to a price structure. In the prescription market the structure of prices is along functional lines with the list price to the consumer forming the basis of the discount schedule. Traditionally the discounts here are 40 per cent from list for the druggist price and an additional margin of between 9 per cent and 13 per cent for the wholesaler. In the hospital market the base price is that of the NPA hospital which is the same as the price to the durggist. CCS hospitals generally receive a discount of 16-1/3 per cent from the NPA price. Sales to government agencies are on a bid basis which introduces a degree of variability into the discount structure. But a figure of 50 per cent from the NPA price seems average.[42] Sales in the bulk market take place according to open market quotations as

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[41] FTC, Economic Report, pp. 143-46; FTC, Proposed Findings of Fact, Conclusions of Fact and Law and Order to Cease and Desist, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, June 1960, pp. 15-18.

[42] FTC, Economic Report, pp. 159-94.

appear in the Oil, Paint, and Drug Reporter.

Data which would indicate the relative importance of these three markets in terms of total antibiotic sales or in terms of broad or narrow spectrum antibiotics is lacking.[43] However, the relative importance of broad and narrow spectrum drugs can be indicated for two points in time. In 1950 the narrow spectrum drugs accounted for 60.8 per cent of total antibiotic sales from manufacturer's own production. The broad spectrum drugs accounted for 38.5 per cent with all but .07 per cent of the sales accounted for by the eight drugs listed in Table 1, Appendix. By 1956 the narrow spectrum drugs accounted for 21.9 per cent, the broad spectrums some 54.7 per cent, with 23.4 per cent of the total market accounted for by antibiotics other than those listed in Table 2, Appendix.

From data presented by the Kefauver Committee the importance of the broad spectrums in the hospital market can be indicated for 1959. In this year three durgs, chlortetracycline, chloramphenicol, and tetracycline accounted for 71.4 per cent of total antibiotic sales in the hospital market and some 50.7 per cent in the prescription market.[44]

In terms of individual concentration of sales by firms data are available for four of the six major antibiotic producers. In 1959 Parke Davis accounted for 47.1 per cent of

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[43]Presumable such material is contained in the in camera record of the FTC v. American Cyanamid Company, et al. case.

[44]Hearings, Part 24, p. 13655.

total antibiotic sales in the hospital market and 14.7 per cent in the prescription market.[45] Bristol upon its entry into the broad spectrum market concentrated its sales efforts in the hospital market and in an undated statement found that 53.6 per cent of its sales were in this market.[46] Both Lederle and Upjohn concentrated their efforts in the prescription market with 68 per cent and 84 per cent respectively of their sales in this market.[47] Data for Squibb and Pfizer would be expected to show the same sort of concentration in the prescription market for with the exception of Parke Davis, those firms with large sales forces seem to concentrate their sales efforts in these markets.[48] It is, of course, in the prescription market that price plays the least important role. For here if the physician can be convinced that a particular brand of antibiotic is more effective, thereby leading to prescription on the basis of brand name, neither the consumer nor the druggist has the authority to substitute a cheaper brand. In the hospital and government agency markets the use of the formulary system seeks to avoid this problem thereby placing the emphasis upon price.

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[45] Loc. cit.

[46] Bristol's Proposed Findings, II, p. 180.

[47] Cyanamid's Proposed Findings, II, p. 104; Upjohn's Brief and Proposed Findings, p. 81.

[48] In the case of Parke Davis' chloramphenicol, its hospital sales can be accounted for by its ability to attack pathogen that have developed resistance to the other broad spectrum antibiotics and to penicillin.

The conclusions from these data must be tentative, but it would appear that the prescription market is the most important in terms of sales revenue followed by the hospital and government agency markets. Between the two broad classes of antibiotics the broad spectrums have been of increasing importance as revenue producers. From the nature of the prescription and hospital markets relative to the question of price flexibility, it would be expected that prices would be more flexible in the latter market. A test of this question is developed below.

In Table 16 average yearly price changes for the antibiotic drugs in various markets are summarized. For the

TABLE 16.--Percentage decreases of average yearly price for antibiotic drugs by markets

Markets	Penicillin	Streptomycin	Dyhydro-streptomycin	Chlortetra-cycline	Chloram-phenicol	Oxytetra-cycline	Tetracycline	Average Narrow Spectrum	Average Broad Spectrum
Prescription	29	25	25	7	5	1	0	26	4
Hospital NPA	29	25	25	7	5	1	0	26	4
Hospital CCS				2		0	1		1
Government VA				2	4	5	6		4
Government MMSA	5		5	0	1	1	*8	5	*2
Bulk	19	24						21	

*Indicates an increase

Source: Hearings on Administered Prices, Part 24, pp.13663, 13778-13782; Part 25, pp. 14209-14224, FTC Economic Report, pp. 168, 184-85, 187; Bristol's Proposed Findings, II, 199-200; Cyanamid's Proposed Findings, pp. 220, 243.

prescription and NFA markets list prices are used, while data for the CCS market are winning bid prices, as are prices for sales to the government. Prices in the bulk market are offer prices. The time period covered is roughly from 1950 to 1960. An effort was made to secure the various price series for comparable periods, however this was not possible in the case of the government market where the series begins in 1956 and runs through 1959.

From this data certain tentative conclusions may be drawn. First, relative to price structures, in the narrow spectrum market price changes are reflected in all markets for which data were available. The apparent exception is in the MMSA market but here, as noted, the price series is somewhat shorter. In the broad spectrum market, on the other hand, this clear relationship is not observed. The implication here is that a greater effort was made to maintain clear separation of markets for pricing purposes. Or in somewhat different terms that the greater elasticities of demand were recognized in the government markets. A further implication here is that given the more elastic demand in the government market and the fact of secret bidding that a greater degree of price competition existed in these markets.[49]

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[49] Here evidence of market sharing in the MMSA market is ignored. Data were developed in the Hearings and in the FTC case against the five tetracycline producers that showed the following market shares for awards from November 1956 through October 1959; Pfizer 46.6%, Lederle, Bristol, and Squibb all about 17%, and Upjohn 9.5%. However, there was disagreement as to what awards were excluded in developing these percentages, especially in the latter period. See Hearings, Part 24, pp. 13700, 13715.

A second obvious conclusion is that the rate of price decrease was greater in the narrow spectrum market than in the broad spectrum market regardless of whether the comparison is on a product or a market basis. In the narrow spectrum market there is a continual decline in price with certain exceptions. These are also reflected in Table 15. But in the broad spectrum market the last price cut to the prescription or NPA hospitals was in 1951. Prices for all four broad spectrum antibiotics did not change until late 1960 or early 1961. For a ten year period price stability was achieved.

A third conclusion from Table 16 is the stability of the agreement on the price variable. Here the broad spectrum drugs are listed in their order of market introduction. The data on price flexibility shows a general decline from the introduction of chlortetracycline to tetracycline in the prescription and NPA markets.

A final conclusion from this data concerns the behavior of price under different market structures. Under the competitive conditions found in the narrow spectrum market price shows a marked tendency to decline as the costs of production decreased. The less competitive character of the broad spectrum market shows relatively inflexible prices. The basic cause of this difference in price performance was the use of patents to exclude competition in the broad spectrum market and, for those operating in this market, a conspiracy not to compete in terms of price in the prescription and NPA markets.

The Price Fixing Conspiracy.--In the price fixing phase of the Federal Trade Commission case against Lederle, Pfizer, Bristol and its two bulk customers, Squibb and Upjohn, the issue is basically a question of whether these firms engaged in a conspiracy to maintain prices or whether their actions could be interpreted as mere conscious parallelism in an oligolopist market. If, as the respondents argued, the patent on tetracycline was obtained without the benefit of misrepresentation of the facts to the patent examiner, then the fact of identical price lists indicates only the recognition of mutual interdependence. That for one firm to cut price in an effort to increase its sales volume would be self-defeating as its cut would be promptly met by rivals. The Commission on the other hand argued these firms engaged in a conspiracy to secure the tetracycline patent thereby excluding additional entry and agreed not to compete in price.

In the initial decision the hearing examiner found that the issue of coproduction revolved around "the amount or substantiality of inherent production. . ."[50] involved in the production of chlortetracycline according to the Duggar-Niedercorn patents. In accepting the Pfizer argument that what it found were useless trace amounts of tetracycline and that the patent examiner was uninterested in such non-commer-

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[50]FTC, Initial Decision, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, 1961, p. 20.

cial quantities, the hearing examiner disposed of the fraud issue.[51] With this issue settled the examiner argued that it was highly unlikely for the respondents to engage in a protracted battle for the patent on tetracycline and at the same time enter into an agreement to fix price.[52] The market behavior of the respondents in publishing similar price lists,[53] in developing a system of similar customer classifications,[54] marketing identical dosage forms and sizes,[55] incidences of identical bids to the CCS hospitals and various government agencies,[56] coercion of independent wholesalers where they bid under the list price,[57] did not begin with the settlement of the Pfizer infringement suit against Bristol. Thus the examiner reasoned that to observe this behavior pattern before the settlement of the infringement suit where a conspiracy could not have existed, and to observe the same pattern later proved that a conspiracy to fix price did not exist.

The examiner buttressed his reasoning by citing the fact that product competition existed in the form of combinations of tetracycline with other antibiotics. In certain cases such competition was not met by rivals or met with a one or two year delay in time.[58] The decline in the share of the antibiotic market held by Lederle with the introduction

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[51] Ibid., p. 49. [52] Ibid., pp. 143-44, 171.

[53] FTC, Proposed Findings, pp. 348-50, 371-77, 568-83.

[54] Ibid., pp. 402-05, 432-40. [55] Ibid., pp. 348-49.

[56] Ibid., pp. 471-75. [57] Ibid., pp. 526-34.

[58] FTC, Initial Decision, p. 132.

of tetracycline indicated competition not conspiracy.[59] The existence of intracorporate memoranda on the subject of rivals prices was interpreted as a "strong effort to ascertain the competitive practices of other marketers."[60] The prices to large NPA hospitals were in effect cut at various times by the giving of "free goods" with the placement of a large order. This behavior was not evidence that the conspiracy periodically broke down, but rather evidence of strong competition.[61] Thus the interpretation of the behavior of the five respondents depends upon the patent phase of the case. If a conspiracy existed it had to be in effect prior to the issuance of the patent on tetracycline.

The full Commission in overturning the examiner's initial decision argued first that the patent examiner was concerned with whether any coproduction occurred in the production of chlortetracycline. In effect it ruled that Pfizer designed its test for coproduction in a manner that would support its statement that only "useless trace amounts were found." That is, the tests were not conducted strictly according to the Duggar-Niedercorn patents and that commercial recovery techniques were employed which were incapable of recovering the small amounts of tetracycline coproduced. Not to have informed the patent examiner of these facts constituted material misrepresentation.[62]

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[59] Ibid., p. 135. [60] Ibid., p. 146. [61] Ibid., pp.152-56.

[62] FTC, Findings As To The Facts and Conclusions of Law, In the Matter of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, 1963, pp.21-27.

In regard to the conspiracy phase of the case the Commission stated that the law did not require that they fix the exact time when the agreement became effective. Reasoning from the 1960 Electrical Equipment case it was entirely possible that while higher echelon management was engaged in a bitter contest for the patent, the sales management personnel of the respondents had entered a conspiracy for the orderly marketing of tetracycline regardless of the outcome of the patent issue.[63] Thus a conspiracy to monopolize the tetracycline market did exist before the settlement of the infringement suit and the observed behavior in both the patent and commercial phases of the case were found to be consistent with this finding.[64]

In the matter of price the Commission agreed that competition did not exist in the prescription market, nor, contrary to the examiner's decision, did it exist in the hospital or government markets. The use of free goods to secure a particularly large order in the NPA market was an example of "chiseling" which was tolerated as it did not effect prices in prescription markets where "75 per cent of the respondents' total sales were made . . ."[65] In the government market while

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[63]FTC, Opinion of the Commission, In the Matter of of American Cyanamid Company, et al., Before the Federal Trade Commission, Docket No. 7211, 1963, pp. 78-81. The Commission also noted that the Broady tapping of the telephone lines of Bristol and Squibb was unauthorized by the top management of Pfizer.

[64]The Commission on the timing of the conspiracy noted that it existed as of early 1955, ibid., p. 79.

[65]Ibid., p. 84.

some variation in price existed they were in fact insignificant and designed to preclude an antitrust investigation.[66]

With regard to the shifts in the market shares which the examiner found inconsistent with a conspiracy theory, the Commission argued that such shifts were to be expected as the respondents did compete in terms of promotion efforts while not in price.[67] Defining the market in terms of both broad and narrow spectrum antibiotics, in 1950 Lederle held about one quarter of this market base on its sales of chlortetracycline. In 1956 it held a bit more than one quarter based chlortetracycline and tetracycline. Thus with the marketing of tetracycline Lederle's relative position in the antibiotic market was slightly improved. If on the other hand a narrow definition of the market is applied to include only broad spectrums Lederle's share moved from close to 100 per cent in 1949 to progressively lower shares as competitive products were introduced. But this smaller relative share was of an absolutely increasing market. Between 1953 and 1956 there was a 50 per cent increase in the volume of sales of tetracycline alone. From the Cournot model employed above it is expected that the innovator's share of the market will decline in a static world as this is an alternative to price warfare. In a dynamic world of shifting demand curves this result is unlikely. For here the leader maintains his absolute sales volume giving up the new customer demand to the followers.

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[66] Ibid., pp. 86-87. [67] Ibid., p. 103.

The totality of evidence in this case would support a finding of conscious parallelism, but this the Commission rejected. To the Commission in the words of Kaysen and Turner, "The essence of the problem is not, Is there parallel action: but rather, Is there anticompetitive action?"[68] The very purpose of Section 5 is to prevent "unfair methods of competition." The act does not require a showing of lessening of competition, only that the techniques employed,in the opinion of the Commission, were in some sense "unfair." The formation of a conspiracy to fix price falls clearly within the context of an "unfair" market technique.

Estimate of Monopoly Revenues.--The older defense of monopoly was that it was necessary for technical progress. The current defense of oligolopy is that the simple inventions have been made and that for continued progress large size in terms of laboratories and supporting research budgets are necessary. From this it follows that the larger the profit margins the larger can be the expenditures on research and the greater the rate of technical progress. This question is examined in detail in the following chapter, but here it seems appropriate to attempt some estimate of the monopoly revenue available from the sale of tetracycline and to allocate this among the various producers. The simple hypothesis to be tested in the following chapter will be whether the firms with a larger excess profit had a higher rate of drug invention.

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[68] Carl Kaysen and Doland Turner, Antitrust Policy (Cambridge: Harvard University Press, 1959), p. 105.

In the absence of cost data any estimate of monopoly revenues must be crude. What is available is the price of tetracycline, output, and an estimate of sales in different markets. The critical assumption in this analysis is that the gains in technology, reflected in the price of penicillin, were also available to the tetracycline producers. Between 1951 and 1960 the average decrease in the price of penicillin was about 5 per cent. This rate is applied to the 1953 price of tetracycline to produce column II in Table 17.[69] By 1960

TABLE 17.--Estimate of monopoly revenue in tetracycline (1953-1960)

Year	Actual Price	Estimated Competitive Price	Difference Col. II - Col. I	Sales, No. of Bottles 16,250 mgs (000,000)	Estimated Monopoly Revenue (000,000)	Total Market Value (000,000)
1953	$5.10	$5.10	$ 0	3.4	$ 0	$
1954	5.10	4.85	.25	22.9	5.7	
1955	5.10	4.61	.49	21.9	10.7	
1956	5.10	4.38	.72	15.8	13.5	72.9
1957	5.10	4.16	.94	25.4	23.9	108.5
1958	5.10	3.95	1.15	20.7	23.8	88.9
1959	5.10	3.75	1.35	21.8	29.4	89.4
1960	5.10	3.56	1.54	21.8	33.6	69.4

Sources: Sales in terms of numbers of bottles computed from FTC, Economic Report on Antibiotic Manufacturer, 1958, pp. 73-75, for 1950 through 1956; for sales for 1957 through 1960, and total market value, U.S. Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale.

[69] The figure of 5 per cent produces a rather conservative estimate of what the decrease in price would have been under competitive conditions. In the case of penicillin the 1946-60 rate of decrease averages 18 per cent, for streptomycin it is 17 per cent and for dyhydrostreptomycin it is 16 per cent.

it is estimated that under a competitive market structure price would have fallen to $3.56.[70]

The reasonableness of the estimate of price in Column II can be shown by a comparison of average prices in foreign markets in 1959. In that year three foreign markets had average prices for tetracycline lower than the estimated price. These were Brazil with an average price of $3.10, France with $2.69, and Argentina with $1.10. In testimony before the Kefauver Committee Lederle stated that the situation in Argentina and Brazil was explained by price controls, but that some profit was made.[71] It would seem that in a price set by a subsidiary some allowance would be included in cost for research and advertising. This would appear to be especially true if such information could be used to convince the price control authorities that higher prices were justified. Lacking direct evidence on this point it can only be concluded that the estimated competitive price seems reasonable as judged by foreign prices in three markets.

The 1953 price of tetracycline can be interpreted as a price that bore a reasonable relationship to the competitive situation in tetracycline. But that over time as technological gains became available at the rate of 5 per cent per year, they were not reflected in price. Thus as average costs shifted downward the margin between costs and price increased.

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[70] In 1964 the price of tetracycline actually was cut to $3.63.

[71] Hearings, pp. 13743, 13744, 13748, and 13750.

Column IV is an estimate of the yearly volume of sales in the prescription market in terms of standard bottles of 16,250 milligram capsules. This estimate is based on the Commission's statement that 75 per cent of the respondents' sales of tetracycline were in the prescription market.[72] Column V is an estimate of the monopoly revenue available from the sale of tetracycline to the five sellers. In comparison with the total value of the market (Column VI), the element of monopoly revenue increased from 18 per cent in 1956 to 43 per cent in 1960.

With the data available there is no method to allocate the monopoly revenue among the five sellers. The best that can be done here is a rough ranking based on market shares. From the data presented by Bristol[73] it is clear that Lederle enjoyed the largest, although declining, share of the market for the period 1954-58 with Pfizer second. Upjohn ranks somewhat ahead of Squibb in third position with Bristol last. This ranking ignores the fact that Bristol was the bulk supplier of Squibb and Upjohn hence profited from the latter firm's sales.

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[72] An upward bias exists in this calculation as the total sales volume reported by the Tariff Commission is divided by the wholesale price in the prescription market of $5.10, resulting in the number of bottles sold. 75 per cent of this figure produces the estimate for the prescription market. Thus the assumption that all sales took place at a constant price of $5.10 overstates the case. But given the conservative estimate of technological gains the bias is not likely to be seriously disrupting.

[73] See Table 6, Appendix, p. 246.

While the conclusion here must be tentative, given the nature of the data and its manipulation, it does appear that profits in the tetracycline market have been substantial and sufficient to provide an inducement for the investment in research. The question in the following chapter is whether any relationship exists between the existence of monopoly power and performance in terms of significant new drugs.

CHAPTER VI

RESEARCH AND DEVELOPMENT

The discussion up to this point has been concerned primarily with the antibiotic segment of the ethical drug industry. In an attempt to examine the record of technological progress the sample has been expanded to include the twenty major firms who have innovated drugs of some consequence since 1945. The purpose of this analysis is twofold. First, it attempts to develop a criterion of technological progress by which the record of the antibiotic producers can be judged; and second, to raise specific questions concerning the effectiveness of the research activity of the industry as a whole. In particular the following questions are asked. How many drug innovations have appeared between 1945 and 1959, and how significant from a medical point of view is this record? Is the spending on research proportionate with firm size and are the larger firms more productive of innovation? Are scale economies present? Finally, in light of the monopoly position of the antibiotic producers, have they been more or less productive than the industry?

THE DATA AND THEIR SOURCES

The basic data required in attempting to answer the questions posed are the record of new drugs introduced by firms in the industry, together with data on sales and various categories of expenditures. A record of new drug introductions was prepared by the Pharmaceutical Manufacturers Association for presentation to the Kefauver Committee.[1]

Data on sales of ethical drugs are provided for one year by the Kefauver Committee for fifteen firms, and it has been possible to separate out estimates of ethical sales from total sales for an additional six firms.[2] Data on various categories of expenditures are provided in the Committee report.[3] Additional data are provided on a time series basis by firms' published statements to stockholders as well as the usual financial reporting publications.

List of Significant New Drugs.--The PMA list of significant new drugs includes 93 entries. The apparent criterion for inclusion of a particular drug was its importance in current drug therapy. Current, indicates those drugs that

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[1] U.S. Congress, Subcommittee on Antitrust and Monopoly, Administered Prices in the Drug Industry, Part 19, 86th Cong., 2d Sess., 1960, pp. 10840-10854.

[2] Ibid., p. 10993. It was necessary to drop CIBA from the Committee list as the research expenditures reported also included those made in Switzerland.

[3] U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Report, Administered Prices Drugs, 87th Cong., 1st Sess., 1961, p. 31.

had not been superseded by newer, more efficient drugs as of 1959. As such it is possible that significant drugs that were later improved upon and replaced as the drug of choice in a particular course of therapy are not included in the PMA list. One such case was found in the drug chlortetracycline which was the first of the broad spectrum family of drugs. Another case was dihydrostreptomycin, an improved version of streptomycin. Both of these drugs have been added to the PMA list, but it is possible that others have been missed.

The second part of the PMA criterion is the importance of a particular drug. The implication is that the drug is of significant market value, but no volume figure was supplied. Again it is possible that a new drug of significance in the treatment of a disease of low incidence was not included. Thus, it is not possible to claim complete coverage for the PMA list even with the noted additions. It is assumed, however, that the coverage is sufficiently complete for the results that follow.

In addition to listing significant new drugs the PMA also supplied data on the inventing firm or individual, the innovating firm or firms with the date of introduction, and a critique of the advantages of the drug.

The PMA list was used only for the period 1945 through 1959. Entries prior to 1945 were deleted on the grounds that it was not until after World War II that the industry was forced to look to its own resources for new drugs. Of the eleven entries prior to 1945, nine are clearly products of

foreign origin, and one could well fall in this category. Of the 84 remaining entries included in the list after 1945 some 33 were the product of foreign research.

Classification of Significant New Drugs.--A simple listing of new drugs would fail to consider that some are of greater importance than others. A solution to this problem is provided by defining three categories of importance and classifying each drug on the basis of the PMA critique and by a standard text on pharmacology.[4]

The first category is defined to include drugs that were the first in a series and/or the first effective treatment for a particular disease or range of diseases. The second category includes drugs that are similar in their range of effectiveness as established drugs, but were either more potent and/or carried a reduced incidence of side effects. The third category includes drugs that appear to be of little or no proven advantage over established drugs. These drugs appear to be perfect substitutes.

Table 18 presents the results of classifying 84 drugs into the three categories of significance as well as data for the 1951 through 1959 period indicating the total new drugs introduced to the market.

The data from Table 18 provides an indicator of the industry's productivity in inventing and innovating new drugs.

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[4]The text chosen was E. Krug, Pharmacology in Nursing (St. Louis: The C. V. Mosby Co., 1963), on the basis of clear statements of the effectiveness and side effects of particular drug in practice, rather than in terms of manufacturers' claims.

TABLE 18.--Distribution of 84 new drugs by categories of significance and by years (1945-1959)

Year	Categories I	II	III	Total	New* Chemical Entries	Per cent Included in PMA List
1945		1		1		
1946	2			2		
1947			1	1		
1948	1		1	2		
1949	4	2	2	8		
1950		2	2	4		
1951		2	2	4	35	.11
1952		2	3	5	35	.14
1953	1	5		6	48	.08
1954	1	3	3	7	38	.21
1955	1		5	6	31	.19
1956		1	4	5	42	.14
1957	1	2	9	12	51	.24
1958	1	1	7	9	44	.20
1959		2	10	12	63	.19
Totals	12	23	49	84		

* New Chemical Entries are the official listing of the United States Pharmacopoeia on new drugs introduced in the domestic market.

Source: U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly Administered Prices in the Drug Industry, Part 19, 86th Cong., 2d Sess., 1960, pp. 10840-10854; and Pharmaceutical Manufacturers Association, Prescription Drug Industry, Fact Book, 1963, pp. 2-5.

In this matter the industry argues that its performance has been more than adequate in comparison with European producers.[5]

[5]The real test here, of course, is a comparison of the rate of invention and innovation with the opportunities to invent and innovate. However, as the latter is indeterminant, analysis of the performance variable is forced to consider secondary indicators.

Since World War II research expenditures have been increased five fold. Lacking a knowledge of the industries' opportunities to invent and innovate we have no way to evaluate this argument with reference to total figures on new drug introductions. On the other hand it is possible to examine the composition of the aggregate figures and arrive at a judgment of the industries' technological performance.

While the data on new drug entries in the United States Pharmacopoeia (New chemical entries) and the total of new drug introductions based on the PMA list, are not strictly comparable, as the former refer to dates of discovery while the latter are based on the dates of market introduction, the series does indicate that between 1951 and 1959, a greater proportion of new drug discoveries are significant in that they are included in the PMA list. But the doubling in the PMA inclusion rate may well be a statistical illusion. That is, the PMA list tends to include in the latter years, drugs that were still in the stage of clinical testing and were marketed as part of this testing program. Drugs that were so indicated by Krug in 1963 were classified in category III. Thus the absolute growth in the numbers of drugs in this category is perhaps slightly overstated.

What does stand out here, however, is that there has been no apparent upward trend in drugs classified in category I or II. So that while there has been an increase in the number of new drugs, an increasing proportion of them have been of little or no significant value in terms of technological advancement of drug therapy.

Industry Research Expenditures.--Data on industry spending for research and development is published by the National Science Foundation for the period 1956 through 1959, and in index form by the PMA from 1948 through 1959. The NSF data is considered more inclusive as all drug firms are included in its survey while the PMA includes only its members, and, in addition, the NSF definition of research and development is more restrictive in what expenditures may be so classified. Thus the NSF data is used as the relevant figures.

The problem with the NSF data is that it does not reflect price level changes. These have been in the order of 6.7 per cent per year,on the average, for research and development for the chemical industry in the period 1945 to 1959.[6] It is assumed that the ethical drug industry faced that same magnitude of price changes for research and development as the chemical industry.

Table 19 presents data on the level of research and development spending by the industry adjusted for price level changes, new chemical drugs, and the average cost per drug. With such data we are in a position to examine the question of whether, over time, it has become more expensive in real terms to invent and innovate new drug products.

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[6]The price index for research and development expenditures for the chemical industry were computed from Tariff Commission data which show the labor costs of research and development activities and employment of scientific personnel. From this it is possible to compute average salaries and the increase in the salaries of scientific personnel. The Tariff Commission data also indicates the proportion of labor costs to total costs. Such was used to weight labor costs in determining the total increase in price. For material costs the wholesale price index was used.

TABLE 19.--Research and development costs per new drug discovery (1951-1959)

Year	Real R & D Expenditures in Millions	New Chemical Entries	Cost Per New Drug Discovery in Millions
1951	40.5	35	1.23
1952	38.4	35	1.09
1953	41.5	48	0.86
1954	40.0	38	1.05
1955	46.8	31	1.48
1956	52.2	42	1.24
1957	56.2	51	1.10
1958	69.0	44	1.53
1959	76.4	63	1.21

Source: R and D Expenditures are from the National Science Foundation, Review of Data on R & D, No. 24, Dec. 1960, Washington. Price Index was computed from U.S. Tariff Commission, Synthetic Organic Chemicals U.S. Production and Sale, Second Series, various issues, Washington.

If we attribute all new drugs discovered and innovated to the ethical drug industry we find that the costs in real terms have increased slightly in the nine year period for which data is available. Dividing the period into three year sub-periods, the average cost rose some 18 per cent between the 1951-53 period and 1954-56, but less than 2 per cent for the 1957-59 period. While it is difficult to associate research and development spending with new drug introductions, the 18 per cent increase in real expenditures for the first two sub-periods is associated with a decline in new drug introductions in category I and II from 10 to 6 (Table 18), and with an increase in category III introduction from 15 to 18. A comparison

of the second and third subperiod associates a 2 per cent increase in real research and development spending with an increase in category I and II drugs from 6 to 7, and an increase in category III from 13 to 33. Thus it would appear that while for the period as a whole real research and development efforts have increased, this increase has resulted in a shift in emphasis to the development of substitute drugs to compete with patented established products.[7]

ECONOMIES AND DISECONOMIES OF SCALE

In this section certain cross sectional data are developed on twenty ethical drug producers later to be used in comparing the performance of the broad spectrum producers. From this data it is possible to answer certain questions pertaining to the industry and compare the results with findings in other industries. In particular have the largest firms been the principle sources of innovations in the industry? Do the largest firms spend a larger proportion of their assets on research and development? Do proportionate increases in research and development expenditures result in proportionate increases in new drugs? Or are their economies of scale in research and development, in selling efforts or in production costs?

In addition to providing tentative answers to these questions there are certain byproducts of the analysis that

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[7]Computation of the correlation coefficient between real R and D spending and new chemical entries yields a value of .74 indicating a fairly strong relationship between these two variables.

extend the work of others. In particular it is possible to extend Mansfield's investigation of the relationship between the size of firms and innovations to the ethical drug industry as well as his investigation of the relationship between research expenditures and inventive output.[8] It is also possible to test Hamberg's thesis that the large industrial laboratory will not be the major source of inventions.[9] Finally, we ask whether any relationship can be discovered between patent statistics and the record of inventive output.

Research spending.--Relative to the question of what determines a firm's research and development budget Mansfield's model seems to yield reasonable results.[10] This model explains the current level of a firm's R & D spending as a function of the desired level of this activity and the fraction of the distance between actual levels and desired levels that the firm is able to move in a budget period. This assumes that the desired exceeds the actual level and that instantaneous adjustments cannot be made because of inefficiencies in rapid adjustments. The desired level of R & D spending depends upon the number of projects generated (a function of the size

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[8]Edwin Mansfield, "Size of Firms, Market Structure, and Innovation," Journal of Political Economy, LXXI (December 1963), and "Industrial Research and Development Expenditures, Determinants, Prospects, and Relation to Size of Firm and Inventive Output," Journal of Political Economy, LXII (August, 1964).

[9]D. Hamberg, "Invention in the Industrial Research Laboratory," Journal of Political Economy, LXXI (April 1963).

[10]Mansfield, "Industrial Research and Development Expenditures, Determinants, Prospects, and Relation to Size of Firm and Inventive Output," op. cit.

of the firm, i.e., larger firms have larger research staffs hence generate more proposals), the probability distribution of their expected rates of return, and the required minimum rate of return for the firm. The fraction of the distance a firm will move towards the desired level depends upon the percentage of the firm's profits that would be absorbed in such a move and the ratio of industry research spending to profits. Thus a firm spending below the industry average and with below average profits, but with a normal distribution of research proposals would be restricted in its movement to the desired level, as such a move would absorb too large a share of the following year's profits. On the other hand a firm in the same situation, but with a particular project with a high probability of a large gain, would be less hesitant to increase its current budget.[11] In addition the effects of patents on the model would be to increase the probability of return and to increase the level of spending. The question of competitive research and the possibility of rivals being first in the Patent Office is a bit more difficult to handle within Mansfield's framework. Such situations would seem to require a side calculation (and an additional equation). Here the firm would have to have knowledge of the projects of rivals, estimate its chances of being first or a sufficiently close second to force a cross-licensing situation, its chances of being first with rivals sufficiently close to force a cross-

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[11] Something of this nature seemed to have occurred with Bristol. See Chapter V.

licensing and the effects of these possibilities upon the rate of return from the project.

Thus while the Mansfield model is perhaps not complete in all details, it does provide a sufficient approximation to determine the level of a firm's R & D spending.

Size and Inventions and Innovations.--In this section we examine the relationship between size, various categories of expenditures, and new drug introductions. In particular we test the hypothesis that the larger the firm the greater its absolute rate of spending on research and development and the greater its productivity. Hence we would expect that if there are no diseconomies of scale in the research activity that the larger the firm the greater the number of new drugs invented and innovated.

To test this hypothesis twenty major drug firms were selected on the basis of their size as measured by sales of ethical drugs and the availability of data on research and development expenditures. These twenty firms accounted for about 87% of the industry's research and development spending in 1958 and 75% of all new drugs introduced between 1945 and 1959.

The scope of the test is limited by the fact that complete data on ethical sales by firms is available only for 1958. Hence, it is assumed that research and development expenditures and sales are representative of the differences between firms over time.

Table 20 provides data on twenty major drug producers using sales as a measure of size. The sample is divided into

TABLE 20.--Ethical drug sales, research and selling expenditures for 1958, inventions and innovations for twenty major drug producers 1945-1959 (in millions)

Firms	Ethical Sales	Selling Expenses	Research Expenses	Gross New Drugs	Inventions	Weighted Index of Significance for Innovations
Lederle	187	43	12.0	8	7	12
American Home Products	180	43	5.8	6	1	10
Merck	176	32	14.2	6	4	13
Parke Davis	172	43	8.3	3	1	7
Lilly	166	30	14.6	6	5	6
Upjohn	144	30	12.7	3	2	5
Pfizer	120	32	5.9	5	3	7
Abbott	112	31	6.3	0	0	0
Squibb	99	19	5.3	7	1	13
Sterling	71	26	2.3	1	1	1
Schering	69	24	5.7	5	3	8
Smith Kline & French	60	12	5.3	4	1	7
Warner Lambert	52	14	2.7	2	2	3
Searle	33	7	4.0	4	4	9
Mead Johnson	31	9	1.8	1	0	1
Carter	23	6	1.7	0	0	0
Vick	22	6	.8	4	2	5
Bristol	19	6	2.6	1	1	2
U.S. Vitiam	14	5	.7	2	1	2
Norwich*	8	3	.3	1	1	2

*Norwich was purchased by American Cyanamid in the middle of 1957.

Source: U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Administered Prices in the Drug Industry, Part 19, 1960, pp. 10993, 10840-10854; Report, Administered Prices Drugs, 1961, p. 31.

three size groups on the basis of reported sales of ethical drugs.[12] Expenditures for research and development and for selling are from the Kefauver Committee Report and apply only to drug operations for the year 1958. Gross new drugs are the total number of new drugs introduced by the firm inclusive of competitive introductions for the years 1945-1959. Inventions are the number of new drugs discovered by the firm in question, while innovations include both the firm's inventions and purchases of marketing rights from domestic and foreign inventors. The weighted index of new drug significant is the result of distributing each firm's innovations among the three categories of importance. A weight of 3 is assigned to drugs falling in category I, 2 for those in category II and 1 in caregory III. This index is on a gross basis as in several cases more than one firm is listed by the PMA as the inventor or innovator.

The focus of the analysis is upon innovations rather than upon inventions. This recognizes the argument of the industry that without the extensive clinical and pre-manufacturing testing of new drugs performed or supported by the drug manufacturers, the rate of such innovations would be considerably lower in a private enterprise system. In addition, the series on innovations is undoubtedly more accurate than that on inventions as it is not clear in all cases how the PMA handled credit where the discoverer was supported by corporate funds in his research.

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[12]The rational for the division of these firms into three categories were the gaps in the sales figures which conveniently resulted in an almost equal number of firms in each category.

We are now in a position to examine the question of whether large firms spend more on research and development than do smaller sized firms. In absolute terms it is obvious that the larger the firm the larger the spending on this activity. But in relative terms the smaller firms in the sample spent on the average a larger percentage of their sales dollar on research and development than did the larger firms. The average expenditure for small firms was 6.8 per cent of sales, for medium sized firms 6.1 per cent and for large firms 6.4 per cent. Major significance is not attached to this result due to the limitation or lack of time series data on research spending by firms. The data here do seem consistent with the conclusion that spending on research and development is proportional with size on the average.

If spending on research and development is proportional with size as measured by sales, are the results of this activity also proportional? In absolute terms the answer is clear that the larger firms do on the average have a higher rate of innovation either in terms of numbers of drugs introduced or in their average relative importance. For firms classified as large, average new drug introductions were on a weighted basis 8.6. For medium sized firms the weighted average was 5.3. For small firms the weighted average was 3.0. In terms of the weighted index large firm introductions were greater than small firm introductions by a factor of 2.87, and medium sized firms had a rate of introductions of 1.77 over small sized firms. Thus in absolute terms large firms on the average were

more productive in innovating new drugs over the 15-year period.

A similar examination of inventions yields the following results. Large firms in the 15-year period between 1945 and 1959, averaged 5.1 new drugs on a weighted basis. Medium sized firms averaged 1.5. Small firms averaged 2.3 on a weighted basis, or almost twice that for the medium sized firms. Again in terms of the weighted index larger firms were more productive on the average over small firms by a factor of 2.22, but small firms were almost twice as productive as medium sized firms. Thus in the case of inventions the advantage seems to lie with the large firms over their two competitive size groups.

While the larger firm is more productive in absolute terms is it also more productive per research dollar? Or in somewhat different terms are their economies or diseconomies in the research and development activity? Each of the three subgroups in a sample differs in their research and development expenditures by a scale factor. Medium sized firms spend on the average 2.7 more on research and development than do small firms, while large firms spend 6.2 times as much on the average as do small firms.[13] Using these scale factors Table 21 compares the expected weighted value of inventions and innovations with the actual average value. If large firms are as efficient as small firms then we would expect increases in

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[13]Comparable figures based on sales are 3.6 and 7.6, which, given the nature of the data, seem reasonably close to the scale factors that apply to research expenditures.

TABLE 21.--Expected and actual values for inventions and innovations

Group	Weighted Values			
	Inventions		Innovations	
	Expected	Actual	Expected	Actual
Large	14.2	5.1	18.6	8.6
Medium	6.2	1.5	8.1	5.3
Small	2.3	2.3	3.0	3.0

absolute research and development expenditures to yield proportionate increases in invention and innovation. In fact, the actual rate of invention and innovation falls below the expected in all cases. Thus it would appear that there are diseconomies of scale in large scale research and development. Or in somewhat different terms small firms appear to be more productive than large firms per dollar spent on research and development.

Within the context of Hamberg's hypothesis are "the proportion of all minor inventions originating in the large industrial laboratories . . . likely to exceed the proportion of all major inventions originating in these laboratories?"[14] Table 22 sheds some light on this question for the ethical drug industry. Here we distribute 39 inventions credited to commercial firms by the PMA by categories of significance and by size groups. In terms of the total number of inventions included in the sample of twenty firms, commercial firms dis-

[14] Hamberg, Journal of Political Economy, LXXI, p. 95.

TABLE 22.--Percentage distribution of 39 inventions of twenty firms by categories of significance and by size groups for 1945 to 1959

Size Group	Categories of Significance			
	I	II	III	Totals
Large	.05	.23	.31	.59
Medium	.00	.05	.13	.18
Small	.05	.08	.10	.23
Totals	.10	.36	.54	1.00

covered about 55 per cent of the total number of all reported innovations. In Table 22 for both the large and medium sized firms it is apparent that inventions of little significance accounted for the greatest proportion of the inventive activity, while for the small firms inventions of some significance (categories I and II) accounted for the greater proportion of the inventive output.

In terms of the total number of drugs from the PMA list, eleven can clearly be identified as discovered by non-commercial laboratories. Of these eleven, seven or 63 per cent fall in category I and II, with four or 36 per cent in category III. Thus the data seem consistent with Hamberg's hypothesis that commercial large laboratories will not account for a disproportionate share of important inventions.

Table 23 is similar to Table 22 except that the distribution is of 70 innovations by twenty firms. Here for the small and medium sized firm the proportion of innovations was about equal for category I and II as compared with category

TABLE 23.--Percentage distribution of 70 innovations of twenty drug firms by categories of significance and by size groups for the period 1945-59

Size Groups	Categories of Significance			
	I	II	III	Totals
Large	.10	.14	.30	.54
Medium	.04	.10	.13	.27
Small	.03	.06	.10	.19
Totals	.17	.30	.53	1.00

III, while for the large firms the proportion in category III was greater by six percentage points. Slightly over half of the drugs marketed between 1945 and 1959 which the PMA considered significant were in fact substitutes for established drugs.

It is difficult to judge the technical performance of the industry from these figures. The marketing of the perfect substitute would seem to increase the degree of competition faced by the innovator and result in a net social benefit if this competition was reflected in price. But if the case of the broad spectrums is any indicator of price competition in the rest of the industry the effect is to increase the flood of advertising in an attempt to increase market shares. Lacking knowledge of the industry's opportunities to invent and innovate perhaps all that can be concluded here is that the industry's claims to technical progress must be heavily discounted with the recognition that product competition and higher advertising expenditures are the result of patent monopolies.

Turning here to selling expenditures the question can be raised whether there are apparent economies or diseconomies of scale in this activity. The method of analysis is similar as in the case of research and development expenditures. Table 24 compares expected and actual selling expenses for

TABLE 24.--Expected and actual values of selling expenses for small, medium sized, and large firms for 1958 (in millions)

Group	Average Sales	Selling Expenditures	
		Expected	Actual
Large	164	46.8	36.8
Medium	77	21.6	21.0
Small	21	6.0	6.0

three groups of firms which differ by a scale factor based on sales of ethical drugs. Here the average level of sales for large firms differ from small firms by a factor of 7.8; medium size firms differ from small firms by a factor of 3.6. If we assume that similar differences appear for assets devoted to ethical drug production, that economies of scale do not exist in production,[15] and that similar rates of return are earned on assets employed, then the average profits on sales would be similar. Data on profits as a percentage of sales is available and shows that for the twenty firms included in the sample, profits on sales are quite similar for the three size groups. After tax profits for large firms averaged 13.8 per cent, for

[15]See Federal Trade Commission, Economic Report on Antibiotic Manufacture (Washington: Government Printing Office, 1958), Chap. IV; and Report, op. cit., pp. 73-74.

medium sized firms 12.4 per cent, and 13.9 per cent for small firms in 1958.[16] Thus, with similar rates of profits earned, the data in Table 24 indicates that larger firms are able to generate a similar level of profits with less than proportionate increases in selling expenses. Then for the large firms it would appear that economies of scale in selling offset diseconomies of scale in research. That for the medium sized firms there are no economies of scale in selling and with diseconomies of scale in research reflected in lower profit rates. And that the firms classified as small make the most efficient use of resource on the average.

Findings in Other Industries.--Mansfield investigated the relationship between size and innovations in three industries--steel, petroleum, and coal. The hypothesis was that if larger firms devoted the same proportion of their resources to innovating as did smaller firms, and if they were as efficient in applying results, then "one would expect their share of the innovations to equal their share of the market."[17] He found that "the largest four coal and petroleum firms carried out a larger number of innovations than this, but the largest four steel producers carried out fewer."[18] The share of the ethical drug market held by the four largest firms was

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[16]Profits as a percentage of sales for 1958 obtained in the Subcommittee Report, p. 31.

[17]Mansfield, Size of Firms, Market Structure, and Innovations, p. 560.

[18]Ibid., p. 561.

in 1958, 31.6 per cent.[19] These firms introduced a total of 23 new drugs out of a total of 84 included in the PMA list, or 27 per cent. In terms of the weighted index of significance, these four firms had an index of 42 out of a total of 183, or 23 per cent. Thus the ethical drug producer would be classified with steel producers.

Mansfield explains the differences in innovations in steel and in petroleum (the only two industries for which he could gather data), on the basis of the size of the market, the size of the firms in the industry, and the minimum investment necessary to introduce the innovation. That is, firms must be of some minimum size relative to the market before it is profitable for them to introduce the invention. Given this information it is possible to estimate the number of firms capable of innovating. If the innovation is expensive in terms of investment costs, this reduces the number of firms capable of making the innovation.

In terms of product innovations, Mansfield found that the number of firms of minimum size were about the same for petroleum and steel, but that the cost of innovating was on the average less in steel, hence more firms tended to engage in the innovating activity thereby reducing the share of the top four. While data is lacking with which to apply Mansfield's model to ethical drugs (assets devoted to ethical drug pro-

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[19] Hearings, Part 19, p. 10993; and 1958 Census of Manufactures, II; Industry Statistics, Part 1; General Survey and Major Groups 20 to 28 (Washington, 1961).

duction over time), we can specify that similar conditions as to numbers capable of innovating are present. That is, in spite of the sharp increased costs of marketing new drugs in terms of direct mailing, journal advertising, free samples, and detailing,[20] the technical character of the product would seem to insure wide market acceptance of a significant new product. Thus in ethical drugs as in steel it would appear that size alone does not insure a high rate of product innovation.

In another test of the relationship between the level of a firm's research and development expenditures and significant inventions, Mansfield found in part that in petroleum and steel, greater rates of spending by larger firms were highly correlated with weighted indexes of new inventions.[21] Here Mansfield assumes that $n_i = R_i [a + bR_i + oS_i]$ where n_i is defined as the weighted index of the innovation of firm i. R_i is the firm's research and development expenditure, and S_i is a measure of size. "The partial correlation of of n_i on R_i, holding S_i constant is .96, .98, and .70 in chemicals, petroleum and steel."[22] In the sample of twenty drug firms the coefficient was found to be .58 indicating a weaker relationship than that found in steel. Thus while Mansfield found a rather strong long run relationship between a firm's spending on research and the significance of its innovation,

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[20] Subcommittee Report, pp. 155-164.

[21] Mansfield, Industrial Research and Development Expenditures, p. 336.

[22] Ibid.

this does not appear to be the case in drugs. (Note however, that this conclusion rests on the assumption that the differences between firms in 1958 is representative of their differences over time.) In part the relationship between research and significant innovations may be due to the nature of research in these industries. Petroleum and drugs spend about the same proportion of their research budgets on basic research, but three times more than steel.[23] In petroleum basic research appears to be along the lines of inventing around an established patent to produce a competitive technical process.[24] In drugs it appears that various approaches to a problem are followed until one stands out as most likely to succeed. Thus the nature of the attack indicates a high rate of failure for accepted projects. In steel many of the recent innovations appear to be products of the European steel industry and are adopted in the domestic industry with spending on development rather than basic research.

In regard to the relationship between the weighted index of innovations and size of firm, with research spending held constant, Mansfield found the relationship negative in all three industries. In drugs it was positive with a value of .62. Thus while Mansfield was able to conclude that in-

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[23] National Science Foundation, Review of Data on Science Resources, I, No. 1, 1964. The 1960 figures for drugs were 17 per cent, steel 5 per cent, and petroleum 15 per cent.

[24] John L. Enos, "Invention and Innovation in the Petroleum Refining Industry," in National Bureau of Economic Research, The Rate and Direction of Inventive Activity (Princeton: Princeton University Press, 1962), pp. 299-321.

ventive output was lower in the larger sized firms, no such clear cut conclusion is possible in drugs. The best that can be said is that the relationship between size and the productivity of the research dollar is weak in drugs.[25]

The final question in this section is that of the relationship between statistics of patents issued and the record of inventive output. Here we would expect that firms engaging in research and development would hold a greater number of patents as their research effort increased.

Data on the numbers of patents in force as of 1955 has been compiled by the Subcommittee on Patents, Trademarks and Copyrights for firms holding 75 or more patents.[26] From this list it is possible to identify twelve drug producers together with the number of patents held as of 1955.

Is there any relationship between the number of patents held and the index of significant innovations? The simple linear correlation coefficient of .12 between these two series would indicate little or no relationship. Is there any relationship between the 1958 level of research spending and patent holdings? Again the correlation coefficient of .52 would indicate a weak relationship. Thus it would appear that

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[25] The gross measure of correlation in drugs was .76, somewhat lower than steel at .87 or chemicals and petroleum at .99. In addition the relationship between size and research spending was .39, again indicating a rather weak relationship.

[26] U.S. Congress, Senate, Subcommittee on Patents, Trademarks and Copyrights, Distribution of Patents Issued to Corporations (1939-55), 84th Cong., 2d Sess., 1957.

the connection between research spending, the productivity of that spending, and patents is in general weak.

Summary and Conclusions.--The analysis of technological change in the ethical drug industry indicates four conclusions. First, while the total number of new drugs introduced between 1945 and 1959 has increased, an increasing proportion of these introductions have been of little significant value from the technological point of view. In real terms the industry has spent increasing amounts on research and development, but not to the extent that the average costs of new drug introductions have shown a significant increase. Thus it would appear that there exists an increasing emphasis on marketing the research product and combining this with selling expenditures to insure an adequate level of profitability.

Second, the twenty firms included in the industry sample accounted for 87 per cent of the 1958 industry spending on research and development and for 75 per cent of all new drug introduction between 1945 and 1959. Spending on research and development was nearly proportional with size as measured by sales, but the index of research productivity indicated that diseconomies of scale were present.

Third, that in terms of inventions small firms seem as productive of category I inventions as large firms, but that large firms are three times more productive of category III inventions.

Fourth, the evidence seems consistent with the thesis that the opportunity for inventive activity has not been greatly

effected by the size distribution of firms, at least for the twenty firms included in the sample. That is, basically the product is technical and that a significant invention could still be marketed in spite of the generally large expenditures in selling.

THE ANTIBIOTIC PRODUCERS

Turning to the broad spectrum antibiotic producers and sellers, questions concerning their productivity can be raised. These firms held a monopoly position in the broad spectrum market either as the only producer or by virtue of the patent cross-license device. The basic question is the necessity for the patent monopoly to insure a flow of new drugs. That is, if the patent monopoly is necessary for technological advance then these firms should have been more productive than their competitors.

Productivity in Research.--In Chapter V an estimate was made of the monopoly profits earned in the tetracycline market and the five producers were ranked in their order of sharing in these profits. Between these producers and the rest of the industry it does appear that they were innovators of more significant drugs. Table 25 compares the distribution of the 84 drugs innovated between 1945 and 1959 with those produced by these five producers. Here half of the new drugs innovated by these five firms fell in category I and II, while for the industry as a whole 42 per cent were so ranked. Thus it would appear that the existence of a monopoly was a neutral factor in research productivity.

TABLE 25.--Percentage distribution of innovations for the five tetracycline sellers and the industry for 84 new drugs (1945-1959)

	Categories		
	I	II	III
Industry	.14	.28	.58
Five Sellers	.08	.42	.50

Summary and Conclusions.--The analysis of the position of the broad spectrum producers relative to the rest of the industry indicates that monopoly is not necessary for advances in technology. This, of course, does not argue that the broad spectrum producers would have had the same record of new drug introduction without patent monopolies. But it does argue that some firms were able to engage heavily in research and development and in a relative sense be more profitable without substantial monopoly positions. The conclusion casts doubt on the hypothesis that sustained monopolies are necessary for technological advancement.

CHAPTER VII

CONCLUSIONS AND PUBLIC POLICY

Public policy recommendations in the ethical drug industry rest upon conclusions of past performance and the expected effect of proposed changes in public policy upon future performance. It is necessary at this point to indicate the major conclusions of the analysis of the antibiotic segment of the industry and where possible to generalize these conclusions to the rest of the industry. The plan of this chapter is then to discuss each of four performance variables together with indications of the type of public policy changes which could reasonably be expected to improve the observed performance.

Research and Technological Progress.--The focus of analysis has been upon technical progress as measured by the innovation of new drugs. The choice of focus was due basically to two factors. First, in the innovation of new drugs the industry makes its greatest net contribution to social welfare. Second, to pick the innovation as opposed to the invention variable simply recognizes the fact that it is in this area that the industry's comparative advantage lies. That is, where the major breakthroughs in drug therapy are generally in the area of basic research and where in a profit orientated firm the probability of success of basic research

is quite low, one should not expect to find a high proportion of significant inventions. It would seem that the primary function of the industry in the matter of technical progress is to provide that necessary link between the inventor and the consumer. Thus it is in the area of development research--direction and support of clinical testing, evaluation of test results, solution of manufacturing problems--where the industry's major contribution to technical progress lies.

The Subcommittee in its analysis of technical progress found that there had been a decline in the number of significant new drugs introduced since the mid-1950's.[1] The explanation was that the firms had allocated their scientific personnel to development and patent circumventing research rather than basic research. In this paper the analysis has been for the 1945-1959 period. The indications are that for the industry as a whole and for the antibiotic producers in particular, the rate of technical progress has not changed significantly in this period. The rate of introduction of category I and II drugs seems rather constant in this 15 year period. However, the increase in spending on research is associated with an increase in the introduction of category III drugs. Thus in real terms the industry seems to be spending about the same proportion of its resources on basic research in grants to medical schools and other research institutions, but the increase in spending has been for projects

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[1] U.S. Congress, Senate, Subcommittee on Antitrust and Monopoly, Report, Administered Prices in Drugs, Senate Report No. 448, 87th Cong., 1st Sess., 1961, p. 126.

designed to produce the near perfect substitute for the established drug.

It was argued that this reaction was to be expected where the rationale for research spending are profits. The affect has been to increase product competition. But the experience in the broad spectrum market indicates that there is a limit to product competition. Since the introduction of tetracycline in 1953 no significant product competition has developed. The original four producers have not been challenged by other members of the industry. This may well follow from the interpretation of the Cournot model where with each instance of entry, price must be cut to insure that the new rival receives an acceptable share of the market. The alternative to the price cut with entry, would be for the rival to institute such a cut leading to the danger of unrestricted warfare. Thus it appears that spending on research to develop a substitute drug is profitable only if conditions of fewness exist in the market. With increasing numbers of sellers, price approached the competitive level thereby reducing the profit potential of the market relative to other markets.

In the case of the broad spectrum market it was concluded that the key invention was the soil screening process. This method of inventing directly resulted in three of the major broad spectrums and indirectly for the fourth. The soil screening process was essentially a product of basic research, while the operation of this technique was defined

as development research. While this relationship between basic and applied research, and the location of the key activity cannot be generalized to the entire industry, it does give an indication of the direction in which public policy ought to move. That is, lacking evidence on the opportunities to innovate, the conclusion on the observed rate of technical progress is that it has been within an acceptable range. But here the question for public policy is can this range be improved upon?

Adding the experience of penicillin to that of the broad spectrums, where it was found that the key technical contributions were made by the NRRL, indicates that the non-profit research organization is more productive of basic technical change than the laboratory of the commercial firms. Thus, if the non-profit research organization is generally a greater producer of the basis for technical progress then it ought to receive a larger share of the society's available resources.

A second area in which public policy can affect the future rate of technical progress is to halt a tendency towards increased concentration in the industry. A rough count of merger activity among the largest twenty firms indicated at least twenty-seven horizontal mergers between 1951 and 1961.[2] Lederle's parent, American Cyanamid, which according to 1958 sales data was the largest producer of pharmaceutical

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[2]U.S. Congress, House, Select Committee on Small Business, Mergers and Superconcentration 87th Cong. (Washington: Government Printing Office, 1962).

products, was also involved in the largest number of mergers at five. One of Cyanamid's acquisitions was Norwich Pharmaceutical which was among the largest twenty producers. In the analysis of the relationship between size and technical progress a rather weak relationship was found. In the analysis of seventy innovations by the twenty largest firms, the largest of these also produced a greater proportion of drugs of no significance. Thus to at least maintain the current rate of technical progress in the industry calls for the application of an anti-merger policy.[3]

Prices and Market Structures.--In the analysis of the narrow spectrum market, the structure of this market was found to have been towards the competitive end of the spectrum with prices reflecting production costs. In the broad spectrum market on the other hand prices for over a ten year period were unchanged, reflecting conditions of monopoly. The basic cause of this difference in market structures was the use of the patent. In the narrow spectrum market exclusive positions in penicillin were not possible as the basic drug was unpatentable, while in the case of streptomycin the patent was held by a non-profit organization which granted unrestrictive licenses. The various penicillins that were developed later as well as dyhydrostreptomycin were patented, but had to

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[3]For a similar conclusion see William S. Comanor, "Research and Technical Change in the Pharmaceutical Industry," The Review of Economics and Statistics, XLVII, May 1965, pp. 182-90; and D. Hamberg, "Size of Firm, Oligolopy, and Research: The Evidence," Canadian Journal of Economics and Political Science, XXX, February 1964, pp. 62-65.

compete in the market with the unpatented substitutes. As a result, a bulk market developed with conditions of relatively free entry. In the case of the broad spectrums, exclusive positions were maintained with patents, and to protect these monopolies the bulk market was not utilized as a source of buyers.

Application of a modified version of the Cournot duopoly model to the problem of entry and product competition gave a reasonable ex post fit to the available data. Here the function of the price leader was to determine the market price which would yield new rivals an adequate share of the expanded market as an alternative to entry and price cutting.

There is in these conclusions essential agreement with the Subcommittee findings that the patent has been used to restrict competition and maintain non-competitive prices.[4] But with regard to the international market insufficient evidence existed to support the thesis that a cartel was in operation.

The performance of price in the broad spectrum market must be judged inadequate. The root of the problem is the patent. The potential effectiveness of public policy on pricing depends on how it can change the patent system. This discussion is delayed to the section on patents.

Non-Price Competition.--The Subcommittee in its analysis of product competition viewed the use of resources to develop substitute products as a diversion of resources from

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[4] Report, pp. 80-88.

basic research thereby lowering the discovery rate of significant drugs.[5] Based on the analysis of the antibiotic segment of the industry it is agreed that basic research is the source of significant new drugs, but it is a mistake to assume that the industry ought to conduct this research. It has not in the past, the key contributions have come from the non-profit organizations. Now it may be possible to argue that the industry has not operated the available research techniques at their optimum rate,[6] but the industry rate of product innovation for the past fifteen years does not in itself support this argument.

It is, of course, true that the increased spending on research has tended to be directed towards the substitute drug. But it is also necessary to recognize that in the antibiotic market in three out of four cases this sort of product competition did result in a fall in price. In the absence of price conspiracy in tetracycline, the record undoubtedly would have been four out of four.

In the Subcommittee's view the quality and quantity of the industry's selling efforts were excessive.[7] While a

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[5] Report, pp. 126-37.

[6] In the case of the broad spectrum market it is possible to argue that with the established monopoly among the four producers the incentive to operate the soil screening process further has declined. And that for the non-producers to attempt to enter now would lower price according to the version of the Cournot model employed earlier. But to sustain this argument one would have to know the opportunities available to innovate new antibiotic drugs from this process.

[7] Ibid., Chaps. IX and X.

detailed analysis of this point was not made it was noted that, over time, selling expenditures as a percentage of sales had increased. This would seem to be an inherent result of the decline in price competition and profitable operations. With the conspiracy in tetracycline, competition in selling continued unabated. Perhaps because of the technical nature of the product such efforts were mutually offsetting.

The concern of public policy in the area of selling expenses can only be with the quality of information associated with drug innovations. The increased control over this variable available to the Food and Drug Administration is at least a step in the right direction.

Patents.--Conclusions on the effects of patents in the antibiotic drugs can be divided into three areas; research, innovations, and markets.

With regard to research it was concluded that basic research is, in the final analysis, the source of technical progress and that in the antibiotic segment of the industry the location of this activity is in the non-profit research organization. There is no evidence available that patents have any effect in allocating resources to these organizations, nor to effect the selection of projects for study. In the case of penicillin and streptomycin the research organizations involved both received patents on their contribution but granted unrestricted licenses to applicants. Thus entry and competition were unaffected by the existence of patent protection.

In the case of development research the available evidence indicates that patents do have an effect in resource allocation but that the results are mixed. With the early penicillin program it was concluded in Chapter I that the effect was negative. Firms participating in the program allocated their resources to projects designed to produce a synthetic penicillin rather than to utilization of the production technique made available by the NRRL and the OSRD, partly in the hope of receiving patents. Here then the effect on technical progress was retardative. On the other hand Lederle and Parke Davis' establishment of patent monopolies undoubtedly had an effect on Pfizer's and Bristol's research programs. The success of these programs in producing substitutes was perhaps neutral in effect on technical progress, but did initially increase competition in the broad spectrum market. From this evidence one could conclude that patents were a net positive or negative force, depending on the weight one gives to technical progress as opposed to product competition which results in price competition.

With regard to the effect of patents on the industry's rate of innovation the evidence is again mixed. There is an increasing reliance upon patent monopolies but also an increasing degree of product competition in the form of category III drugs, and no apparent change in the innovation of more significant drugs. In the broad spectrum market it was found that being the innovator and establishing the brand name of the drug was of greater importance in market shares

than the fact that a patent monopoly existed on a particular drug. On the other hand, since tetracycline no significant broad spectrums have been marketed. Whether this is due to complacency arising from monopoly, to the relative unprofitable level of price with entry, or to the fact that the soil screening process produced the ultimate with tetracycline, cannot be stated on the basis of the available evidence.

Thus to the question of the effects of the patent on invention and innovation one is inclined to agree with the Subcommittee that the "mere existence of patent protection is not a guarantee of invention, nor its absence much of a barrier."[8]

Perhaps the primary effect of the patent lies in the commercial strategy employed by the various broad spectrum producers. The patent prevents immediate duplication forcing rivals to "invent around" the innovation and allows the innovator time in which to build a lead in the market. With entry through product competition,prices are adjusted downward to make room for the rival in recognition of the mutual interdependency of the participants. With the entry of a sufficient number of sellers, either through competitive research or through a bulk market, the competitive price would be approximated. If this were the only effect of the patent it could be passed off as merely a lag in the adjustment process of a competitive system. But the question is more involved. The evidence of the tetracycline patent proceedings

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[8] Ibid., p. 120.

indicate that the patent can become the vehicle for conspiracy not only to secure a patent but the basis for agreement on price. The effect is then to delay further the adjustment process giving the participants time in which to become entrenched in the market.

The present antitrust laws are adequate to attack conspiracy based upon the patent grant.[9] The problem here is that the attack is upon the symptom rather than the mechanism which facilitates the conspiracy. It is in this area where recent changes in public policy as well as certain proposed changes can be effective.

The 1962 Drug Industry Act contained several features that will effect the future conduct of the industry. Section 2 provides that the Department of Health, Education and Welfare is vested with the authority to conduct any necessary research on drug patent applications at the request of the Commissioner of Patents. This provision gives the patent examiner access to independent opinion thereby removing the major absurdity in Patent Office proceedings where the examiner was forced to rely upon the self-serving statements of the applicant. If this section had been in effect during the tetracycline proceedings,it is highly probable that this drug would not have been patented and with bulk suppliers such as Heyden and Bristol in the market the broad spectrum market would have repeated the experience of the penicillin market.

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[9]In 1963 the Department of Justice brought suit in a Southern District Court of New York to revoke Pfizer's tetracycline patent.

Section 10 of this act provides the Secretary of HEW with the power to designate the official name of a new drug if such action would be "in the interest of usefulness and simplicity."[10] The effectiveness of this provision upon future competition depends largely on the physician's writing of prescriptions in terms of official names rather than brand names. To reduce the importance of the brand name could reduce the degree of entrenchment of the innovator and reduce the lag in the adjustment process with the appearance of product competition.

Section 7 provides an amendment to the Federal Food, Drug, and Cosmetic Act which requires that the firm not only demonstrate that its drug is non-toxic but that it is effective as well. In combination with the requirement that the firm supply the FDA with more information in support of new drug applications, the effect will be to reduce the numbers of perfect substitutes that reach the market each year. This reduction in product competition may well be offset by keeping inferior drugs off the market.

The Kefauver hearings produced three proposed changes in public policy. The first of these proposals provided for compulsory licensing of all drug patents after a three year period of exclusive manufacture and sale. The objective here was to allow smaller firms to obtain licenses at royalties not to exceed 8 per cent of the gross sales value, and thereby

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[10] U.S. Congress, Senate, Committee of the Judiciary, Report on the Drug Industry Act of 1962, 87th Cong., 2d Sess., 1962, p. 6.

"inject price competition into the industry and thus break down the established structure of unreasonable and usually identical prices charged by the large companies."[11] In fact, however, the exclusive period would be somewhat longer as the three year period would have begun with the issuance of the patent. Given the normal delays between filing of patent applications and issuance, the actual period of protection would run closer to five years. Under this proposed legislation the actual period of protection coincides with the industry's experience in the market. That is, on the average under the current patent law, a new drug is considered a good revenue producer for about five years before product competition forces prices down. Thus the major effect of this type of legislation would have been to prevent long run monopolization of the market as in tetracycline. In addition the firm contemplating directing its research to product competition could achieve the same result by simply waiting the required period and entering on the basis of a license. The advantages of this sort of proposal indicate that it would be a useful direction in which to move.

A second feature of the Kefauver approach was the provision that molecular modifications and combinations of drugs would not be patentable unless the Secretary of HEW determined that the drug in question offered a significant therapeutic advantage.[12] The purpose here was first an

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[11] Ibid., p. 49.

[12] Hearings, Drug Industry Antitrust Act., p. 28.

attempt to eliminate the type of substitute drug which led to confusion among members of the medical community, and second, to remove the rational for the large advertising expenditures that accompany such innovations. While the objectives here are commendable the effect would be a tendency to eliminate a source of competition, and in connection with the first proposal, tend to reinforce the short run monopoly position. The case of the broad spectrums provided a case in point. Product competition in the form of oxytetracycline, chloramphenicol had the effect of reducing the broad spectrum price structure. Under this proposal it is doubtful if oxytetracycline or tetracycline would have been patentable. And if they had not been patentable it is doubtful that they would have been marketed for in doing so the entire broad spectrum market would have been thrown open to unrestricted entry. If the analysis of the tetracycline case is correct, then the development of such substitutes would be for purposes of forcing a license from the patent holder under threat of unrestricted entry. Thus, the net effect of this proposal would be to reenforce the short run monopoly position of the patentee, along with that of the licensees, where their research was successful in providing a substitute.

The third major feature of the Kefauver policy concerned the prosecution of the patent application. Here it was proposed to amend the Sherman Act making it an unlawful restraint of trade to; (1) the withdrawal of any pending

patent application, (2) to concede priority of invention to another party under an agreement to split royalties, grant licenses at discriminatory royalties, or to grant licenses only to other applicants for the patent, (3) to refrain from granting any license under any drug patent.[13] The effect of this proposal would have meant the virtual elimination of patent protection on drug products. The first and second amendments eliminate private settlement of patent disputes, while the third would insure that entry via the license approach would remain open. This, of course, is what might be termed the ideal solution to the problem of patents. It insures either immediate entry and direct product and price competition or forces the innovator to initially select a price close to production costs thereby making entry unattractive. The fact that this proposal was not incorporated into the 1962 Drug Industry Act is a tribute to the industry's political power.

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[13] Ibid., pp. 20 and 28.

APPENDIX

TABLE 1.--Percentage distribution of manufacturer's production of antibiotics (1950)

Firm	Potassium Penicillin	Procaine Penicillin	Sodium Penicillin	Streptomycin	Dihydro-streptomycin	Oxytetra-cycline	Chlortetra-cycline	Chloramphenicol	Total Share of the market
Lederle							26.6		26.6
Pfizer	1.1	0.9	0.6	0.7	4.1	4.3			11.7
Merck	0.4	1.4	2.4	1.9	4.9				11.0
Lilly	5.0	5.2	0.5	0.2	0.1				11.0
Squibb	3.3	5.9		0.2	1.4				10.8
Bristol	1.9	3.6	0.3						6.0
Parke Davis								5.9	5.9
Schenley	1.2	1.5		0.2	0.3				3.2
Heyden	0.9	0.6	0.2	0.2	0.9				2.8
Abbott	1.2	1.5							2.7
Commercial Solvents	1.1	0.7	0.1						2.5
Wyeth		1.8							1.8
Monsanto								1.7	1.7
Vick	0.1	0.6	0.1						0.8
Upjohn	0.2	0.4			0.1				0.7
Cutter	0.2	0.5							0.7
									99.9*
Total	16.6	24.8	4.2	3.4	11.8	4.3	26.6	7.6	99.3

* The difference in the column and row totals is due to the exclusion of Commercial Solvents' Bacitracin which accounted for 0.6 per cent of the total market.

Source: Computed from Federal Trade Commission, Economic Report on Antibiotic Manufacturer, Washington, 1958, pp. 94-95.

TABLE 2.--Percentage distribution of manufacturer's production of antibiotics (1956)

	Potassium Penicillin	Procaine Penicillin	Sodium Penicillin	Streptomycin	Dihydro-streptomycin	Oxytetra-cycline	Chlortetra-cycline	Tetracycline	Chloramphenicol	Total Share of the Market
Lederle					0.2		11.2		16.5	28.1
Pfizer	0.4	2.1	0.2	0.6	2.3	12.0			4.1	23.4
Merck	0.8	1.5	0.2	0.5	1.8					7.2
Lilly	0.3	1.1		0.1	0.7					11.7
Squibb	1.3	1.9	0.2	0.8	1.1					6.7
Bristol	0.1	0.6							3.6	4.3
Parke Davis								7.3		7.3
Schenley										
Heyden										
Abbott		0.3								1.1
Commercial Solvents										0.4
Wyeth	0.3	0.6								5.0
Monsanto										
Vick										
Upjohn	1.0	0.4								4.4
										99.6*
Totals	4.7	8.5	0.6	2.0	6.1	12.0	11.2	7.3	24.2	76.6

*The difference in the column and row totals of 23.0 percentage points is accounted for by other antibiotic products.

Source: Same as Table 1.

TABLE 3.--Estimated distribution of revenue from sale of antibiotics from manufacturers' own production (1950, 000 omitted)

Firm	Total Revenue	Potassium Penicillin	Procain Penicillin	Sodium Penicillin	Streptomycin	Dihydrostrep-tomycin	Oxytetracycline	Chlortetracycline	Chloramphenicol
Lederle	$ 56,975							$56,975	
Pfizer	25,061	$ 2,356	$ 1,928	$1,285	$1,499	$ 8,782	$9,210		
Merck	23,561	857	2,999	5,141	4,070	10,495			
Lilly	23,560	10,710	11,138	1,071	428	214			
Squibb	23,134	7,068	12,637		428	2,999			
Bristol	12,852	4,070	8,139	643					
Parke Davis	12,637								$12,637
Schenley	6,854	2,570	3,213			643			
Heyden	5,997	1,928	1,928	428		1,928			
Abbott	5,783	2,570	3,213						
Commercial Solvents	5,355	2,356	1,499	214					
Wyeth	3,855		3,855						
Monsanto	3,641								3,641
Vick	1,714	214	1,285	214					
Upjohn	1,285	428	857						
Cutter	1,499	428	1,071						
Totals	$214,369	35,556	53,120	8,242	7,283	25,275	9,210	56,975	16,279

Source: Total size of the markets for 1950 from U.S. Tariff Commission, Synthetic Chemicals U.S. Production and Sale, Second Series, Washington, 1951. Percentage market shares from Table 1.

TABLE 4.--Estimated distribution of revenue from the sale of antibiotics from Manufacturers' own production (1956, 000 omitted)

Firm	Total Revenue	Potassium Penicillin	Procain Penicillin	Sodium Penicillin	Streptomycin	Dihydrostrep-tomycin	Oxytetracycline	Chlortetra-cycline	Chloramphenicol	Tetracycline
Lederle	$76,216					$ 543		$30,396		$44,780
Pfizer	63,505	$1,086	$5,699	$ 543	$1,628	6,242	$32,567			11,127
Merck	19,540	2,171	4,071	543	1,357	4,885				
Lilly	31,753	814	2,985		271	1,900				
Squibb	18.183	4,885	5,156	543	2,171	2,956				
Bristol	11,670	271	1,628							9,770
Parke Davis	19,812								$19,812	
Schenley										
Heyden										
Abbott	2,985		814							
Commercial Solvents	1,086									
Wyeth	13,570	814	1,628							
Monsanto										
Vick										
Upjohn	11,941	2,714	1,086							
Cutter										
Totals	$271,391	12,755	23,067	1,629	5,427	16,555	32,567	30,396	19,812	65,677

Source: See Table 3.

TABLE 5.--Production and unit value of medical grade antibiotics (1945-1960)

	Penicillin*		Streptomycin		Dihydrostreptomycin		Tetracycline	
	Production	Unit Value	Production	Unit Value	Production	Unit Value	Production	Unit Value
1945	7,454							
1946	27,000		3	$2,866				
1947	42,000		23	1,224				
1948	92,945	$1,600	82	576				
1949	138,102	796	54	269	139	$232		
1950	219,903	509	44	161	158	146		
1951	318,622	549	36	168	315	154		
1952	342,326	288	41	117	337	113		
1953	371,589	164	104	104	305	83		
1954	476,658	164	75	73	446	68		
1955	344,243	130	99	52	369	49		
1956	478,259	142	147	38	492	42	220	$391.95
1957	525,738	145	169	40	582	43	404	362.76
1958	391,574	162	166	35	561	38	287	365.88
1959	429,891	154	240	22	470	28	307	347.97
1960	498,130	138	329	23	392	23	287	271.09

*Production and Unit Value of Penicillin is in terms of billions of Oxford Units. Other production figures in terms of pounds.

Source: U.S. Tariff Commission, Synthetic Organic Chemicals, U.S. Production and Sale, Second Series, Washington, various issues.

TABLE 6.--Percentage Market Shares for Tetracycline* (1954-1958)

	1954	1955	1956	1957	1958
Lederle	76.3	59.7	55.5	53.1	45.3
Pfizer	14.9	14.3	17.3	15.1	21.4
Bristol	.8	1.5	2.8	4.9	5.2
Squibb	2.2	9.0	13.5	15.3	12.7
Upjohn	5.8	15.5	10.9	11.6	15.4

* Bristol indicated that these figures were derived from in camera documents.

Source: Bristol's Answering Brief, In the Matter of American Cyanamid Company, et al., Docket No. 7211, New York 1962, Appendix, p. 16.

TABLE 7.--Pharmaceutical markets and percentage distribution by products. 1954 and 1958

Major Markets	1954	Percent	1958	Percent
Total Pharmaceutical Preparations for Human Use	$1,498,918	100.0	$2,256,914	100.0
Antibiotics, broad and medium range ..	252,892	16.9	361,941	16.0
Vitamins	215,074	14.3	300,659	13.3
Analgesics, including narcotics	194.262	13.0	256,319	11.4
Tranquilizers, sedatives and hypnotics	42,684	2.8	236,802	10.5
Cough and cold preparations	97,025	6.5	171,580	7.6
Laxatives and stomach preparations	123,368	8.2	158,902	7.0
Hormones	103,532	6.9	151,354	6.7
Antiseptics	45,863	3.1	58,905	2.6
Hemantinecs	32,548	2.2	39,094	1.7
Sulfonamides	23,691	1.6	36,447	1.6
Anti-obesity preparations	21,289	1.4	29,852	1.3
Tonics and altratives	23,859	1.6	19,890	.9
Anesthetics	15,111	1.0	15,620	.7
Diagnostic aids	n.a.		9,343	.4
Central nervous system stimulants	2,000	.1	6,024	.3
Other pharmaceutical preparations	305,556	20.4	404,182	18.0

Source: U.S. Department of Commerce, 1958 Census of Manufacturers, Vol. II, Industry Statistics, Part 1, General Survey and Major Groups 20 to 28, Washington, 1961.

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