INNOVATION AND FOREIGN INVESTMENT BEHAVIOR OF THE U.S. PHARMACEUTICAL INDUSTRY

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Introduction and Summary

This paper deals with the links between the development of new drugs, and particularly of innovative new drugs, and the international activities of U.S. drug companies. While U.S. drug companies have developed new production processes--the most notable being the fermentation process for making penicillin--we concentrate in this paper on new products. Since production costs comprise less than 40 percent of the selling price of drugs[1] and since the person choosing the drug rarely pays for it,[2] growth in company sales and profits comes more from introducing new products than from cutting costs and prices of old products.[3]

The main novelty of our study is our examination of "innovative" as contrasted with "imitative" new drugs. Previous studies have generally focussed on the total number of new drugs produced each year, but since

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[1]For example, in 1973 materials and production costs were 36 percent of Merck's sales of $1.1 billion. Marketing and administrative expenses comprised 29 percent, research and development expenses were 8 percent, and profits before taxes were 28 percent of sales. Merck & Co. 1973 Annual Report. Materials and production costs were 34 percent of Miles' 1973 sales of $348 million. Miles Laboratories 1973 Annual Report. As discussed in Section III, Merck is a very "innovative" drug company, and Miles is a very "imitative" drug company.

[2]The physician selects the drugs; the government or an insurance company usually pays for it, at least in the U.S. and Western Europe.

[3]For a discussion of the stability of drug prices, see Michael H. Cooper, Prices and Profits in the Pharmaceutical Industry (New York: Pergamon Press, 1966), Ch. 3.

our interest is in the causes and consequences of innovation, we have concentrated on the products we have rated as innovative. Section I explains our criteria for this distinction and presents our enumeration of the innovative new drugs for each of the 22 companies in our sample from 1963 through 1972.

In Section II we discuss trends in the rate of drug innovation and the factors influencing those trends. We conclude that while the 1962 changes in the Food, Drug, and Cosmetic Act did produce an increase in research costs, there were other influences acting in the same direction, particularly the exhaustion of the stock of knowledge previously accumulated over a period of years.

Section III describes our sample of drug companies and characterizes them with respect to their size, research investment, and innovativeness. All the available measures of innovativeness, which can be divided into those measuring inputs and those measuring outputs, are flawed to some degree. Those we consider indicators of output, such as the ratio of innovative drug sales to total drug sales, are positively correlated with each other, and also with measures of the quality of new drugs, such as R&D expenditures per new drug or sales per new drug introduced. However, they are not related to the frequently used indicators of input, such as the ratio of R&D expenditures to sales, and they are negatively related to what we refer to as measures of R&D efficiency, such as R&D expenditures per dollar of sales of new drugs.

Section IV examines the relation of innovativeness to the foreign activities of individual firms. We conjecture that the more innovative

drug companies were less likely to open up new foreign manufacturing subsidiaries in the 1960's; the regressions reported in Section IV are consistent with this conjecture. Lack of data for our sample precludes our testing a corollary of this conjecture: that the more innovative drug companies are more likely to serve foreign markets via exporting from the U.S. and via licensing.

In Section V we analyze, for a sample of 7 new drugs introduced by two companies, the rate at which use of the drugs was diffused among various countries and the impact of the presence of manufacturing plants on the rate of diffusion. Our results hint that the lag between first introduction of a new drug and its introduction into a particular country tended to be shorter if there were a U.S.-owned manufacturing affiliate in that country and if the drug were an innovative one.

We should make explicit that our results, by themselves, do not indicate the economic benefits to either the U.S. or foreign countries of the activities of these companies. To estimate such benefits, one would need to look also at the prices of individual drugs in various markets; for example, an "imitative" drug sold at a cheaper price than an "innovative" drug may greatly benefit the consumer.[1]

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[1]Any estimate of such benefits depends on one's values and cannot, because we are dealing with new products, be derived from the analysis of formal welfare economics. This analysis assumes that at each point in time consumers could purchase, perhaps at a very high price, any product. However, nobody, for example, could purchase penicillin or its equivalent in the 1920's. "The introduction of new things is more serious. Indeed, they cannot be introduced into the analysis at all." I.M.D. Little, A Critique of Welfare Economics (Oxford University paperback, 1960), p. 39.

I. Input and Output Measures of the Flow of Innovation

Any manufacturing firm can be thought of as producing goods of at least two different kinds: on the one hand, a specific industrial commodity, and on the other hand, a flow of minor and major innovations which eventually find their way into the product turned out by the firm or into the production process used for such purposes. This flow of innovations can be looked at both in terms of the resources its gestation actually absorbs or, alternatively, in terms of the specific units of output which emerge from the knowledge-creation section of the firm.[1]

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[1] The lack of an explicit department engaged in R&D activities is not enough evidence on which to argue that any given firm does not produce any new knowledge. A great deal of knowledge new to the firm, and subsequent minor and/or major technological changes at the plant level, emerge either as a by-product of production, or as a consequence of technical activities performed by the engineering sections of the firm which normally receive names such as 'Trouble-shooting' or 'Technical assistance to production' departments. Furthermore, the evidence indicates that a large fraction of the observed total factor productivity growth of any given plant has to do precisely with the application of incremental knowledge coming from such sources. See, in this respect: S. Hollander, The Sources of Increased Efficiency. A Study of the Dupont Rayon Plants (Cambridge, 1966; MIT University Press); R. Shishko, "Technological Change Through Product Improvement in Aircraft Turbine Engines" (Rand Corp., Monograph 1061, May 1973); G. E. Box, "Some General Considerations in Process Optimization," Journal of Basic Engineering, No. 82 (March 1960); J. Katz, Importacion de Tecnologia, Aprendizaje e Industrializacion Dependiente (Bs.As. Forthcoming, Fondo de Cultura, 1974).

Measures of the input into innovation include data on R&D expenditure or manpower figures on the size of the R&D operation plus other knowledge-creation activities performed within the firm. Output measures of the flow of innovation in the context of the pharmaceutical industry might be: (1) Number of compounds synthesized, (2) Number of new product candidates, (3) Patents filed, (4) Written scientific monographs, (5) NDA's (New Drug Applications), (6) IND's (Investigative new drug applications), (7) Sales value of new products, (8) Numbers or sales of particularly innovative products.

Conceptual and statistical difficulties in empirical research in this field are: a) Where to draw the line between R&D activities and those other knowledge-creation activities also performed by the firm[1] and b) How to take into account quality changes which obtain with the passage of time? The first of these set of problems is associated with input measures of innovation, the second set with output measures. Let us briefly examine some of these problems.

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[1]Surveys on contemporary R&D expenditures in the U.S. and in Europe are currently carried out by NSF and OECD respectively. The instruction manuals distributed by both agencies indicating what and how to measure as R&D expenditure are far from being conclusive concerning the so-called "Associated Technical Activities" also performed by the firm. See, for example, NSF, a) Research and Development in Industry (Washington: U.S. Government Printing Office, June 1968), in particular p. 125 with the instructions for R&D measurement; b) OECD, Proposed Standard Practice for Surveys of R&D, Doc. DAS/PD/62.47, Paris, 1966.

Besides carrying out explicit R&D activities, manufacturing firms also perform other technical jobs such as: process development and pilot plant production, quality control, clinical evaluation, research and development carried out with the purpose of assisting other areas of the firm such as patenting, medical information, etc. The accounting treatment of expenditures in these activities varies widely among pharmaceutical firms. It therefore follows that inter-firm differences in R&D expenditure should be expected and that such data should be handled in a cautious way. The recent study by the National Economic Development office (NEDO) on the British pharmaceutical industry presented valuable information on this respect. It shows that "...the majority of clinical evaluation was invariably included in R&D and the majority of quality control was excluded."[1] Such uniform practice, however, was not found to prevail in relation to process development and pilot plant production. "Thus, the only really significant variation in accounting practices appears to relate to process development and pilot plant production...exclusion which could possibly lead a company to understate its R&D expenditure by as much as 15%."[2]

Moreover, quality considerations are difficult to incorporate when dealing with input measures of the flow of innovation. Presumably we could speak of R&D personnel of various different levels and abilities and about scientists of different calibre, but the economists' tool-box is still poorly furnished to handle questions of this sort. Summarizing,

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[1] Innovation Activity in the Pharmaceutical Industry, NEDO (London: HMSO, 1973), p. 7.

[2] Ibid., p. 7.

though R&D expenditure data are normally employed as a 'proxy' variable for innovative effort, their potential hazards should be kept in mind. Inter-firm differences in accounting practices can be rightly suspected, and changes in the quality of the knowledge-creation process which do take place through time are only imperfectly captured.

Output measures of the flow of innovation are also far from being faultless. On the one hand, some firms synthesize all the compounds they test, while yet other firms buy from third parties a great deal of the compounds they study. Similarly, a new product brought to the market can be the result of internal R&D activities, but can also be the outcome of license, thus not being a true indicator of internal knowledge-creation processes. On the other hand, quality differentials among products, patents, scientific papers, etc., are clearly present, making it a rather heroic assumption to work with straight counts of these variables as if they were homogeneous entities.[1]

Consider briefly the differential quality of some of the various indicators mentioned before. The number of compounds actually synthesized by any given firm greatly depends on the approach such a firm has towards

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[1] A valuable discussion of this point in relation to the usefulness of patent statistics can be found in Chapter 2 of J. Schmookler's book, Invention and Economic Growth (Cambridge: Harvard University Press, 1966). The value of scientific papers as a 'proxy' for the rate of innovation is examined by R. Evenson and Y. Kislev, "Research and Productivity in Wheat and Maize" (New Haven: mimeo, 1972); see also Derek de Solla Price, "Measuring the Size of Science," Proceedings of the Israeli Academy of Sciences, 1969.

R&D activities. The more 'rational' the R&D strategy, i.e., "based on theoretical biological propositions that certain types of compounds should be expected to demonstrate a certain type of pharmacological activity,"[1] the smaller the number of synthesized compounds to be expected. Contrariwise, the more random the screening, the larger the number of compounds actually handled. Thus, inter-company differences in research strategy qualify the usefulness of the number of compounds synthesized by each firm as an adequate 'proxy' for inter-firm differences in innovation. Similarly, and as a consequence of the fact that a great deal of cross-licensing takes place in this market, inter-firm differences in the number of new products brought to the market might not be a good 'proxy' variable either.

There were large inter-firm differences in the propensity to patent, with size and nationality appearing as the principal determinants of these differences.[2] Thus, also the number of patents filed by each company should be used in a very cautious way as a 'proxy' for the firms' innovative

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[1] Innovative Activity in the Pharmaceutical Industry, op. cit., p. 15.

[2] W. D. Reekie has recently shown that "Continental and particularly German companies appear to file more patents in Britain than their record of commercially successful innovations would have led one to expect." Also that "...very large firms tended to file fewer patents in relation to expenditure on R&D than smaller companies." W. D. Reekie, The Economics of Innovation with Special Reference to the Pharmaceutical Industry (Unpublished Ph.D. thesis, University of Strathclyde, 1969). A similar finding has been reported in J. Katz, op. cit.

output.[1]

NDA submissions also have problems of their own. A growing rate of attrition--and what's more, unknown inter-firm differences in the rate of attrition--cast some doubt upon the use of NDA's as an indication of the actual innovative effort performed by the firm. Finally, the number of product candidates, or the number of IND applications, have been singled out by industry officials as probably the best 'proxy' for the variable we want to measure, but such data are not published by pharmaceutical companies and are not available for detailed examination. The FDA--the only government agency with ready access to such information--does not provide company figures in this respect.[2]

So much then for possible publicly available quantitative indicators of the flow of innovation. It should be noted that none of the previously mentioned 'proxy' variables takes into account quality differentials which presumably exist among products, patents, NDA's, IND's, etc. Quality

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[1]See, for example, H. G. Grabowsky, "The Determinants of Industrial R&D A Study of the Chemical, Drug and Petroleum Industries," Journal of Political Economy (1973). Also, W. S. Comanor and F. M. Scherer, "Patent Statistics as a Measure of Technical Change," Journal of Political Economy, (May 1965); D. C. Mueller, "Patents, Research and Development and the Measurement of Inventive Activity," Journal of Industrial Economics (November 1966).

[2]Mr. H. Clymer has recently claimed that "...the FDA has shed little light on this all important question, for they do not separate IND's for clinical investigation of new chemical agents from all the rest of the mish-mash of IND's that must be filled prior to undertaking other types of clinical

differentials can be captured through chemical evaluation and from clinical or therapeutic investigation of each specific drug. Whereas in the first case the molecular structure of any given drug has to be examined in order to decide whether or not such molecular structure has been previously used by the industry, in the second case judgment has to be passed at the clinical and therapeutic level, considering for such purposes whether or not the drug introduced identifiable advances over pre-existing substitutes. We have attempted to evaluate innovation through a selective pharmacologic assessment of 196 single entity drugs produced by 22 major U.S. firms between 1963 and 1972. The Paul de Haen New Drug Analyses and Nonproprietary Name Index were used as primary sources for the listing of new drugs marketed in the U.S. during this period.

Our sample consists of the 22 U.S. drug companies that met either of the following criteria: (1) U.S. drug sales in 1972 were in excess of $70 million or (2) the company first marketed in the U.S. at least four single entity drugs between 1963 and 1972.[1] We include 19 companies under the first criterion and three (Armour, Dow, and U.S.V.) under the second.

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trials." See Clymer, "The Economics and Regulatory Climate of U.S. and Overseas Impact Trends" (Paper read at the Conference on Drug Development and Marketing, the American Enterprise Institute for Public Policy Research, Washington, July 1974), p. 22.

[1]We treat Parke-Davis, which was acquired by Warner-Lambert in 1970, as a separate company and consider only the Schering part of Schering-Plough. Appendix Table A-1 shows the subsidiaries we included for each company.

As shown in Table I-1, these 22 companies accounted for about 75 percent of the 1972 drug sales in the U.S. by all U.S. companies and about 49 percent of the new drugs (including vaccines, diagnostics, and vitamins) introduced into the U.S. by U.S. companies between 1963 and 1972. As shown in Table I-2, the new drugs (excluding vaccines, diagnostics, and vitamins) introduced by these 22 companies, as a share of all new drugs introduced in the U.S., rose from 44 percent in 1963-1967 to 51 percent in 1968-1972.

A "proprietary product" usually does not require a prescription, has a brand name, and is advertised to the public.[1] An "ethical pharmaceutical" is promoted primarily to the medical, pharmacy, and allied professions and includes both prescription and non-prescription products. One should note that a drug which does not require a prescription in the U.S. may require one in some other countries; conversely, some drugs requiring a prescription in the U.S. may not require one in some foreign countries. A "non-proprietary" drug, sometimes called a "generic" drug, does not involve a trade name. So a prescription drug could be either proprietary or non-proprietary. Finally, one must distinguish a "drug" from "cosmetics," "toiletries," and "medical and surgical supplies."

For our purposes, we have defined a "drug" as a single chemical entity belonging to a chemical class which exerts a major pharmacologic action on people (e.g., diuretic, analgesic, ataraxic, antihistaminic, etc.). We have

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[1]Our definitions in this paragraph are based on those of the Pharmaceutical Manufacturers Association, Fact Book 1973 (Washington, 1973).

Table I-1

Relative Importance of 22 Companies

	1972 U.S. Drug Sales, $ Million[4]	New Drugs in U.S. 1963-1972[1]	
		Single Entity[1]	All[2]
	(1)	(2)	(3)
22 U.S. drug companies	3,331	254	485
Other U.S. drug companies	1,176	198	443
Total U.S. companies	4,507	452	928
Foreign drug companies[3]	864	52	103
Grand Total	5,371	504	1,031

[1]Including drugs already being sold in the U.S. by another firm.

[2]Single entities and combinations. Includes vaccines, diagnostics, and vitamins.

[3]Astra, Beechem, Burroughs Welcome, E. Fougera, CIBA-Geigy, Hoeshst, Hoffman-LaRoche, ICI America, Knoll, Organon, Pharmacia, Philips Roxane, Sandoz-Wander, Syntex.

[4]At wholesale prices. Includes vitamins and non-prescription drugs.

Source: Column (1)-- based on data from IMS America; Columns (2) and (3)-- New Drug Analysis U.S.A. 1968-1972 and New Drug Analysis U.S.A. 1963-1968 (New York: Paul deHaen).

Table I-2

New Single Entity and Combination Drugs Introduced in U.S.

	Sample of 22 Companies (1)	Industry (2)	(1)/(2) percent
1958-1962	601	1,241	48
1963-1967	280	630	44
1968-1972	205	401	51
1958	156	370	42
1959	135	315	43
1960	141	306	46
1961	92	260	35
1962	77	250	31
1963	90	199	45
1964	60	157	38
1965	55	112	49
1966	30	80	38
1967	45	82	55
1968	51	87	59
1969	34	62	55
1970	41	105	39
1971	47	83	57
1972	32	64	50

Source: Various issues of New Products Parade, Annual Review of New Drugs (New York: Paul deHaen).

excluded combination products (two or more chemicals), vitamins, vaccines, and diagnostics.

The new drugs listed in the de Haen sources have been analyzed to determine if they are innovative or novel products, or if they are imitative of pre-existing entities already marketed. Innovation has been assessed through an examination of both the pharmacologic action and the chemical class or structure of the drug. Thus, the diuretic ethacrynic acid (Edecrin, Merck, 1967), a new chemical entity, is classified as innovative because it acts on the kidney differently from the diuretic chlorothiazide (Diuril, Merck, 1957) even though it produces the same fundamental result, diuresis.

Modifications of pre-existing structures (additions or deletions of chemical groups), although marketed as new chemical entities, are not necessarily considered as innovative by these criteria. These modifications often enhance a drug's pharmacologic action and therapeutic effectiveness while decreasing undesired side effects. However, the modified structure is considered imitative of the original drug if it exerts the same basic pharmacologic effect and is marketed for the same therapeutic purpose. For example, cyclothiazide (Anhydron, Lilly, 1963), although a new potent thiazide-type diuretic, is nevertheless similar in its chemical structure and pharmacologic action to chlorothiazide, and is therefore regarded as imitative by our definition. As another example, two of the most popular drugs in the U.S. and Europe, Librium and Valium (Roche),[1] benzodiazepine

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[1]This example is illustrative, as Hoffman-LaRoche is excluded from our sample because it is a non-U.S. company.

tranquilizers, are very similar in chemical structure and have fundamentally the same pharmacologic effects. Thus, by the criteria developed here, alium, marketed in 1963, does not represent any significant pharmacologic innovation over its antecedent, Librium, which was marketed in 1960.

There are some cases, however, in which pharmacologic innovation can be achieved by slight modification of a pre-existing drug. For example, methotrimeprazine (Levoprome, Lederle, 1966) is a drug similar in structure and effects to other tranquilizers of the phenothiazine class, such as chlorpromazine (Thorazine, Smith Kline and French, 1954). However, the analgesic properties that are present to a negligible degree in Thorazine are greatly increased in Levoprome. Therefore, although of the same chemical class, the pharmacologic effects of Levoprome are significantly different from earlier phenothiazines to justify its rating as a pharmacologic innovation by our definition.

It is therefore seen that pharmacologic action, as well as chemical novelty, are evaluated to determine innovation in pharmaceuticals. Each drug was assigned[1] to one of the following categories: (1) innovative, (2) imitates a drug of the same company marketed in the U.S. between 1960 and 1972, (3) imitates a drug of another company marketed in the U.S. between 1960 and 1972, (4) imitates a drug of the same company marketed in the U.S.

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[1]References included Goodman and Gilman, The Pharmacologic Basic of Therapeutics; Cutting, Handbook of Pharmacology; Meyers, Jawitz and Goldfien, Review of Medical Pharmacology; Wilson and Jones, American Drug Index; Lewis, Modern Drug Encyclopedia, 12th edition; Unlisted Drugs; A.M.A. Drug Evaluations.

before 1960, and (5) imitates a drug of another company marketed in the U.S. before 1960. For the purposes of this paper, we combine categories (2) - (5) into a single imitative category.[1]

The annual number of innovative and imitative drugs introduced by the companies in our sample is shown in columns (1) and (2) of Table I-3. Table I-4 shows the innovative drugs for each company in our sample.

Carpenter[2] has evaluated new drugs for 1958-1967 in terms of their "chemical novelty," and McVicker[3] has evaluated new drugs for 1960-1969 in terms of their "therapeutic advance." As these studies are unpublished, we present only a summary comparison of their results with ours for 1963-1967. As shown in Table I-5, we considered 30 of the 82 drugs introduced in this period by these firms to be innovative, as compared to 36 for study A and 20 for study B. The Chi-square coefficient for our evaluation is 13.46 when compared with study A and 29.56 when compared with study B, which indicates that at a significance level of less than 1 percent, we can say that our evaluation is not independent of each of the other evaluations.[4]

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[1]We have not tried to differentiate among different degrees of innovativeness or of imitation.

[2]John Carpenter, "Innovation in Chemical Structure in a Group of 267 Recently Marketed Drugs" (mimeo, 1969).

[3]W. McVicker, "New Drug Development Study" (mimeo, 1972).

[4]We note that our evaluation was completed before we saw either study A or study B.

Table I-3

Number of New Drugs Introduced in the U.S.
by 22 U.S. Companies

	Single Entity[2]				
	Innovative (1)	Imitative[1] (2)	Total[1] (3)	Combinations (4)	Grand Total[2] (5)
1963	7	10	18[3]	60	78
1964	5	11	17[3]	38	55
1965	7	10	17	31	48
1966	2	5	7	20	27
1967	9	16	25	17	42
1968	2	17	19	18	37
1969	4	11	15	15	30
1970	5	20	25	13	38
1971	4	29	33	10	43
1972	3	17	20	10	30
Total	48	146	196[3]	232	428

[1]Including drugs already being sold in the U.S. by another firm.

[2]Excluding vaccines, diagnostics, and vitamins.

[3]Includes drugs whose classification is uncertain.

Source: Columns (3)-(5)--based on data in various publications of Paul de Haen, Inc.

Table I-4

Innovative Drugs, 1963-1972

	Trade Name (1)	Year (2)
Abbott	Eutonyl	1963
	Tham E	1965
American Home Products	Protopam chloride	1964
	Atromid-S	1967
	Inderal	1968
Armour	None	
Bristol-Meyers	Polycillin	1963
	Mucomyst	1963
	Ketaject	1970
	Halotex	1972
	Megace	1972
Dow	Rifadin	1971
Johnson & Johnson	Haldol	1967
Lederle	Amicar	1964
	Levoprome	1966
	Myambutol	1967
Lilly	Keflin	1964
	Capastate Sulfate	1971
Merck	Aldomet	1963
	Cuprimine	1963
	Cosmegen	1965
	Cuemid	1965
	Indocin	1965
	Edecrin	1967
	Mintezol	1967
Miles	None	
Parke-Davis	Ponstel	1967
	Ketalar	1970
Pfizer	Sinequan	1969
	Mithracin	1970
	Lithane	1970
	Antiminth	1972
Richardson-Merrell	Clomid	1967
A. H. Robins	Dopram	1965
Searle	Flagyl	1963
Schering-Plough	Tinactin	1965
	Garamycin	1966

Table I-4 (continued)

	Trade Name (1)	Year (2)
Smith Kline & French	Stoxil	1963
	Direnium	1964
	Vontrol	1967
	Eskalith	1970
	Urispas	1971
Squibb	Hydrea	1968
	Teslac	1969
Sterling	Negram	1964
	Talwin	1967
Upjohn	Lincocin	1965
	Cytostar	1969
	Trobicin	1971
U.S.V.	None	
Warner-Lambert	Quilene	1969

Table I-5

Comparison of Evaluations of Drugs Introduced in 1963-1967 by 22 Firms

Cohen-Katz-Beck

		Innovative	Imitative	Total
Study A	Innovative	22	15	37
	Imitative	8	37	45
	Total	30	52	82

Chi-square = 13.46

Study B	Innovative	18	2	20
	Imitative	12	50	62
	Total	30	52	82

Chi-square = 29.56

Finally, in Table I-6 we show the number of innovative drugs introduced in each of the first five years following the introduction of the Food and Drug Amendments. None of the three studies shows any downward trend.

Table I-6

Number of Innovative Drugs
Introduced by 22 Firms

	Cohen-Katz-Beck (1)	Study A (2)	Study B (3)
1963	7	6	2
1964	5	8	4
1965	7	10	6
1966	2	4	1
1967	9	9	7
Total	30	37	20

II. Trends in Pharmaceutical Innovation

Two kinds of observations are available for studying drug innovations and their relation to foreign investment: time series on new products, or on various types of new products, and cross-sections of pharmaceutical firms, some of which are active innovators and some of which are responsible for few, if any, innovations. In this section we discuss the main trends in the rate of pharmaceutical innovation.

We shall concentrate here on three types of new products emerging from drug firms. They are: a) New Single Chemical Entities, b) Duplicate Products, and c) Combinations. The first item indicates products which are new single chemical agents, not previously marketed in the United States. Duplicate products are drugs which are offered as single chemical entities and which are already sold by another manufacturer within the U.S. market. Finally, a combination is a preparation consisting of two or more active ingredients. While drug firms also produce such items as New Dosage Forms (tablets, ampuls, solutions, etc.), Biologicals, and Hospital Solutions, our study concentrates upon the three previously mentioned groups of commodities. New chemical entities and duplicate products are classified by Paul de Haen and do not always correspond to our distinction of innovative and imitative, as developed in the previous Section.

Table II-1 presents information regarding the number of Single Chemical Entities, Duplicate Products, and Combinations introduced into the U.S. market during the period 1950-1972.[1] Using such data, Chart 1 describes

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[1]The data presented in Table II-1 and Chart 1 come from different numbers of Paul de Haen's publication, New Products Parade, Annual Review of New Drugs. We hereby thank Mr. de Haen for letting us have access to this valuable information.

Table II-1

New Product Introductions in the Ethical Pharmaceutical Industry 1950-1972

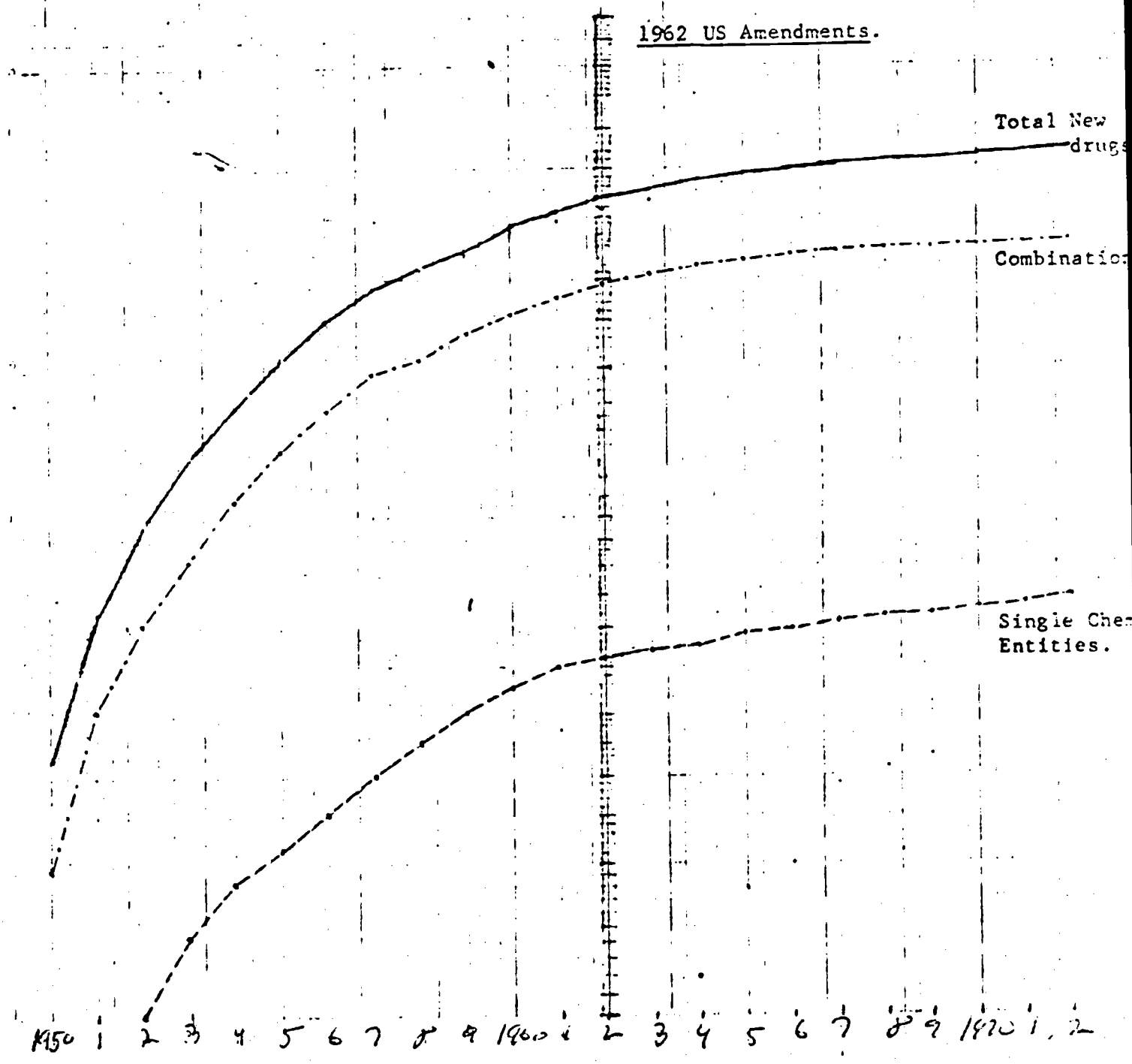
	Total New Products		New Single Chemicals		Duplicate Products		Combinations	
		Σ		Σ		Σ		Σ
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1950	326		28		100		198	
1951	321	647	35	63	74	174	212	410
1952	314	961	35	98	77	251	202	612
1953	353	1314	48	146	79	330	226	838
1954	280	1694	38	184	87	417	255	1093
1955	403	2097	31	215	90	507	282	1375
1956	401	2498	42	257	79	586	280	1655
1957	400	2893	51	308	88	674	261	1916
1958	370	3268	44	352	73	747	253	2169
1959	315	3583	63	415	49	796	203	2372
1960	306	3889	45	460	62	858	199	2571
1961	260	4149	39	499	32	890	189	2760
1962	250	4399	27	526	43	933	180	2940
1963	199	4598	16	542	34	967	149	3089
1964	157	4753	17	559	29	996	111	3200
1965	112	4867	23	582	18	1014	71	3271
1966	80	4947	12	594	15	1029	53	3324
1967	82	5029	25	619	25	1054	32	3356
1968	87	5116	11	630	26	1080	50	3406
1969	62	5178	9	639	22	1102	31	3437
1970	105	5283	16	655	50	1152	39	3476
1971	83	5366	14	669	40	1192	29	3505
1972	64	5430	11	680	35	1227	18	3523

Source: Various issues of New Products Parade, Annual Review of New Drugs (New York: Paul de Haen).

Chart 1

ACCUMULATED NUMBER OF NEW DRUG INTRODUCED TO THE USA MARKET. 1950 - 1972. (*)

(*) Source : Paul de Haen, Annual new product parade. New York, (various issues)



in a semi-logarithmic scale, the time path of the cumulated number of new products in each one of the three above-mentioned categories. The year 1962, in which the U.S. Congress passed the so-called Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act which regulated the introduction of new pharmaceuticals to the U.S. market, is distinguished in the chart. The Amendments significantly changed the regulatory climate underlying the operation of the pharmaceutical industry, and they need to be taken into account as one of the possible determinants of the observed decline in the rate of new product introduction.

Both Table II-1 and Chart 1 provide a distinct impression of a long-term tailing off in the rate of new product introduction. This trend is certainly present in all the series, but is more dramatic in Combinations than in Single Entities. There appears to be a long-term relative shift away from Combinations. Thus, we can observe both an absolute fall in the rate of new product introductions and a change in relative composition within the aggregate.

There is another sense in which the aggregate series for new product introductions has shown significant changes in its relative composition. This is related to the rate of product innovation in specific therapeutic classes. In many therapeutic areas in which well established and useful agents were already marketed, innovation practically dried up in the 1960's. Comparing the number of new drugs introduced in the U.S. in 1957-1962 with 1963-1967, one finds a marked decline for nine categories (antihistamines, antitussives, antispasmodics, muscle relaxants/antiparkinson drugs, thiazide-type diuretics, sulfonamide antibacterials, antiobesity drugs, corticosteroids, and antinauseants), a slight decline for tranquilizers and psychostimulants,

and no change for antibiotics and cancer chemotherapy drugs.[1] Thus, the aggregate fall in new product introductions hides a dramatic abandonment of many areas of research and a gradual concentration of efforts in a smaller number of fields.

At least two different explanations have been offered for this long-term decline in the rate of new product introductions. On the one hand, industry officials and some members of the academic community have blamed the fall in the rate of product innovation entirely on the FDA and the 1962 Amendments.

> "I conclude from these data that: a) The 1962 Amendments significantly reduced the flow of new chemical entities and, what is perhaps more interesting, b) that all of the observed differences between the pre- and post-1962 New Chemical Entities flow can be attributed to the 1962 Amendments."[2]

On the other hand, it has been suggested that the rate of innovation has

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[1]Barry M. Bloom, "The Rate of Contemporary Drug Discovery," Lex et Scienta, 8 (January-March 1971), p. 4.

[2]S. Peltzman, "The Benefits and Costs of New Drug Regulation," ed. R. L. Landau, Regulating New Drugs (Publication of Center for Policy Study, Chicago University Press, 1973), p. 126.

Other authors have presented essentially the same, though less extreme, diagnosis of what is going on in the industry. Company officials are particularly inclined to take this line of reasoning. See, for example, Harold A. Clymer from Smith Kline & French, "The Economic and

slowed because the pharmaceutical industry has exhausted a stock of knowledge that took some time to exploit.

> "Despite all efforts, useful results nowadays are rarer and rarer, and some drug houses have to face the problem of how long it will be possible for them to support their research departments....My first prediction is that, like other golden ages, the golden age of drugs will not return, and never again will so many new and efficient drugs become available within such a short period as during the fifties and sixties."[1]

A similar view is expressed by de Haen. "...traditional methods in new drug development seem to be impeded and less fruitful....we have reached a temporary plateau of knowledge in new drug development because so much has been made in the short span of 30 years."[2]

Regulatory Climate--U.S. and Overseas" (Paper presented at the Conference on Drug Development and Marketing: Aspects of Public Policy, American Enterprise Institute, Washington, July 1974). Also, the very valuable paper by Dr. L. H. Sarett, from Merck, "FDA Regulations and Their Influence on Future R&D," Research Management (March 1974).

[1] F. Gross, "Future Drug Research, Drugs of the Future," Clinical Pharmacology and Therapeutics, 14 (January 1973), pp. 1, 2, 4.

[2] P. de Haen, "Pharmaceutical Research," New York State Journal of Medicine, 72 (October 1972), p. 4. It should be noted that this last view of the long-term growth process of the industry has quite a distinctive classical flavour and describes a scenario which is by no means novel to the

More likely than not, both of these views can claim a certain degree of explanatory power,[1] their relative significance varying as between therapeutic classes.[2] Both theories would predict and be compatible with: a) A prominent escalation of product research and development costs, b) A marked lengthening of product development times, and c) An increased level of uncertainty in new drug development.[3] Let us briefly consider these

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economics profession. As far back as 1930, S. Kuznets developed the idea of an eventual exhaustion of an industry's inventive potential--which in his view obtains when the industry's techniques approach a certain plateau of perfection--which in turn leads to a retardation of the rate of technical progress and, eventually, to a tendency for output to describe an S-shaped curve through time. He called that the Law of Industrial Growth. See, S. Kuznets, Secular Movements in Production and Prices (Boston: Houghton Mifflin, 1930). The same causal mechanism has been later re-discovered by W.E.G. Salter in his Productivity and Technical Change (Cambridge: Cambridge University Press, 1960).

[1]See Martin Neil Baily, "Research and Development Costs and Returns: The U.S. Pharmaceutical Industry," Journal of Political Economy, Vol. 80 (January/February 1972), p. 77.

[2]If one uses supply and demand analysis, one could say the FDA regulations impose "a tax" on the development of new drugs and the exhaustion of knowledge reflects an upward shift in the supply curve. Increased expenditures on medical care suggest an upward shift in the demand for all drugs. For a supply and demand analysis, ignoring "taxes," see N. Rosenberg, "Science, Invention and Economic Growth," Economic Journal, 84 (March 1974), pp. 90-108.

[3]The inference is frequently made that increased development costs or

three aspects, which pretty much reflect the contemporary trends underlying the innovative process of the pharmaceutical industry.

Consider first research and development costs. The available evidence indicates that these have been rocketing upwards at the incredible pace of about 30 percent per annum. "The industry was getting a new chemical entity in the 1950's for 1.5 million dollars of R&D. Today it is costing between 10 and 20 $US million and even more."[1] Increases in R&D costs have not resulted exclusively from increased research requirements imposed under the 1962 amendments. From 1951 to 1962 research and development costs per single new chemical entity grew at the rapid pace of 20 percent per annum. Research and development in drugs is becoming an increasingly expensive proposition through time partly because science and research today is more rigorous than a decade (or two) ago.[2] It is not clear how we can isolate how much of the

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the lengthening of the development times result from FDA increased requirements prior to approval. Though this is clearly so, there is nothing to preclude the possibility that such features also result from research gradually shifting towards more complex and time consuming therapeutic fields as a consequence of the exhaustion of the profit potential (and intellectual attraction) of more conventional therapeutic areas. Such an effect might be present quite independently of increased regulatory measures.

[1]V. A. Mund, "The Return on Investment of the Innovative Pharmaceutical Firm," ed. J. D. Cooper, The Economics of Drug Innovation (Washington: American University, 1970), p. 130.

[2]H. A. Clymer, "The Changing Costs and Risks of Pharmaceutical Innovation," ed. J. D. Cooper, op. cit., p. 121. "Perhaps more interesting is the fact that our methodology is superior to what it was only a few years

increased costs in new drug development is due to a more advanced (and more expensive) knowledge-creation process and how much of it is a consequence of imposed new standards by the FDA.

There are indications that rising U.S. costs of drug development and declining rates of innovation are not solely a consequence of changes in FDA regulations, since the same phenomena have been noted in Europe, which is not directly affected by such regulations. After studying the British case, Cooper finds that:

> "Since 1951 a six-fold increase in expenditure has yielded half as many drugs per unit expenditure (This statement applies to the U.S. case). This has been blamed on the FDA and its slowness in giving clearance to new drugs, but the findings of the last chapter, and the fact that this tendency is certainly equally true throughout Europe, cast some doubt on the claim that this is the sole reason. It is probably that the world awaits the next major therapeutic advances which are likely to be in the cancer or cardio-vascular fields."[1]

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ago. Our science is more rigorous, more likely to find hazards in an experimental compound."

[1] M. H. Cooper, op. cit., p. 178.

The European scene in general shows pretty much a similar trend. Data recently published by Paul de Haen indicate that: "Marketing of newly synthesized drugs in England, France, Germany and Italy has declined over an eleven-year period. For the period 1960-1965 marketing of 521 drugs has been recorded, and for the period 1966-1971 only 344 drugs have been counted."[1] The European trend receives independent confirmation from a study which found a drop in the number of new discoveries through the 1960's.[2]

At least four important consequences follow from the rapidly increasing research and development costs demanded for new drug introduction. First, fewer firms are now able to maintain their innovative effort. Whereas 89 companies introduced new pharmaceutical products in 1963, only 33 did so in 1972.[3] Second, the number of research and development projects effectively pursued by any given company has tended to fall.[4] Third, research aimed at

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[1]Paul de Haen, New Products Parade, Annual Review of New Drugs (New York: mimeo, February 1973), p. 15.

[2]E. Reis-Arndt and D. Elvers, "Results of Pharma Research. New Pharmaceutical Agents 1961-1970," Drugs Made in Germany, Vol. 15, No. 3, 1972, Aulendorf. Also P. de Haen, "Pharmaceutical Research," New York State Journal of Medicine, 72 (October 1972), p. 2536.

[3]P. de Haen, New Product Parade, various issues, op. cit.

[4]Dr. L. H. Sarett, Director of Merck Research Labs, says: "In our own laboratories, for example, the number of research projects has dropped 10% from 1969 to the present year." L. H. Sarett, "FDA Regulations and Their Influence on Future R&D," Research Management (March 1974).

"me too" drugs has significantly declined, as previous evidence (in Table II-1) on the introduction of Duplicate Products has already shown. Finally, R&D resources are gradually being reallocated away from the U.S. and brought into operation elsewhere, particularly in the UK, France, Germany and Italy.[1]

The available evidence indicates an upward trend in drug development times. At the end of the 1950's, the time span from the selection of a product candidate to the filing for regulatory approval was estimated at about two years. By the middle 1960's, this same period had gone up to about four years, and during the early 1970's, industry officials already spoke of seven to eight years.[2]

Finally, not only did R&D costs and development time increase during the last decade, but the uncertainties and risks underlying new drug development rose pari passu with the former two. The attrition rate of compounds entering the development process, i.e., having passed the filing of an IND (investigational new drug application) and entering into clinical trials, is frequently used by the industry as an indicator for risk and uncertainty. The evidence shows that the attrition rate has been going up or, in other words, that a growing number of compounds are falling by the way somewhere between the start of human trials (transfer of animal data to humans) and the submission of an NDA[3] (new drug application).

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[1]H. A. Clymer, "The Economic and Regulatory Climate--U.S. and Overseas Impact Trends," op. cit.

[2]The evidence in this respect comes from L. H. Sarett, op. cit.

[3]H. A. Clymer in his paper, "The Changing Costs and Risks of Pharmaceutical Innovation," op. cit., gives statistical information concerning the rate of attrition. Whereas in 1965, 32% of the IND filed during that same

Summarizing, we can say that both the cost and time of new drug development are rapidly increasing through time and so also are the uncertainties and risks which underlie the process of innovation in this area of manufacturing. Industrial firms presumably react in different ways to these structural trends. Some of them might decide to drop the innovative race altogether. Yet others might try to concentrate on fewer research projects. While some companies will probably increase their efforts at the marketing end of the spectrum, reducing their commitments to basic research, other companies will do just the opposite and invest more heavily in more basic research.[1] Some companies might try to compensate for their inability to grow through new product introductions in the U.S. market by giving priority to foreign markets, or to industrial diversification. One specific aspect of these behavioral differences is to be explored later on in Section IV of this paper, where we shall try to explain the number of foreign subsidiaries opened up by each drug company during the 1960's, using the relative quality of the firm's portfolio of new products as an independent variable.

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year had been terminated, 42% of these same filings had been terminated by the end of 1966, and 53% by the end of 1968. "We have taken a look at the SK&F record of IND's filed during the last five years and find that 70% never reached the NDA stage. It is too early to know the exact fate of those still active. However, my guess would be that only about one in ten of those that started will reach the market," p. 120.

[1]There are clear indications that some of these trends are very much among us already. Hoffman-LaRoche, Lilly, and Merck have in recent years adopted a heavier commitment towards basic research activities, developing

III. Characteristics of U.S. Drug Firms

As discussed in Section I, our sample consists of 22 U.S. drug companies. The main characteristics of these 22 companies are described in Table III-1. We use as a measure of company size in this industry total U.S. drug sales. Total U.S. sales of the parent company are included on the possibility that investment behavior is related to the size of the firm as a whole. The numbers of R&D personnel in laboratories devoted to pharmaceutical research and estimated R&D expenditures for pharmaceutical research are measures of research input, while numbers and sales of new drugs, single entity drugs, and innovative drugs are measures of R&D output. Promotional expenses are included as a possible alternative or supplement to R&D investment as a source of sales.

Our use of 1972 sales of new or innovative drugs might be thought to bias this measure against companies that developed drugs early in our period, if the use of these drugs had run its course by 1972. Table III-2 tests this possibility by comparing 1972 sales for drugs introduced at different dates. If there is any bias, rather than only chance variation or the results of a rise in the cost of successful innovation, it seems to be in the opposite direction. It is the earliest years' innovations that may be disproportionately represented in 1972 sales. Perhaps the most recent innovations had not yet reached their peaks in sales in 1972 and the innovativeness of recently successful companies may therefore be understated.

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special centers for this purpose. There is no doubt that diversification towards cosmetics, pesticides (or even breweries!) is presently going on as yet another response to the reality of the falling rate of innovation.

Table III-1

Company Data

	1972 Sales, $ Million				Promotional Expenses in U.S. as Per Cent of U.S. Drug Sales[a]	Number of New Drugs Introduced in U.S., 1963-1972			Pharmaceutical Research and Development		Antibiotics as Per Cent of U.S. 1972 Drug Sales
		U.S. Drug					Single		1969	1971	
	Total	Total	Innovative	New		Total	Total	Innovative	Personnel	$ Million	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Abbott	529	139	1	15	8	20	11	2	865	28.8	18
American Home Products	1,587	305	27	99	8	22	13	3	1,261	52.5	10
Armour (Greyhound)	2,908[b]	22	0	9	n.a.	9	5	0	140	n.a.	0
Bristol-Myers	1,201	251	23	75	6	45	18	5	896	31.2	22
Dow	2,404	24	2	5	20	10	4	1	n.a.	-	7
Johnson & Johnson	1,318	141	9	63	4	12	3	1	725	29.5	0
Lederle (American Cyanamid)	1,359[c]	103	3	23	12	26	15	3	876	15.4	23
Lilly	820	368	63	143	5	23	11	2	2,123	67.5	45
Merck	958	276	76	131	7	13	10	7	1,663	65.6	0
Miles	319	82	0	1	n.a.	10	4	0	n.a.	12.2	0
Parke-Davis	n.a.	130	1	38	8	28	13	2	785	18.9	12
Pfizer	1,093	195	17	66	11	16	12	4	350	32.0	27
Richardson-Merrell	447	71	1	9	8	11	2	1	712	16.7	0
A.H. Robins	167	93	0	15	13	15	8	1	125	6.0	0
Searle	272	120	8	35	7	4	2	1	587	23.6	0
Schering-Plough	504	131	40	82	8	19	7	2	659	15.4	27
Smith, Kline & French	402	152	3	26	12	16	12	5	876	35.1	0
Squibb	385	165	0	47	7	28	13	2	967	30.8	23
Sterling	721	104	27	29	8	8	5	2	780	22.0	0
Upjohn	511[d]	168	12	42	10	18	13	3	851	29.5	18
U.S.V. (Revlon)	439[e]	56	0	19	n.a.	22	11	0	n.a.	6.3	0
Warner-Lambert	1,428[e]	84	0	8	8	26	4	1	556	22.1	0

Notes to Table III-1

SOURCES: Col. (1) - Moody's Industrials, various issues.

Cols. (2)-(4) - based on data from IMS America.

Col. (5) - Drug Statistical Handbook (Washington: FDA, 1973).

Cols. (6) and (7) - based on data in various publications of Paul de Haen, Inc.

Col. (8) - see Section I.

Col. (9) - Industrial Research Laboratories of the United States, 13th ed. (New York: R.R. Bowker Co., 1970)

Col. (10) - totals from financial statements multipled by ratios of pharmaceutical to total R&D personnel from same source as col. (9).

[a] Promotional expenses for 1970. Includes expenditures for advertising in professional journals, direct mailing, and detail man.

[b] Total sales are for Greyhound Corporation, parent of Armour.

[c] Total sales are for American Cyanamid, parent of Lederle.

[d] Total sales are for Revlon, parent of U.S.V.

[e] Includes Parke-Davis.

Table III-2

1972 U.S. Average Sales of Single Entity Drugs

	Year Drug Introduced		
	1963-66 (1)	1967-69 (2)	1970-72 (3)
	$ Million		
Abbott	.2	.3	.5
American Home Products	3.9	3.6	.1
Armour	S[1]	-[2]	2.1
Bristol-Meyers	4.7	.5	1.1
Dow	-[2]	-[2]	.8
Johnson & Johnson	-[2]	4.6	S[1]
Lederle	.3	.9	1.3
Lilly	12.3	S[1]	11.4
Merck	12.3	.8	-[2]
Miles	0	-[2]	S[1]
Parke-Davis	1.0	2.7	.7
Pfizer	S[1]	10.9	2.4
Richardson-Merrell	-[2]	.7	-[2]
A. H. Robins	S[1]	.7	.9
Searle	4.1	-[2]	-[2]
Schering-Plough	10.0	4.8	-[2]
Smith Kline & French	.9	0	.7
Squibb	0	3.3	2.8
Sterling	3.2	6.9	-[2]
Upjohn	10.4	1.0	1.9
U.S.V.	.1	1.6	.6
Warner-Lambert	S[1]	.1	-[2]

[1]Suppressed because only one new drug.

[2]No drug introduced.

Source: Based on IMS America data.

A number of possible indicators of innovativeness and related characteristics of companies are listed in Table III-3. R&D expenditures and personnel per dollar of total drug sales are indicators of R&D effort. R&D expenditures and personnel per new or innovative drug introduced can be thought of as indicators of the investment in each new drug, and thus possibly of the quality of the companies' innovations. Ratios of new or innovative drug sales to total drug sales, of innovative to total new drug sales, or of numbers of single entity or innovative drugs to total new drugs introduced are all indicators of the output from R&D input. The two other measures, R&D expenditures and personnel per dollar of new drug sales, are, possibly, indicators of the efficiency of the R&D effort, or the extent to which it is aimed at objectives other than innovation or new drug production.

We refer to these as indicators because they are mostly imperfect proxies for the characteristics they are supposed to measure. The investment per drug and per dollar of drug sales should be measured by relating the input of R&D to the particular drugs produced by that input, or at least to the drugs produced by inputs preceding their introduction. Our output measures relate to 1963-72 or to 1972 alone while our input data are for single years, 1969 and 1971. The relevant inputs for some of these outputs may have been made in the early 1960's, and in any case the outputs are not the product of single year's input. The R&D data should refer to ethical drugs only, but we were not able to exclude inputs for proprietary drugs. The R&D expenditure data, in fact, refer to whole companies, rather than to pharmaceutical portions of them, and we had to assume that the division of expenditures between drugs and other products was the same as

Table III-3

Indicators of Innovativeness and Investment in R&D, by Company

	Company	R&D Expenditures: Per $100 of U.S. Drug Sales	R&D Expenditures: Per $100 of U.S. Sales of New Drugs	R&D Expenditures: Per New Drug Introduced	R&D Expenditures: Per New Single Entity Drug Introduced	R&D Personnel: Per $ Million of U.S. Drug Sales	R&D Personnel: Per $ Million of U.S. Sales of New Drugs	R&D Personnel: Per New Drug Introduced	R&D Personnel: Per New Single Entity Drug Introduced	New Drug Sales as % of Total U.S. Drug Sales	Innovative Drug Sales as % of U.S. Drug Sales	Innovative Drug Sales as % of U.S. Sales of New Drugs	Single Entity New Drugs as % of All New Drugs	No. of Innovative New Drugs as % of: No. of New Drugs	No. of Innovative New Drugs as % of: No. of New Single Entity Drugs
1	Armour (Greyhound)	-	-	-	-	6.36	15.6	15.6	28.0	-	0	0	55.6	0	0
2	American Home Products	17.2	53.0	2.38	4.04	4.13	12.7	57.3	97.0	32.5	8.85	28.72	61.9	14.29	23.1
3	Abbot	20.7	192.0	1.44	2.88	6.22	57.7	43.3	73.6	10.8	.72	6.67	38.5	7.69	20.0
4	Bristol-Myers	12.4	41.6	.69	1.73	3.57	11.9	19.9	49.8	29.9	9.16	33.33	42.9	11.90	27.8
5	Dow	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	Johnson & Johnson	20.9	46.8	2.46	9.83	5.14	11.5	60.4	241.7	44.7	6.38	14.29	25.0	8.33	33.3
7	Lilly	18.3	47.2	2.94	6.14	5.77	14.8	92.3	193.0	38.9	17.12	44.06	47.8	8.70	18.2
8	Lederle (American Cyanamid)	15.0	67.0	.59	1.03	8.50	38.1	33.7	58.4	22.3	2.91	11.54	57.7	11.54	20.0
9	Merck	23.8	50.0	5.05	6.56	6.10	12.8	129.5	168.3	47.5	27.54	56.72	76.9	53.85	70.0
10	Miles	14.9	1,220.0	1.22	3.05	-	-	-	-	-	0	0	40.0	0	0
11	Parke-Davis	16.5	56.6	.68	1.65	6.04	20.7	28.0	60.4	29.2	.77	2.44	46.4	7.14	15.4
12	Pfizer	16.5	48.5	2.00	2.67	1.80	5.3	21.9	29.2	34.0	8.76	25.76	75.0	25.00	33.3
13	A.H. Robins	6.5	40.0	.40	.75	1.34	8.3	8.3	15.6	16.1	.32	2.00	53.3	6.67	12.5
14	Richardson Merrell	23.5	185.6	1.52	8.35	10.03	79.1	64.7	356.0	12.7	1.69	36.36	18.2	9.09	50.0
15	Searle	19.7	67.4	5.90	11.8	4.89	16.8	43.7	293.5	29.2	6.67	50.00	66.7	33.33	50.0
16	Schering-Plough	11.8	18.8	.81	2.2	5.03	8.0	34.7	94.1	62.6	30.53	48.78	36.8	10.53	28.6
17	Squibb	18.6	65.5	1.10	2.37	5.86	20.6	34.5	74.4	15.7	2.41	1.08	46.4	7.14	15.4
18	Sterling Drug	21.0	75.8	2.75	4.40	7.50	16.6	97.5	156.0	44.8	25.71	93.10	62.5	25.00	40.0
19	Smith, Kline & French	23.1	135.0	2.19	2.92	5.76	26.9	54.8	73.0	19.1	1.97	13.04	75.0	31.25	41.7
20	Upjohn	17.8	70.2	1.64	2.27	5.06	33.7	47.3	65.5	25.5	7.27	28.57	72.2	16.67	23.1
21	U.S.V.	11.2	33.2	.29	.52	-	-	-	-	32.1	0	0	52.2	0	0
22	Warner-Lambert	26.3	276.2	.85	5.52	6.62	69.5	20.6	139.0	9.5	.60	6.41	14.8	3.70	25.0

the division of R&D personnel.

Some indication of the relationships among these indicators is given by Table III-4 which shows the simple correlations between each pair. Those we describe above as relating to output from R&D are positively correlated with each other, although not closely in all cases. The output measures are not related in any clear way to the indicators of research effort. R&D expenditures and personnel per new drug introduced, which we called an indicator of the quality of new drugs, are positively related to the output indicators. On the other hand, R&D expenditures and personnel per dollar of new drug sales are negatively related to the quality and output indicators, a result which suggests that there may be an efficiency factor involved. High R&D per new drug is associated with high sales per new drug and with high shares of new drugs in total sales and innovative drugs in new drug sales, or, in other words, with success in innovation. High R&D per dollar of new drug sales is associated with low shares of new or innovative drugs, which we might interpret as lack of success in innovation or an indication that for these companies R&D is not devoted to innovation.

From the data in Table III-3 we can judge whether the companies fall into natural groupings which may reflect different research strategies. We have used the ratio of sales of innovative drugs, by our definition, to sales of all drugs in 1972 as our most logical indicator of innovativeness, and have separated the firms, by this criterion, into four most innovative, six of medium innovativeness, and eight least innovative. Table III-5 shows the average characteristics of these three groups with respect to all the

Table III-4

Simple Correlations among Company Indicators of Innovativeness and Investment in R&D

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
	R&D Expenditures														
1	Per $ U.S. drug sales	1.00	.652	.434	.570	.605	.584	.467	.554	-.232	-.030	.088	-.118	.330	.529
2	Per $ U.S. sale of new drugs		1.00	-.159	.168	.479	.918	-.117	.241	-.718	-.442	-.332	-.392	-.188	.052
3	Per new drug introduced			1.00	.738	.026	-.225	.942	.564	.293	.387	.426	.317	.707	.726
4	Per new single entity drug introduced				1.00	.267	.158	.739	.918	.128	.105	.132	-.048	.212	.003
	R&D Personnel														
5	Per $ U.S. drug sales					1.00	.719	.285	.526	-.229	.003	.101	-.312	-.023	.264
6	Per $ U.S. sales new drugs						1.00	-.086	.359	-.701	-.417	-.295	-.451	-.209	.093
7	Per new drug introduced							1.00	.676	.270	.463	.531	.212	.627	.718
8	Per new single entity drug introduced								1.00	.052	.121	.165	-.473	.091	.587
9	New drug sales as % of total U.S. drug sales									1.00	.762	.504	.091	.269	.221
	Innovative Drug Sales														
10	As % of U.S. drug sales										1.00	.903	.228	.494	.437
11	As % of U.S. sales of new drugs											1.00	.306	.508	.448
12	Single entity new drugs as % of new drugs												1.000	.683	.164
	Number of Innovative New Drugs														
13	As % of number of new drugs													1.00	.803
14	As % of number of new single entity drugs														1.00

Table III-5

Comparison of Four Most, Six Medium, and Eight Least Innovative Companies[a]

		Four Most Innovative Companies	Six Medium Innovative Companies	Eight Least Innovative Companies
	Innovativeness Measures			
1	New drug sales as % of total U.S. drug sales, 1972	48.5	32.6	16.9
2	Innovative drug sales as $ of U.S. drug sales, 1972	25.2	7.8	1.4
3	Innovative drug sales as % of new drug sales, 1972	60.7	30.1	9.9
4	No. of single entity new drugs as % of all new drugs, 1963-72	56.0	57.3	43.8
5	No. of innovative drugs as % of new drugs, 1963-72	24.5	18.3	10.5
6	No. of innovative drugs as % of single entities, 1963-72	39.2	31.8	25.0
7	Average rank by above measures	5.1	7.5	13.1
	R&D Effort			
8	R&D expenditures (1971) per $ of U.S. drug sales (1972)	18.7	17.4	18.8
9	R&D personnel (1969) per $ of U.S. drug sales (1972)	6.1	4.1	6.3
	Quality of R&D or New Drugs			
10	R&D expenditures (1971) per new drug introduced (1963-72)	2.9	2.51	1.1
11	R&D personnel (1969) per new drug introduced (1963-72)	77.8	42.3	36.1
12	R&D expenditures (1971) per new single entity drug introduced (1963-72)	4.8	5.4	3.2
13	R&D personnel (1969) per new single entity drug introduced (1963-72)	152.9	129.5	106.9
	R&D Efficiency			
14	R&D expenditures (1971) per $100 U.S. sales of new drugs (1972)	48.0	54.6	127.2
15	R&D personnel (1969) per $ U.S. sales of new drugs (1972)	13.1	15.3	40.1
	Size			
16	U.S. drug sales, 1972 ($ million)	219.8	196.7	117.2

SOURCE: Table III-3

[a] As defined by line 2.

other measures.

With one exception, the ratio of single entities to all new drugs, the indicators we describe as measuring innovativeness, and the average ranking of these indicators, vary appropriately with our preferred measure. The firms that are most innovative by that standard are innovative by the other standards also. The indicators of R&D effort, on the other hand, show very little relation to the production of innovative drugs. The drug quality measures, also with one exception, are positively related to innovativeness, as is efficiency. That is, the least innovative companies spent the most per dollar of new drug sales. Size of firm varied directly with innovativeness, quality of new drugs introduced, and R&D efficiency.

Of course, these figures and the description of the companies is based on the assumption that R&D has as its only purpose the development of new or innovative drugs. Since the firms may have other objectives of R&D in mind (safety, quality, dosage reduction, process improvements, development of non-prescription drugs), what appears here as inefficiency or lack of innovativeness may really reflect a smaller interest in innovation and a concentration on other objectives.

IV. Impact of New Drugs on Foreign Investment

As an innovative drug for a rare disease may be less important to a company than an innovative drug for a common disease, we weight each drug by its 1972 sales in the U.S. Lack of data precludes our looking at sales in the U.S. prior to 1972. Although consumption of specific drugs and types of drugs differs considerably among countries of similar climate and per capita income,[1] lack of data also precludes our looking at foreign sales of specific drugs.

The empirical work on multinational firms has stressed differences among industries. Vernon, for example, allocated his 187 multinational firms among 23 industries and found that their importance in the 1966 sales of the entire industry ranged from 85 percent (motor vehicles and equipment) to 4 percent (printing and publishing); the 15 multinational drug firms in his sample accounted for 77 percent of all sales in 1966 by U.S. drug companies.[2] He explained these differences by arguing that in comparison with other firms the multinational firms are "of extraordinary size and high profitability, committed to activities that involve the relatively heavy use of skilled manpower and of advertising outlays."[3] The pharmaceutical

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[1]Cooper compared the prices of 1,042 drugs sold in 1964 in Great Britain and at least one of the following: Germany, Italy, France, and Spain; only 50 drugs were sold in all five countries. Antibiotics accounted for 23 percent of pharmacy drug sales in Great Britain in 1964, compared to 15 percent in the U.S., 8 percent in France, and 4 percent in Germany. Michael H. Cooper, op. cit., pp. 141, 132.

[2]Raymond Vernon, Sovereignty at Bay (New York: Basic Books, 1971), p. 14.

[3]Ibid., p. 12.

industry spends a great deal on both R&D and advertising. R&D expenditures fluctuated between seven and nine percent of the value of pharmaceutical shipments in the 1960's,[1] compared with two percent of sales for the average firm in Vernon's group of 187 multinationals. Advertising expenditures in the U.S. drug companies, as shown in column (5) of Table III-1, are well above the three percent of sales of Vernon's 187 multinational firms.

Will these three variables[2]--size, emphasis on research, and emphasis on advertising--explain differences in foreign investment within the drug industry? Table III-1 shows total corporate sales in 1972, total U.S. drug sales in 1972,[3] U.S. sales in 1972 of innovative drugs, U.S. sales in 1972

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[1] Drug Statistical Handbook (Washington: FDA, 1973), p. 10.

[2] Many of these companies also sell "proprietary drugs," and many of them also sell items other than drugs. So we cannot derive profit data on the drugs in our list from published data on company profits. The advertising data are mainly for ethical pharmaceuticals. Some of the R&D personnel may be for products other than the drugs we are considering. There is also the problem with profit data that reported profit rates may not be relevant for managerial decisions, since current accounting practice treats expenditures on research and development as a current expense rather than as an investment. See T. R. Stauffer, "Profitability in a Discovery-Intensive Industry: Pharmaceuticals," (paper read at the Conference on Drug Development and Marketing, The American Enterprise Institute for Public Policy Research, Washington, July 1974).

[3] Drug sales are to drug stores and civilian hospitals and exclude vitamins and non-prescription drugs; these latter two categories are included in Table I-1.

of new drugs, the number of research and development (R&D) personnel per million dollars of U.S. drug sales, and promotion expenses as a percentage of U.S. drug sales.

Preliminary analysis showed that the Latin American experience was so different from that of the rest of the world that one obtained no significant results by using combined data. One might expect that result by looking at Table IV-1. Latin America has 35 percent of the manufacturing subsidiaries and has more than all of Europe, even though Western Europe has a higher per capita income and a larger population.[1] So throughout the regression analysis we report results separately for Latin America and for the rest of the world.

It is conceivable that total corporate sales might influence a drug company's propensity to establish foreign drug plants. For example, Lederle and A. H. Robins each had about $100 million of U.S. drug sales in 1972, but Lederle is part of American Cyanamid, which had worldwide sales in 1972 of $1.4 billion. Lederle may acquire from its parent corporation knowledge about foreign investment opportunities.

Table IV-2 shows the ordinary least squares regressions in which the dependent variable is the number of non-Latin American countries[2] with

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[1]In 1970 Latin America had about 280 million persons and Western Europe had about 371 million persons. Per capita income in the average Latin American country was about one-fourth that of Western Europe. Data from Trends in Developing Countries (Washington: World Bank, 1973).

[2]Data for number of countries with manufacturing plants in 1959 and 1970, for Latin America and non-Latin American countries, are shown in Table A-2.

Table IV-1

Number of U.S. Drug Firms with At Least One Manufacturing Plant in Area

	Date of Establishment of First Plant			
	Prior to 1950 (1)	1950-1959 (2)	1960-1970 (3)	Total (4)
Canada	10	6	4	20
Europe	7	41	64	112
E.E.C.[1]	0	25	35	60
U.K.	7	8	3	18
Other	0	8	26	34
Latin America	6	65	55	126
Argentina	1	11	4	16
Brazil	0	11	3	14
Mexico	4	12	5	21
Other	1	31	43	75
Australia and New Zealand	3	12	7	22
Asia & Middle East	0	21	38	59
Philippines	0	8	3	11
Other	0	13	35	48
Africa	2	7	13	22
South Africa	2	7	7	16
Other	0	0	6	6
TOTAL	28	152	181	361

[1]Belgium, France, Germany, Italy, Luxembourg, Netherlands.

Source: Questionnaires.

Table IV-2

Regressions for 1970 Countries Outside Latin America
(T-Ratios in Parentheses)

	(1)	(2)	(3)	(4)	(5)
1972 Worldwide Sales	.007 (2.34)[1]	- .0004 (-.33)	- .001 (-.71)	--	--
1972 U.S. Drug Sales	.005 (.29)	.03 (1.99)[2]	.63 (1.34)	.03 (2.37)[1]	.03 (1.55)
R&D/1972 U.S. Drug Sales	.33 (.54)	--	--	--	--
Promotion/1972 U.S. Drug Sales	53.9 (.98)	--	--	--	--
Percent New Sales, 1972	--	-9.72 (-1.01)	--	-10.6 (-1.23)	--
Percent Innovative Sales, 1972	--	--	- .572 (-.38)	--	- 5.60 (-.40)
Percent Antibiotic Sales, 1972	--	--	.02 (.04)	--	.02 (.17)
R^2	.36	.25	.21	.23	.18
F	1.65	1.85	1.06	2.91[2]	1.33
n	17	21	21	22	22

[1] Significant at 5 percent

[2] Significant at 10 percent

manufacturing plants in 1970; Table IV-3 shows the ordinary least squares regressions in which the dependent variable is the number of Latin American countries with manufacturing plants in 1970; Tables IV-4 and IV-5 show the corresponding regressions when all variables are expressed as logarithms.[1]

Column (1) of Tables IV-2 through IV-5 uses as independent variables two measures of firm size (total corporate sales in 1972 and U.S. drug sales in 1972), R&D personnel as a percentage of U.S. drug sales in 1972, and promotional expenses as a percentage of U.S. drug sales in 1972. Neither Latin American regression is significant at the 10 percent level; the logarithmic equation for non-Latin America is significant,[2] and the only significant variable is the value of 1972 total corporate sales. Since R&D personnel is a measure of input, it is perhaps not surprising that it fails to explain foreign investment.

Column (2) of Tables IV-2 through IV-5 uses as independent variables the two measures of firm size and the share of 1972 U.S. drug sales accounted for by all the new drugs--single entity and combinations--introduced in the U.S. by the firm between 1963 and 1972. The sample size can now be increased from 17 to 21. Again none of the Latin American regressions is significant. The logarithmic regression for the non-Latin American countries is significant,

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[1]When doing the logarithmic regressions, we let innovative sales be $.1 million when they were in fact zero and let percentage of drug sales accounted for by antibiotics be .1 percent when it was in fact zero.

[2]In the rest of this section, unless otherwise stated, significant means that the observed coefficient would occur by chance five percent of the time if the true coefficient were zero.

Table IV-3

Regressions for 1970 Latin American Countries
(T-Ratios in Parentheses)

	(1)	(2)	(3)
1972 Worldwide Sales	.001 (.21)	- .001 (-.98)	- .001 (-.95)
1972 U.S. Drug Sales	- .003 (-.18)	.006 (.56)	- .003 (-.26)
R&D/1972 U.S. Drug Sales	.06 (.11)	--	--
Promotion/1972 U.S. Drug Sales	-29.6 (-.58)	--	--
Percent New Sales, 1972	--	-.48 (-.07)	--
Percent Innovative Sales, 1972	--	--	17.5 (1.79)
Percent Antibiotic Sales, 1972	--	--	.02 (.29)
R^2	.04	.11	.26
F	.12	.67	1.40
n	17	21	21

Table IV-4

Regressions for Log 1970 Countries Outside Latin America
(T-Ratios in Parentheses)

	(1)	(2)	(3)	(4)	(5)
Log 1972 Worldwide Sales	.53 (3.30)[1]	.17 (1.14)	.06 (.37)	--	--
Log 1972 U.S. Drug Sales	.05 (.20)	.74 (4.49)[1]	.68 (3.29)[1]	.66 (4.45)[1]	.65 (3.61)[1]
Log R&D/1972 U.S. Drug Sales	.19 (.94)	--	--	--	--
Log Promotion/1972 U.S. Drug Sales	.48 (1.47)	--	--	--	--
Log Percent New Sales, 1972	--	-.29 (-1.90)	--	-.21 (-1.52)	--
Log Percent Innovative Sales, 1972	--	--	-.06 (-.77)	--	-.06 (-.88)
Log Percent Antibiotic Sales, 1972	--	--	.01 (.18)	--	.02 (.38)
R^2	.54	.55	.48	.51	.48
F	3.57[1]	7.05[1]	3.68[1]	10.0[1]	5.50[1]
n	17	21	21	22	22

[1]Significant at 5 percent level

Table IV-5

Regressions for Log 1970 Latin American Countries
(T-Ratios in Parentheses)

	(1)	(2)	(3)
Log 1972 Worldwide Sales	.25 (.72)	.04 (.17)	-.08 (-.39)
Log 1972 U.S. Drug Sales	.02 (.04)	.41 (1.66)	.23 (.81)
Log R&D/1972 U.S. Drug Sales	-.04 (-.10)	--	--
Log Promotion/1972 U.S. Drug Sales	-.15 (-.21)	--	--
Log Percent New Sales, 1972	--	-.16 (-.69)	--
Log Percent Innovative Sales, 1972	--	--	-.003 (.02)
Log Percent Antibiotic Sales, 1972	--	--	.07 (.97)
R^2	.07	.16	.18
F	.21	1.06	.90
n	17	21	21

and size as measured by 1972 U.S. drug sales is the only significant variable.

Column (3) of Tables IV-2 through IV-5 uses as an independent variable the two measures of firm size and the share of 1972 U.S. drug sales accounted for by the innovative drugs introduced in the U.S. by each firm between 1963 and 1972. We also include as an independent variable the share of U.S. 1972 drug sales accounted for by antibiotics.[1] Throughout the world, antibiotics are considered the "wonder drugs" of the last twenty years.[2] Many governments insist that antibiotics be produced locally.[3] As antibiotics' importance in company sales in the U.S. in 1972 ranged from zero (for 11 companies) to 45 percent, the political pressures to invest in foreign countries differs greatly among the drug companies. As shown in Table IV-9, firms that have large antibiotic sales tend to have large innovative sales, but the relationship is weak. Again neither of the Latin American regressions is significant. For non-Latin American countries, the logarithmic equation is again significant, with the firm's 1972 U.S. drug sales being the only significant variable.

As the firm's total corporate sales tends not to be significant, we show in columns (4) and (5) of Tables IV-2 and IV-4 the regressions omitting

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[1]These data are shown in Table A-2.

[2]Tranquilizers are a "wonder drug" only in the rich countries, which devote more resources to the treatment of mental illness.

[3]Only the final processing is done locally. A drug company will have a few fermentation plants to serve many processing plants.

it as a variable. This allows us to increase the sample size to 22.[1] The logarithmic equations are again significant, and the size of the firm is a significant variable. While the coefficients on new drug sales and on innovative drug sales are negative, they are not significantly different from zero at the 10 percent level.

The importance of firm size for explaining foreign investment outside Latin America partially confirms Horst's econometric analysis of 1,191 U.S. manufacturing firms. He found that R&D effort and advertising effort did not explain whether a firm was a multinational. He concluded that "once interindustry differences are washed out, the only influence of any separate significance is firm size."[2]

It is perhaps not surprising that the variables measuring the importance of the firm's new drugs are not significant in the regressions reported in Tables IV-2 through IV-5. The new drugs are for the period 1963-1972. The dependent variable in these tables is the number of countries with plants in 1970; many of these plants were opened up in the 1950's. So in Tables IV-6 through IV-8 we present the regression results using as the dependent variable the change between 1959 and 1970 in the number of countries with a manufacturing plant. Since this change was zero for Latin America for

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[1]Parke-Davis was absorbed by Warner-Lambert in 1970. While we have data on Parke-Davis's 1972 U.S. drug sales, we do not have data on Parke-Davis's worldwide 1972 sales.

[2]Thomas Horst, "Firm and Industry Determinants of the Decision to Invest Abroad: An Empirical Study," Review of Economics and Statistics, 54 (August 1972), p. 261.

Table IV-6

Regressions for Additional Countries in 1960's Outside Latin America
(T-Ratios in Parentheses)

	(1)	(2)	(3)	(4)	(5)
1972 Worldwide Sales	.003 (2.30)[1]	.0002 (.31)	-.0001 (-.17)	--	--
1972 U.S. Drug Sales	.004 (.43)	.02 (2.72)[1]	.01 (1.54)	.02 (2.87)[1]	.01 (1.67)
R&D/1972 U.S. Drug Sales	-.29 (-.90)	--	--	--	--
Promotion/1972 U.S. Drug Sales	2.12 (.07)	--	--	--	--
Percent New Sales, 1972	--	-5.86 (-1.22)	--	-5.22 (-1.20)	--
Percent Innovative Sales, 1972	--	--	-4.96 (-.68)	--	-5.59 (-.82)
Percent Antibiotic Sales, 1972	--	--	.06 (1.05)	--	.06 (1.14)
R^2	.43	.32	.33	.30	.32
F	2.21	2.70[2]	1.96	4.14[1]	2.88[2]
n	17	21	21	22	22

[1]Significant at 5 percent level

[2]Significant at 10 percent level

many firms, we do not present logarithmic regressionsffor Latin America.

Column (1) of Tables IV-6 through IV-8 uses as independent variables the two measures of firm size, the importance of R&D, and the importance of promotional expenses. Again none of the equations is significant.

Column (2) of Tables IV-6 through IV-8 uses the two measures of firm size and the importance of new drugs; column (3) uses the two measures of firm size and the importance of innovative drugs. Again none of the Latin American regressions is significant. The logarithmic non-Latin American regression is significant, and firm size as measured by 1972 U.S. drug sales is significant.

Concentrating only on non-Latin America, we consider columns (4) and (5) of Tables IV-6 and IV-8. In terms of R^2, the logarithmic equations are superior and are both significant at the 1 percent level. The logarithmic regression using the share of innovative drugs is somewhat superior to the one using the share of new drugs--column (5) as compared to column (4) of Table IV-8--in terms of R^2 (.52 versus .42). Throughout the analysis the coefficients for the importance of new drugs and the importance of innovative drugs have been negative, but their significance levels have not been overwhelming. In the regressions shown in column (5) of Table IV-8, the coefficients of the independent variables are different from zero at the following levels of significance: size of firm--1 percent, importance of innovative drugs--15 percent, importance of antibiotics--9 percent. With this sample size, the large degree of multicollinearity (see Table IV-9) makes it difficult to obtain significant T-ratios for all the independent variables.

Table IV-9

Correlation Coefficients, 22 Firms

		(1)	(2)	(3)
Log U.S. 1972 Drug Sales	(1)	1.00	.44	.41
Log Innovative U.S. Sales as Percent of Total U.S. Drug Sales	(2)		1.00	.32
Log Antibiotic U.S. Sales as Percent of Total U.S. Drug Sales	(3)			1.00
		(4)	(5)	(6)
U.S. 1972 Drug Sales	(4)	1.00	.42	.57
Innovative U.S. Sales as Percent of Total U.S. Drug Sales	(5)		1.00	.26
Antibiotics U.S. Sales as Percent of Total U.S. Drug Sales	(6)			1.00

Table IV-7

Regressions for Additional Latin American Countries in 1960's
(T-Ratios in Parentheses)

	(1)	(2)	(3)
1972 Worldwide Sales	.001 (.75)	.0002 (.39)	.0000 (.09)
1972 U.S. Drug Sales	-.004 (-.49)	.007 (1.16)	.003 (.39)
R&D/1972 U.S. Drug Sales	-.44 (-1.58)	--	--
Promotion/1972 U.S. Drug Sales	-22.9 (-.91)	--	--
Percent New Sales, 1972	--	-3.36 (-.90)	--
Percent Innovative Sales, 1972	--	--	-.25 (-.05)
Percent Antibiotic Sales, 1972	--	--	.02 (.52)
R^2	.24	.08	.06
F	.93	.52	.24
n	17	21	21

Table IV-8

Regressions for Log of Additional Countries in 1960's Outside Latin America
(T-Ratios in Parentheses)

	(1)	(2)	(3)	(4)	(5)
Log 1972 Worldwide Sales	.50 (2.12)[2]	.26 (1.55)	.12 (.75)	--	--
Log 1972 U.S. Drug Sales	.09 (.25)	.77 (4.09)[1]	.66 (3.11)[1]	.65 (3.70)[1]	.60 (3.19)[1]
Log R&D/1972 U.S. Drug Sales	-.38 (-1.24)	--	--	--	--
Log Promotion/1972 U.S. Drug Sales	-.19 (-.39)	--	--	--	--
Log Percent New Sales, 1972	--	-.29 (-1.63)	--	-.16 (-.98)	--
Log Percent Innovative Sales, 1972	--	--	-.11 (-1.45)	--	-.11 (-1.50)
Log Percent Antibiotic Sales, 1972	--	--	.07 (1.44)	--	.09 (1.81)[2]
R^2	.40	.50	.52	.42	.52
F	1.99	5.59[1]	4.39[1]	6.85[1]	6.40[1]
n	17	21	21	22	22

[1]Significant at 1 percent level

[2]Significant at 10 percent level

In conclusion, the total number of non-Latin American countries with manufacturing plants in 1970 is positively related to the size of the firm as measured by U.S. drug sales (Table IV-4). The number of non-Latin American countries with manufacturing plants first established in the 1960's is positively related to the size of the firm as measured by U.S. drug sales in 1972 and the relative importance of antibiotics to the firm and is negatively related to the relative importance of innovative drugs to the firm (Table IV-8). We conjecture that innovative firms are more able to serve these foreign markets via exporting from the U.S. or via licensing;[1] unfortunately, we do not have data on exports or licensing income for all the firms in our sample and so cannot test this part of the hypothesis.

Within Latin America neither the total number of countries with manufacturing plants in 1970 nor the number of countries with plants first established in the 1960's is related to any of the variables we measured (Tables IV-3, IV-5, and IV-7). Noting that in the 1960's 78 percent of these new plants were established outside Argentina, Brazil, and Mexico, we feel that the import substitution policies of the various Latin American governments[2]

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[1]See, for example, Vernon, Sovereignty at Bay, op. cit., and Raymond Vernon, "International Investment and International Trade in the Product Cycle," Quarterly Journal of Economics (May 1966).

[2]For a discussion of these policies, see S. Marcario, "Protectionism and Industrialization in Latin America," Economic Bulletin for Latin America, 9 (March 1964), pp. 61-103, and Albert O. Hirschman, "The Political Economy of Import-Substituting Industrialization in Latin America," Quarterly Journal of Economics, 82 (February 1968).

were the principal determinant of the investments by U.S. drug companies in the 1960's, but we are unable to measure these policies in a way that could be used in a regression.

V. Diffusion of Individual Drugs

Table V-1 shows for seven new drugs the average lag between the first sale and the sale in each major world market.[1] One should remember that the first sale, as shown in column (1), did not always take place in the U.S. The extremely small size of the sample makes it difficult to control for the company, the type of drug, and the calendar date, and so we use the data to state three conjectures rather than to draw conclusions:

(1) the time lag for the diffusion of drugs has fallen over time in rich countries and shows no trend in developing countries;

(2) as between rich countries and developing countries, there is not much difference in the rate of diffusion;

(3) company B diffused its sole innovative drug more rapidly than its three imitative drugs.

To what extent does the presence of a foreign manufacturing plant affect the speed with which a new drug is introduced in foreign countries? We conjecture that the lag (in years) between the date of first introduction of a new drug and its introduction into country x (L_i) depends on whether there is a manufacturing plant in country x (M), on whether country x is a rich country or a developing country[2] (R), and on whether the drug is

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[1]The two companies kindly provided us with this information on the condition that they remain anonymous. The specific drugs were chosen by us to be representative of the company's portfolio of single entity drugs introduced into the U.S. between 1963 and 1972; the companies did not know that we considered some drugs as innovative and some as imitative. "Major markets" were defined by each company.

[2]Rich countries are U.S., Europe, Canada, Australia, New Zealand, Japan,

Table V-1

Average Number of Years from Year of First Sale to Sale in Major Markets

Company	Year of First Sale (1)	Innovative Drugs		Imitative Drugs	
		Rich[a] (2)	Developing[b] (3)	Rich[a] (4)	Developing[b] (5)
A	1962	2.5	1.0		
	1963	0	0		
	1966	1.0	1.0		
B	1963			2.5	2.0
	1967			1.0	.6
	1969	0	.7		
	1970			.5	2.3

Source: Questionnaires and interviews.

a United States, Europe, Canada, Australia, New Zealand, Japan, South Africa.

b Other countries.

innovative or imitative (I). The three independent variables are dummy variables as follows:

M = 1 if manufacturing plant in country x at time drug introduced in country x and zero if no plant

R = 1 if x is a rich country and zero if x is a developing country

I = 1 if drug is imitative and zero if innovative.

The least squares regression, for n = 48, is:

$$L_i = 1.69 - .91\ M + .30\ R + .52\ I \qquad R^2 = .10$$

$$\qquad\quad (-1.24)\ \ (.87)\ \ (1.51) \qquad\qquad F = 1.60$$

While neither the overall regression nor any of the individual variables is significant at even the 10 percent level, the regression is consistent with the hypotheses that the presence of a manufacturing plant increases the speed with which a drug is diffused around the world and that innovative drugs are diffused more rapidly than imitative drugs.

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and South Africa. All other countries are treated as developing countries.

INCLUDED SUBSIDIARIES OF DRUG COMPANIES IN SAMPLE

ABBOTT--Borcherdt, Courtland Lab.

AMERICAN HOME PRODUCTS--Ayerst, Campbell, Doho, Ives, Wyeth

ARMOUR--none

BRISTOL MYERS--Bristol, Mead Johnson

DOW--Pittman-Moore

JOHNSON & JOHNSON--McNeil, Ortho, Johnson Health Care

LEDERLE--none

LILLY--none

MERCK--none

MILES--Ames, Dome

PARKE-DAVIS--none

PFIZER--Leeming, Pfizer Lab., Roerig

RICHARDSON-MERRELL--Merrell, National Drug, Walker

ROBINS-Whittier

SCHERING--National Bio-Serums, White

SEARLE--none

SMITH KLINE & FRENCH--none

STERLING--Breon, Winthrop

SQUIBB--none

UPJOHN--none

U.S.V.--none

WARNER-LAMBERT--Warner-Chilcott, Texas Pharmacal

Source: De Haen New Drug Analysis 1968-1972.

Table A-2

Supplemental Data

	Number of Foreign Countries With Manufacturing Plants				Antibiotics as Percent of U.S. 1972 Drug Sales
	Latin America		Other		
	1959	1970	1959	1970	
	(1)	(2)	(3)	(4)	(5)
Abbott	2	10	5	16	18
American Home Products	3	7	6	15	10
Armour	1	2	1	2	0
Bristol Meyers	3	8	6	14	22
Dow	0	3	1	3	7
Johnson & Johnson	1	2	3	8	0
Lederle	4	5	5	13	23
Lilly	3	6	2	9	45
Merck	4	7	9	17	0
Miles	4	6	2	8	0
Parke-Davis	6	7	5	13	12
Pfizer	5	8	13	24	27
Richardson-Merrell	3	3	13	15	0
A. H. Robins	0	3	0	4	0
Searle	1	4	1	5	0
Schering-Plough	3	7	4	9	27
Smith Kline & French	1	1	9	10	0
Squibb	6	8	5	12	23
Sterling	16	18	5	10	0
Upjohn	1	2	0	6	18
U.S.V.	0	2	0	4	0
Warner-Lambert	2	9	9	19	0

Sources: Columns (1)-(4) - Questionnaires
Column (5) - based on IMS America data