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REGULATION AND INNOVATION IN THE PHARMACEUTICAL INDUSTRY

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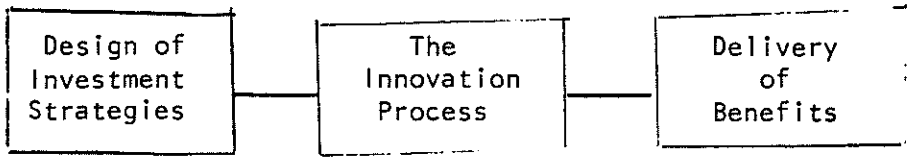
1. INTRODUCTION

The process of pharmaceutical research and development, investment strategies, marketing activities, patent protection and medical practices utilizing drugs are all likely to be influenced by both regulatory and non-regulatory intervention on the part of government. The consequences of this influence have resulted in the Food and Drug Administration being the focus of much criticism. Criticism has flowed from several sources: the Pharmaceutical Industry, Senate committees, GAO reports, the HEW Review Panel on New Drug Regulation, State legislatures, Nader's Health Research Group, medical and economic journals and large full-page paid advertisements in the New York Times. Whether the subject be saccharin or laetrile, gerovital or beta-blockers, the FDA by virtue of its important and sensitive position has attracted much attention through its inevitably controversial decisions.

One area which has been the subject of much concern is the impact of regulation on innovation and market behavior in the pharmaceutical industry. Major attempts at investigating the effects of regulation include the works of Peltzman[1], Baily[2], Jadlow[3], and Jondrow[4]. Efforts to reconcile conflicting views and to offer subsequent analysis are to be found in four principal sources: (1) papers presented at a series of seminars on pharmaceutical public policy issues arranged by the American University[5], (2) writings of Wardell and Lasagna[6], (3) the work of Grabowski[7], and (4) a recent major publication by Schwartzman[8]. Despite the considerable amount of research performed in the area, we do not believe that the effects of regulation on innovation and market behavior are adequately understood. The nature of the policy trade-offs has not been adequately defined, and the methodological approach to solving the trade-off problems has not been sufficiently developed. In the literature, anecdotes often substitute for data and value judgements are sometimes confused with analysis.

The development and marketing of pharmaceuticals may be thought of as consisting of three interconnected activities: the design of investment strategies, the innovation process [sometimes, but not

always involving extensive R & D] and the delivery of benefits.



Previous studies have addressed either the strategy for investment in pharmaceutical research or the effects of regulation on the number of new drugs marketed, with little attention paid to one aspect of the process of technological innovation -- i.e. the bringing together of manpower and financial resources to design a pharmaceutical solution to a disease problem. The innovation process has been treated as a sort of "black box" or the result of a serendipitous process, leaving pharmaceutical innovation to chance. Some new drug development is of this variety, and some new drug applications are discovered by searching for new uses by trial-and-error rather than by matching a drug's pharmacological action to a specific disease mechanism. However, more rational approaches to pharmaceutical developement do exist. Before one can begin to ask what the effects of regulation are on the ultimate delivery of new drugs to the consumer and at what cost, it is imperative that one understand more clearly the *intrinsic benefits** of innovative pharmaceuticals and the rational process by which these pharmaceuticals can be developed.

Changes in product or process characteristics in the manufacturing of pharmaceuticals may depend on regulatory intervention, non-regulatory changes in market factors or inherent limitations of pharmaceuticals in addressing certain disease problems. Regulation may alter (1) economic factors and investment strategies [e.g. by shortening effective patent life] and/or (2) the actual process of technological development and innovation [e.g. by encouraging new methods of production/testing procedures or a different skill mix or organization of professionals].+

*Intrinsic benefits are those therapeutic and functional uses (and accompanying side effects) that would be achieved if a particular drug were correctly prescribed and appropriately administered, and not the benefits that are actually realized via the medical care delivery system.

+Economic effects may, of course, also directly affect the innovative process.

2. UNRESOLVED ISSUES *

In a report presented to the HEW Review Panel on New Drug Regulation, we attempted to identify the issues important for policy design in the regulation of pharmaceuticals.[9] These issues may be conveniently grouped into five topical areas:

(1) *Problem Definition* - i.e., selection of the appropriate governmental actions and responding portion of the pharmaceutical "industry" as well as the choice of alternative bases against which to compare the consequences of government action.

(2) *Difficulties in Analytical Approaches* - e.g., with regard to conceptualizations of investment strategies by firms, the determiners of demand, and opportunity costs of continuing the utilization of ineffective drugs.

(3) *Difficulties in Assessing Regulatory Effects* - e.g., the appropriateness of New Chemical Entities (NCE's) as a measure of innovative activity and the problem of defining objective criteria of drug efficacy and safety.

(4) *Alternative Hypotheses for the [alleged] Decline* - i.e., the examination of the mismatch between models of disease causation and pharmacological action, and the possible distortion of the market by both regulartory and non-regulatory intervention by the government.

(5) *The Nature of the Trade-Offs* - i.e., the identification of the winners and losers of government intervention, equity and efficiency consequences and the characteristics of the elements of costs and benefits.

We next address these issues in detail.

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*This section is adopted from Ashford, Butler and Zolt, "Comment on Drug Regulation and Innovation in the Pharmaceutical Industry," A Report Presented to the HEW Review Panel on New Drug Regulation on January 10, 1977.

The process of technological innovation is just beginning to be understood in the manufacturing sector; it is not at all well-understood in pharmaceuticals. In order to design policy alternatives for regulatory reform it is important to distinguish what might be called predominantly economic from technological effects of regulation. For example, to the extent that regulation decreases the "effective patent life" of a new pharmaceutical, policy directed towards increasing the economic rewards to firms for successful innovation might be sensible. On the other hand, to the extent that the actual development process of drug development is altered, entirely different policy solutions may be in order -- e.g. the transfer of technical information or relaxation of antitrust laws.

Drugs are not appropriately viewed as merely a consumer item, where value can be expressed in dollars. The "products" in the various therapeutic areas perform such a variety of complex biological functions that their "value" is probably not well-understood by the consumer or, in some cases, by the prescribing physician. Furthermore there is no facile way of valuing the relative importance of safety and efficacy, let alone different aspects of safety and efficacy. Regulation may bring changes in efficacy and safety in a particular area under development as well as affect the total number of drugs reaching the market. Both changes represent consequences for benefits to the consumer, but they are different. Benefits related to innovative changes brought about by regulation require an understanding of the *process* by which regulation changes innovative activity. Addressing that issue, however, requires an understanding of how innovation occurs in the absence of strong regulatory signals.

We believe that previous studies of the impact of regulation (addressing both investment strategies and the delivery of benefits) must be viewed within the context of the fundamental changes occurring in product and process development in pharmaceuticals. Only then will it be meaningful to compare costs and benefits of pharmaceutical regulation.

2.1. Problem Definition

The process of pharmaceutical research and development, investment strategies, marketing activities, patent protection, and medical practices utilizing drugs are all likely to be influenced by government intervention in both the regulatory and research areas. An initial reading of recent research, analysis and commentary is likely to give the impression that the area of pharmaceuticals is in a hopeless state of confusion. At the root of this impression is the omission of different critical factors in the various analyses made by the various commentators. Analyses are incomplete to the extent that:

- Some regulatory actions of government are not taken into account in this area which is attended by rapid policy changes.
- Data are analyzed in an inappropriately aggregated fashion with a resulting failure to recognize likely important distinctions characterizing specific therapeutic areas.
- Safety and efficacy requirements are treated together although they operate in different ways, at different stages of drug development, undergo policy shifts in different time frames and may affect the various therapeutic areas differently.
- Government intervention of a non-regulatory nature--e.g., in research and utilization of technical manpower --is not adequately taken into account.
- The alleged effects of regulation are not measured against alternative changes which may have arisen in the absence of specific regulation or under different regulation. Furthermore, the level of drug development in the 1950's is often taken as the proper baseline representing the "no regulation" case without adjusting for the complicating effects of other events or changes in the environment which occurred during the period under examination.

In general, the problem of the effects of regulation on the pharmaceutical industry has not been defined properly for one reason or another. We will attempt to address briefly the important definitional factors described above.

Selection of Regulatory Actions to be Examined

While the 1962 Amendments represent the major stimulus to changes brought about by regulatory action, the amendments have been implemented in an evolving fashion since 1962 and policy and agency practice are changing all along. Thus, the "signals" seen by the pharmaceutical industry are constantly changing. It is, therefore, simplistic to regard the analysis of regulation-response as a single cause and effect task. Lasagna, et al. made this point very strongly in a proposal for a study now being undertaken for the National Science Foundation.[10] Actual or proposed changes in the regulatory framework in need of evaluation include[11] those resulting from:

> 1970: Definition [by FDA] of what is meant by the 1962 Amendments' requirements for evidence of "efficacy" and "well controlled investigations."
>
> 1972: Clarification of the FDA's attitude to the use by physicians of a drug for indications outside those listed on the labelling.
>
> 1973: Proposal of criteria by which foreign clinical data on a drug would be accepted as evidence for an NDA. (Prior to that time, foreign data had been given no "pivotal" weight; all important clinical research on a new drug had to be repeated in the U.S. before it could be deemed acceptable.) [Adopted April 1975][12]
>
> 1975: A proposal recently made by FDA is that additional hold and review steps should be instituted within the IND procedure itself, at the end of Phase I and Phase II, in addition to the final NDA review that currently occurs at the end of Phase III.

1975: The FDA is considering a petition from Mr. Ralph Nader's Health Research Group which would require two-year carcinogenicity tests in animals before an IND can be issued.

The delay of almost eight years in establishing the 1970 regulation leaves uncertain the early effects of the efficacy requirement. Therefore, conclusions reached from the examination of data in the 1960's must be viewed cautiously. Agency practice must be carefully researched to appreciate the nature of the regulatory signals given to industry. In addition, agency attitude towards efficacy and safety in different therapeutic areas varies significantly.

The 1962 Amendments' removal of the requirement for a sixty day adverse response from the FDA regarding NDA approval has resulted in delay for FDA action.[13] This delay may be far more significant in that it altered FDA's *attitude* towards IND applications than because of the effects of a six months delay per se. This aspect of agency response needs investigation.

The Appropriate Unit for Analysis (Therapeutic Areas)

Therapeutic areas are (1) differentially affected by the various regulatory actions, (2) subject to a different trade-off between efficacy and safety, (3) in a different stage of technology evolution (4) administered differently by physicians, (5) dependent to a varying extent on government research, and (6) subjected to a different amount of market competition. Lasagna, et al. have suggested that the conservative nature of FDA medical review officers differs among therapeutic areas.[14] For these reasons, the construction of a single behavioral model for the regulation-response which can apply to all therapeutic areas is fraught with difficulty. The therapeutic areas are somewhat well-defined markets although there is some competition and substitution between them.[15] For purposes

of analysis it may be desirable to use subcategories of therapeutic areas or in some cases treat several areas together. This is all part of a rational process of model-building which is largely undeveloped at this time.

Separation of Safety from Efficacy Requirements

Since for each therapeutic area, the safety and efficacy requirements (1) may differ in stringency, (2) may occur at different stages of drug development, (3) may undergo policy shifts in different time frames, and (4) elicit different technological responses, it is probably imperative to separate these requirements as much as possible. Additional research is also required to better delineate the relationship between safety and efficacy for each therapeutic area. Furthermore, as mentioned previously, different therapeutic areas are likely to be at a different stage of technological development and hence respond differently to both sets of requirements.

Government Intervention in R&D

Government affects the pharmaceutical industry by its participation in drug research and development and by being a prime utilizer of technical manpower. These activities are crucial and may themselves explain part of the alleged decline in significant therapeutic advances. Government intervention is discussed more fully in Section 2.4.

The Choice of Alternative Bases for Comparing the Effects of Regulation

The alleged affects of regulation are usually not measured against alternative changes which may have arisen in the absence of specific regulation or under different regulations. Yet this is a crucial part of an evaluation methodology. The critical questions for

policy purposes are what *differential* effects government action brought about and whether different action would change certain results.

In order to carry out this analysis completely, one has to examine the complicating effects of other events or changes in the environment which occurred during the period under examination. Hansen has suggested several factors that may be relevant:[16]

- scientific standards of acceptable evidence for research have become more stringent, adding cost and time to drug development;
- a greater concern with the carcinogenic effects of drugs would probably have resulted in increased testing and more conservative introduction by firms, even in the absence of FDA requirements;
- the increase in consumer suits against manufacturers and the resulting liability hazards facing firms would also have prompted firms to expand their testing prior to introducing new products;*
- likewise, the increase in malpractice claims against physicians may reduce their willingness to prescribe drugs which have not undergone extensive testing;
- the coincidence of the effects is heightened by the fact that the thalidomide tragedy, which is often given credit for prompting the regulatory changes in the 1962 Amendments, would have probably also made drug firms much more cautious about their products even without formal legislative changes.

The choice of alternative bases for analytical purposes is related to alternative explanations of the [alleged] decline in pharmaceutical innovation. Some of the alternative explanations are considered in Section 2.4.

*See, for example, Roginsky v. Richardson Merrell, Inc., 378 F.2d 832 (2nd Cir. 1967); Tinnerholm v. Parke Davis & Co., 285 F.Supp. 432 (S.D.N.Y. 1968); O'Hare v. Merck & Co., 381 F.2d 286,291 (8th Cir. 1967).

The pre-regulation baseline is also crucial to examine. It is by no means clear that the level of drug development in the 1950's can be taken as the proper baseline representing the "no regulation" case.

The suggestions of Wardell & Lasagna that we regulate drugs in hospitals differently from those used in the home[17] and regulate the practice of medicine rather than the efficacy of drugs[18] need to be considered as possible alternatives to the present regulatory scheme. Non-pharmaceutical approaches to disease prevention represent a still larger alternatives framework against which to measure the present system.[19]

2.2. Difficulties in Analytical Approaches

Before socially beneficial policies can be formulated for the pharmaceutical industry, we need to have a better understanding than we now have of how the industry behaves, how the industry will respond to new legislation, and how this response will affect consumers, workers, stockholders, and others. One of the first steps that must be taken is an examination and assessment of the different conceptualizations of the industry that are reflected in the opinions of scholars, regulators, and managers. In this section, we identify some of the analytical issues that appear in the economic literature.

"Demand Pull" versus "Technology Push" Innovation

Though agreement is not unanimous on the point, there does appear to be a consensus that the 1962 Amendments were followed by some decline in innovative activity. Several issues of measurement and interpretation of innovative activity in the industry are discussed in Section 2.3 of this paper. We raise some of these issues here only to suggest the extent of the diversity of opinion that exists.

For example, even if it is agreed that the decline in new chemical entities (NCE's) can be correctly interpreted as a reduction in innovative activity, there is not unanimous opinion as to whether the decline in NCE's was a demand or a supply phenomenon. While Baily's study [20] investigates the effects of the Amendments on the supply side, Peltzman[21] looks at the effects on demand. We believe that, in order to address this problem responsibly, a better understanding of pharmaceutical research and development is required.

Peltzman's view that increases and decreases in demand respectively pull and retard technological change may well be a correct interpretation of the innovation process for many types of products. He relies on the work of Schmookler.[22] However, there is a distinction between an overall shift in the demand for drugs and a change in the kinds of drugs demanded. The latter phenomenon results in changes in innovative strategy by the firm. The former results in a change in the supply for new drugs whether they are developed in recognition of specific market needs or determined by the technology in house, giving innovation of the technology push variety. The fact that a firm innovates by technology push or market pull has little to do with Peltzman's demand pull explanation. Even where drug innovation is stimulated by "technology push" rather than "market pull", the choice of which particular products to develop is affected by the results of market studies. For example, recent investigations of fat-cell mechanisms by at least two pharmaceutical companies may well have been spurred by the commercial potential of an anti-obesity drug.[23]

(B) *Patent Life Expiration and the Cost of Pharmaceutical Research and Development*

On the supply side of the analysis, the high-cost and high-risk aspects of pharmaceutical research and development (R&D) have received much attention. Detailed comparisons of the development cost per NCE before and after the 1962 Amendments show that the increases have

been formidable.[24] In addition, the average length of time between IND submission and NDA approval for NCE's is estimated to have increased from 2.7 years in 1966 to 6.6 years in 1973.[25] By reducing the expected rate of return from R&D investment, these costs can be expected to adversely affect the level of pharmaceutical innovation.

It seems to us that another cost that ought to be explicitly factored into the supply (cost) analysis is the decline in effective patent life brought about by regulation. Schwartzman uses the case of Hyperstat--hopefully an extreme example--to illustrate the problem.[26] Patented in 1961, Hyperstat will be able to be produced by any pharmaceutical firm in 1978. However, its effective patent life at that time will have been only 5 years, not 17. Its NDA was submitted to the FDA in 1963, and then not given final approval until 10 years later. Wardell and Lasagna report that the effective patent lives of some cardiovascular drugs have been severely shortened in similar fashion. Indeed, Schwartzman has observed an increase in price competition in the industry, indicating an increase of drugs on the market with no patent protection.[27]

(C) *Problems in the Application of Conventional Demand Theory to Drug Regulation Assessment*

To date, the most elaborate attempt to quantify the cost and benefits of the 1962 Amendments has been made by Peltzman.[28] At the foundation of this work are some very basic and well-known concepts in the theory of demand, particularly the notion of consumer surplus. It is our opinion that this concept is appropriate for the drug area only when several ever-present conceptual pitfalls are properly handled. Even then, its inherent limitations require accompaniment of a host of caveats and qualifica-

tions. We argued elsewhere that Peltzman has inadequately addressed many theoretical subtleties in ways that cast serious doubt on his empirical results.*

Other Empirical Analysis

Two important attempts to measure the effects of the 1962 Amendments have employed regression analysis in which the post-Amendment period was used as a dummy variable. This approach was used first by Baily,[29] whose results indicated that the decline in NCE's per dollar spent on R&D was explained by both the depletion of research opportunities and regulatory change. Grabowski, Vernon, and Thomas,[30] applying multiple regression to additional observations and constructing a depletion variable based on pharmaceutical innovation in Great Britain, also showed a strong statistical relationship between the post-Amendment period and a perceived decline in NCE's. Neither set of results supported Peltzman's statistical findings, which indicated that the Amendments were solely responsible for the post-1962 decline in pharmaceutical innovation.

The regression results, though *statistically* significant are of doubtful validity. In both studies just cited, pre- and post-1962 periods were used as dummy variables to indicate the absence and presence of regulation respectively. However, in addition to acting as a surrogate for regulation, 1962 and the years that followed also reflect a number of non-regulatory influences on innovation, including a greater concern for possible carcinogenic side effects of drugs, a growing number of malpractice claims and suits against drug manufacturers, and a greater degree of caution by drug firms resulting from the thalidomide incident. Moreover, several years were required to fully implement the Amendments. The regression results do not allow the regulatory and non-regulatory influences on drug innovation to be separated and thus add little to the evaluation of the Amendments.

*See Ashford, Butler, Zolt, "Comment on Drug Regulation and Innovation in the Pharmaceutical Industry", A Report Presented to the HEW Review Panel on New Drug Regulation on January 10, 1977.

2.3 Difficulties in Assessing Regulatory Effects

Before the regulatory effects can be adequately assessed there must be a clear understanding on how to measure the changes brought about by the regulation or other government intervention. A review of the literature reveals there is no consensus on such fundamental issues as (1) the proper index of innovative output, (2) objective criteria of efficacy and safety, (3) how to to assess regulatory effects using international comparisons, (4) number of NCE's versus claims for uses, and (5) market life as a factor in the calculus.

NCEs as an Index of Innovative Output

In order to examine the level of new drug introduction, it is necessary to construct an adequate measure of innovative output. The roughest measure would be to analyze the FDA figures for total new products, which include NCEs, combinations of previously introduced drugs, new manufacturers for previously introduced drugs and new indications for previously introduced drugs.[31] The new product totals are clearly a poor measure of innovative output as a large percentage of these products[32] do not represent any therapeutic gain over existing drugs.

A more refined measure would be to utilize the annual number of NCEs approved by the FDA. NCEs represent new compunds not previously marketed. This is the measure adopted by most studies analyzing the effect of regulation on innovation. It has been suggested, most notably by the FDA, that a simple counting of NCE introductions is not sufficient as an index of innovative output. This is because when an NCE reaches market it commonly appears in a number of different dose forms (e.g., different salts or esters[33]) which, while having only small biological differences, are nevertheless

chemically different and are classified as separate NCEs in compilations such as deHaen lists.[34]

The FDA has contended that the decline in NCEs has been concentrated in drugs that may be classified as having little or no therapeutic gain over existing drugs. Thus, the FDA's position is that the appropriate index of innovative output is NCEs which represent important therapeutic gains--a fundamental discovery as distinguished from additional pharmaceutical development.

Henry Grabowski presents four FDA assessments of important therapeutic advances for the years 1950-1973.[35] Grabowski states that the FDA has not provided any real discussion of the criteria for determining important therapeutic advances and that there is a wide variance in the four FDA rankings.[36] Closer examination of the data, however, indicates that except for the first ranking, the 1971 assessment, the assessments are remarkably consistent.

A number of other experts have attempted to determine the number of NCEs representing important therapeutic advances over the last twenty-five years.[37] No complete consensus exists at this time about which NCEs represent important therapeutic advances. Yet, this approach of using only important NCEs as a measure of innovative output is potentially a better index of innovation if satisfactory criteria for classifying drugs by therapeutic gain could be developed.

In an unpublished paper[38] prepared for the National Science Foundation, Wardell discusses an entire list of possible measures of innovation:

- Number of compounds (New Chemical Entities, "NCE's") synthesized
- Novelty of their molecular structure
- Number of patents issued
- Number of screening tests performed

- Novelty of pharmacologic action
- Number of new product candidates identified
- Number of NCE's tested in man [as Investigational New Drugs, "IND's"]
- Number of NCE's submitted for marketing [as New Drug Applications, "NDA's"]
- Number of NCE's marketed
- Therapeutic value ratings of marketed compounds
- Market ratings of marketed compounds
- Various combinations of the above measures
- Number of scientific publications

In this section, we will address only some of the above. However, all possible indexes should be considered by the careful analyst.

Lasagna, Wardell and Hansen contend that the number of NCE's marketed are an inadequate measure of innovative output:

> ...most existing analyses use the number and type of new drugs that reach the *market* as an index of innovative output. However, since arrival of a drug at the market depends on both innovation by the industry and, among other things, on regulation by government, any inferences about innovation that are drawn from data about marketing will always be confounded by the effect of regulation, and vice versa.[39]

Lasagna *et al.* proposed to study the impact of regulation by examining innovations at the point where they first become visible, at the IND stage,[40] and when they gain FDA approval to be marketed as approved NDA's. The rationale for measuring at the IND stage is that this is the point at which the output of the pharmaceutical industry first comes under direct regulatory control and the point at which the output first becomes visible in a meaningful form outside the industry.

The idea of using IND's as a measure of innovative output is a creative approach that certainly merits further consideration. Our

communications with Lasagna and Hansen revealed that there has been good co-operation with the U.S. drug industry in providing the requisite information.[41] Because IND information did not exist prior to 1962, it is not possible to use this measure for before-and-after analysis of the 1962 drug regulation. In addition, there will still be indirect regulatory effects on the number of IND's filed as a result of the increased total cost of NCE development. Nevertheless, IND's still can provide a useful measure for comparisons with Great Britain's counterpart of IND--Clinical Trial Certificate (CTC). (There are, however, important differences.)

An important point about innovation deserves repeating here. There are many barriers that can arise, both governmental and non-governmental, between the initial stages of drug development and a drug's ultimate use in the market. The effect of regulation may be felt strongly at the IND stage, but the consequences of regulation may be of smaller relative importance in the final tallying of significant therapeutic advances brought to market. Studying the effects of regulation (or any other economic disturbance) at an earlier stage is useful to assess its effects *there* and to improve its operation at that stage. However, implications of the regulation under study and all other influences at each stage is required to fully describe the regulation-innovation consequences for ultimate users of drugs.

Lasagna's group is also attempting to determine the scientific, therapeutic, and economic value of the INDs and CTCs under investigation. When completed,[42] this study should shed some light on the issue of to what extent the 1962 regulations were responsible for a decline in new drug introduction and to what extent the decline is concentrated in non-important thereapeutic drugs.*

*An unpublished preliminary analysis of this research has been prepared.[43]

A further improvement of the Lasagna approach over the existing studies is the stratification of the analysis by therapeutic categories. The disaggregation of the measure of innovative output by therapeutic category would allow for further investigation in the following areas:

(1) the inapplicability of traditional disease models in certain therapeutic areas (see Section 2.4)
(2) the distortion from government intervention in certain therapeutic areas (see Section 2.4)
(3) the relative stringency of the implementation of regulation among therapeutic category[44]
(4) the relative effect of regulation on new drug development given the fact that efficacy is more easily tested in certain therapeutic categories (e.g., antibiotics) than other categories[45] (e.g., chemotherapy).

It is indeed surprising that, given the potentially valuable information derivable from an analysis stratified by therapeutic category, this approach was not adopted in earlier studies.

An alternative index of innovative output would examine the economic importance as measured by the sales of the NCE. This approach builds on a Peltzman assumption that ineffective drugs realize a steady decline in sales as doctors have unsatisfactory experiences with these drugs.[46] The major problem with this approach is that there may not be a high correlation between the importance of a drug's therapeutic gain and its market share and sales. A relatively minor therapeutic improvement may succeed in capturing a large share of the market[47] while a major therapeutic advance will achieve modest sales due to the rareness of the disease the drug attempts to treat.

In summation, a critical step in any assessment of regulatory effects is the construction of a meaningful index of innovative output. Although additional problems will arise as one moves away from a simple counting of NCEs to a more sophisticated analysis of chemical entities by relative importance, number of IND's, and therapeutic category, we feel that this additional information is indispensable to a sufficient understanding of regulatory effects.

Assessment of Efficacy/Safety

In order to properly assess the costs and benefits of the U.S. drug regulations, it is necessary to construct objective criteria of safety and efficacy. Without such criteria, it is difficult to understand how meaningful estimates can be attempted for such measures as the number of *ineffective* NCE's prevented from being marketed or the number of *safe* drugs used abroad but not available in the U.S. Wardell and Lasagna state the difficulty of establishing unequivocal definitions of drug safety and efficacy in legal norms.

> Most of the debate between the pharmaceutical industry and the Food and Drug Administration stems from disagreement as to what constitutes evidence of safety and efficacy, whether the available data satisfy the present perceived requirements, whether a particular degree of safety or efficacy is sufficient for the intended use, and what uses should be deemed appropriate. We are deluding ourselves by suggesting that safety and efficacy are adequately or even clearly defined concepts in the present state of the art of clinical pharmacology.[48]

This confusion as to what constitutes safety and efficacy creates uncertainty in the drug industry which leads to either over-testing and the concomitant waste of resources or under-testing and the inevitable delay as the drug must be further tested and re-submitted to gain FDA approval. While (1) there are difficulties in establishing workable definitions, (2) it may be desirable to change them over

time, and (3) there are trade-offs between safety and efficacy for any particular drug used in a therapeutic area, it would be beneficial to receive FDA guidance limiting the definitions within reasonable ranges for both evaluation purposes and for providing clear signals to the industry.

The Multinational Nature of the Pharmaceutical Industry

International comparisons have been utilized in analyses of the effect of regulation on innovation for two distinct purposes:

(1) as additional information for those studies concentrating on the pre and post 1962 amendment effects, and

(2) as a basis of comparison for those studies concentrating on the effects of U.S. drug regulation vis-a-vis a possible alternative regulatory system (e.g. the U.K. system of drug regulation).

Note, that by comparing innovation in the U.S. and in a foreign country over the same time period the effects of a research depletion will be similar and the regulatory effect will be better isolated.* This section will attempt to highlight some of the difficulties in attempting to assess regulatory effects using international comparisons.

It is first important to understand the multinational nature of the pharmaceutical industry. Grabowski emphasizes that U.S. firms collectively have a large share of the total ethical drug sales in foreign countries and many foreign multinational firms market a significant percentage of their drugs in the United States.[49] Lasagna et al state that most major U.S. based pharmaceutical firms have

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* But, the relationship between disease models and the development of drugs may differ according to the tradition of preventive medicine in each country. See also Section 2.4.

foreign subsidiaries and some firms operating in the U.S. are subsidiaries of the foreign firms.[50] Changes in U.S. and foreign regulations may result in shifting of R&D effort to foreign subsidiaries, the effect of a shift of R&D effort on the level of R&D expenditures in both countries is unclear. Lasagna et al. further state that the initial R&D expenditures may take place in a subsidiary in one country then be followed by further drug testing and first market introduction in another country.[51] Thus because of the multinational nature of the pharmaceutical industry, it is sometimes difficult to determine whether the country of NCE introduction is the same country where the innovation activity occurred.

Second, the regulations and the implementation of the regulations may vary within the countries being examined. As discussed in Section 2.1., a decision must be made whether the study is of a particular regulatory event (e.g., 1962 drug amendments) or a regulatory system (e.g., the composite effect of drug regulations including post-1962 changes). For example, the 1975 FDA decision to accept foreign test data for efficacy certainly affects a pharmaceutical company's decision about where to conduct testing.[52] Studies which analyze trends in R&D shifts and do not adjust for this major 1975 policy change may be grievously defective.

Third, there are a multitude of other factors which affect the decision of the country in which to conduct research and development. We agree with Grabowski in his conclusion that:

> "...further investigation is necessary to determine the extent to which regulation is important in causing these shifts in research and development abroad as well as to determine the exact causal mechanism. Since research and development is an activity in which highly trained scientific and educated personnel are critical inputs, the availability and costs of such personnel also can be expected to influence these shifts. In addition, differences in the tax treatment of research and development and legal factors such as tort liability and patent protection may significantly influence location decisions."[53]

Therefore, a study which attributes the entire shift of R&D abroad to the 1962 drug regulation and does not consider changes in the factors mentioned by Grabowski--or even changes in the relative value of the British pound--may overestimate or underestimate the effects of the U.S. drug regulation.

Number of NCEs versus Claims for Uses

An alternative measure to new chemical entities developed is the total number of uses for which the NCEs are approved.[54] Before the 1962 drug amendments, companies frequently listed multiple uses for NCEs. With the regulations necessitating efficacy tests for each use claimed there has been a significant reduction in NCEs with multiple uses. This observation alone however does not mean that an NCE developed now is not researched and confirmed for multiple uses more efficiently. Once safety is established, there are incentives through economies of scale for finding multiple uses. Furthermore, in the development of drugs, choosing candidates for development which may have multiple uses is a sensible strategy since safety needs to be determined less often.

Market Life as a Factor in the Calculus

The value of an NCE over its useful lifetimes does not lie only in the extent of therapeutic advance, but also may depend on the magnitude of its market life. While there is no simple weighting procedure for integrating therapeutic advance and lifetime into a single index of value, both are important. In cost-benefit evaluations, the delay/rejection of an NCE must be measured against the drugs remaining. Since innovation competition rather than price-competition seems to drive the firms and since physicians probably are performance elastic and price indifferent, drugs may be retired before their economic life expires as judged by efficiency criteria. (See Section 2.2. on the effects of the 1962 Amendments on effective patent life.)

2.4. Alternative Explanations for the [Alleged] Decline in Significant Pharmaceutical Innovation

If, in fact, there has been a decline in significant pharmaceutical innovation, factors other than (or in addition to) cost increases and time delays attributed to the 1962 Amendments may be important. Two alternative explanations concern (1) the increasing scientific difficulties inherent in finding new drugs for the diseases which are receiving attention and (2) market distortions traceable to government involvement of a non-regulatory nature in the pharmaceutical area, e.g., government research and utilization of technical manpower. Neither of these factors has received the attention in analysis that it deserves.

Schwartzman[55] states the depletion-of-research-opportunities hypothesis in its most polar form:

> "One may question whether the major drug discoveries of the 1940's and 1950's exhausted the promise of drug research; there may be no undiscovered potential drugs for the remaining unconquered diseases."

He makes the important observation that development in pharmaceuticals is different from other technological areas in that our knowledge of disease mechanisms is incomplete.[56] In addition, Schwartzman observes that the areas receiving attention recently are "intrinsically more difficult" such as arthritis and atherosclerosis.[57] Ashford makes a different point by suggesting that *occupational and environmental factors* may well play a far more significant role than is presently realized in the causation of the major diseases

or major health problems which face us, especially cancer and respiratory disease.[58] Since the nature of the cause of disease has changed, the cure will not necessarily lie in the technology of drugs. Furthermore, there may be a serious *mismatch* between the conception of disease *causation* and *the drug action mechanisms* which makes innovation even more unlikely, i.e., our drug development models are most inappropriate.[59] Indeed, animal models which are a central part of drug development are often absent or inappropriate for some diseases, such as arthritis. These possible explanations deserve study. However, a better understanding of the *process* of pharmaceutical innovation and its *relationship* to disease models is required before much progress is likely to be made.

Grabowski, et al.[60] have concluded that both the depletion of research opportunities *and* increased regulation can explain the observed reduced productivitiy of drug R&D in a comparison of productivity trends in the U.S. and the U.K. Their regression-analysis suggests that a (cumulative) decline in NCE's per R&D dollar existed for many years prior to 1962, thus pointing to the importance of non-regulatory factors in explaining part of the observed decline.[61] (But see the limitations of these studies, discussed in Section 2.2.) For reasons already stated, it seems that the effects of research depletion as well as regulation should be disaggregated into suitably defined therapeutic areas. Otherwise, the relative importance of those factors may not be discovered or indeed be discoverable. In a paper prepared for the National Science Foundation, Hansen[62] provides a useful discussion of the work of Jondrow, Baily, and Grabowski as well as Peltzman. He concludes that no clear answer emerges from the work to-date regarding the relationship between regulation or research depletion and the changes in pharmaceutical innovation.

Most of the focus of attention paid to government involvement and possible distortion of the pharmaceutical market has concerned the regulatory activities of government. Government direct participation in pharmaceutical research and development[63] may also distort the market. Ashford has questioned the distortion effects of both directing research into areas that would not otherwise be taken by the private sector and of inappropriately relying (from a social investment perspective) on pharmaceuticals as the preferred way to address disease problems.[64] Distortion resulting in the development of drugs which treat a minority of patients, who would otherwise be neglected may, of course, be desirable from an equity perspective. Zubrod has made this point regarding the mission of the National Cancer Institute.[65]

Schwartzman notes that research expenditures outside industry have increased at a faster rate than those within the industry.[66] (See his table reproduced below.)

TABLE 1-1
National Support for Performance of Medical Health-Related Research by Source of Funds ($ Millions)

	1960	1965	1970	1972
Government	$471	$1,229	$1,740	$2,223
Federal	488	1,174	1,664	2,144
State & Local	23	55	76	79
Private	121	158	193	211
Foundations & health agencies	76	88	108	124
Other private contributions	12	25	32	33
Endowment	19	19	19	19
Institutions' own funds	14	26	34	35
Industry	206	328	566	668
Industry percentage of Total	26	19	23	22
Total	798	1,715	2,499	3,102

Sources: Industry expenditures: Pharmaceutical Manufacturers' Association. Other expenditures: Associate Director for Program Planning and Evaluation, Office of Resources Analysis, National Institutes of Health, March 1973.

Note: 1972 figures for industry represent budget amounts rather than actual expenditures. Other 1972 figures are estimates of actual expenditures.

Schwartzman goes on to say:

> "This spending pattern will divert the limited supply of trained research personnel into basic research and will thus reduce the resources available to the industry for drug discovery and development. The diversion will take place through bidding up the costs of research; to retain their present research staffs, the pharmaceutical manufacturers will have to pay higher salaries. Thus, a paradoxical result of the additional government funding of research may be a reduction in the flow of new drugs."[67]

As with the several other possible causes of change in pharmaceutical development, a disaggregation into therapeutic or other suitable units of analysis is needed for a full appreciation of the many forces which determine the direction and level of pharmaceutical development.

2.5. The Nature of the Trade-Off

There have been two major attempts (Peltzman[68] and Jondrow[69]) to do comprehensive cost-benefit analyses which have reached definitive conclusions concerning changes in consumer welfare as a result of the 1962 drug amendments. In this section, we will first discuss some general limitation of cost-benefit analysis, and then put forth some of the trade-offs which must be considered in making major policy changes.

General Limitations of Cost-Benefit Analysis

Results of cost-benefit analysis could be definitive only if it were possible to aggregate all costs and all benefits associated with a given decision in a common metric and combine them in a single ratio, such as a benefit to cost ratio. Cost-benefit analysis leading

to a single-dimensional measure of efficacy of a regulatory decision is generally not sensible, because it would depend upon:

(1) attaching monetary values to non-traded, unpriced health effects;

(2) making difficult or impossible intertemporal comparison of welfare;

(3) overlooking the equity implications of the fact that different people bear the costs and reap the benefits of drug regulations.

First, there is no generally accepted approach to the problem of valuing such elements as a human life disfigured by thalidomide or a life lost because of FDA delay in approving beta-blockers for angina. For the analyst to place his own value judgments on such elements would disguise the basic trade-offs that confronted or should have confronted the policymaker. Whether the trade-off is dollars vs. dollars, or health effects vs. dollars, or health effects vs. health effects, the reader of these analyses should be explicitly confronted with these choices--the value judgments should not be hidden in the assumptions on which the calculations are based.

Second, because regulation of drugs often gives rise to costs and benefits over long time horizons, it is necessary to be able to compare costs and benefits occurring over such long periods of time or at different points in time. The solution traditionally suggested by economists is that the present discounted value criterion be applied to problems involving intertemporal resource allocation. However, several conceptual questions arise in the straight applications of the discounted value criterion: (1) What is the appropriate social rate of discount?; (2) What is the appropriate discount rate for non-monetized benefits?; (3) What is the appropriate discount rate for intergenerational welfare comparisons (e.g., How are dollars today to be traded off against dollars two generations hence; dollars today against lives five generations hence?)

Choice of discount rate for evaluating regulatory decisions is important because the present value of the effects of any given regulation, or the rank ordering of the effects of alternative regulatory regimes, can change markedly depending upon the discount rate used in the cost-benefit calculation.

Finally, cost-benefit analyses have generally ignored the equity implications of the fact that the benefits and costs accrue to different parties in different income classes. What is required is the development of a method of integrating distributional equity and economic efficiency in the analysis of the effects of regulatory decisions.* The aggregation of cost and benefit without consideration of equity is value-laden itself--it is a decision to ignore equity.

Cost-benefit analysis, in particular, and economic theory, in general, do not give absolute answers to the problems of designing optimal regulations on the production and use of drugs. They are fundamental tools for analyzing the problems. *Optimizing* social welfare should not be confused with *maximizing* social welfare. If society chooses to overrule the market and pass legislation which is not economically efficient, society is not violating any absolute laws. Optimizing welfare, however, may require adoption of a collective approach or method (e.g., because it enables consideration of non-market costs which the market cannot deal with) instead of a market approach.**

*An interesting approach integrating distributional equity and economic efficiency in the planning of public expenditure appears in Martin S. Feldstein, "Distributional Preferences in Public Expenditure Analysis", Harvard Institute of Economic Research, Discussion Paper #239, (May 1972). See also, Burton A. Weisbrod, "Income Redistribution Effects and Benefit-Cost Analysis", in S.B. Chase, Jr. (ed.), Problems in Public Expenditure Analysis, Washington, D.C., the Brookings Institution (1968).

**The above discussion is an adaptation of Guido Calabresi's discussion on the role of economic theory in decision-making in The Cost Of Accidents: A Legal & Economic Analysis, New Haven Yale University Press (1970), p. 18-20.

The Nature of the Trade-Offs

Listed below are some of the trade-offs that resulted from the U.S. drug regulation. It is important to realize that while many of the costs and benefits are inevitable results of the regulation, care must be taken to ensure that the regulation and its implementation are achieved in a *cost-effective* or *health-effective* manner. For example, one of the consequences discussed below is the delay of introduction of drugs previously introduced in foreign countries. For those drugs of exceptional therapeutic importance, the FDA should, and indeed has, significantly accelerated its approval process.

The trade-offs which characterize the effects of drug regulation can be classified as (1) dollars versus dollars, (2) health effects versus health effects, and (3) health effects versus dollars. It is also important to take into account the parties affected by the regulation.

Safer and more efficacious drugs yield a health benefit for those taking the new drugs, while drugs not being marketed limit the therapeutic opportunities available to those who might otherwise receive their benefit. Those who benefit may be different from those who are harmed, although this is not necessarily the case.

Higher costs may result from safer and more efficacious drugs. These higher costs may be borne by the consumer through higher prices, by the producer through reduced profits and by the government through lower tax revenues.

Safer and more efficacious drugs may result in changes in market structure such as increased concentration of the industry.[70] Some firms will benefit and others will lose. Concentration itself may or may not result in more efficient innovation as well as greater innovation.

It is not clear whether any analytical approach can determine the "correctness" of these trade-offs. The aggregate effects of these trade-offs must be evaluated within the rubric of a cost-benefit analysis for which a methodology needs to be developed.

3. ADDITIONAL RESEARCH REQUIRED FOR POLICY FORMULATION

In the previous section we discussed issues which need to be resolved in order to begin to design policy alternatives for pharmaceutical development and regulation. The eventual assessment of the effects of regulation must address six questions.

(1) What are the effects of regulation on investment decisions in pharmaceutical development -- e.g. what therapeutic areas to pursue and in what manner?

(2) What are the effects of regulation on the actual way ideas are generated or actual technical solutions are attempted -- e.g. what chemical changes are made in the synthesis of a new drug or what attempts are made to match pharmacological action to a specific disease mechanism?

(3) What are the "intrinsic benefits" of an innovation deriving from a new drug or drug use?

(4) What are the effects of regulation on the delivery of benefits to the consumer -- e.g. as a result of prescribing practices of physicians, etc.?

(5) What are the costs of regulation--dollar costs, e.g., testing or efficacy requirements and health costs, e.g., drug lags?

(6) How are net dollar costs to be compared with net health benefits?

The weakest parts of past analyses are (1) an understanding of the process of technological innovation in the drug industry and (2) the treatment of the benefits that stem from drug regulations. What is needed at this time is research which examines these two critical areas. First, the analysis must focus on the process of technological innovation--rather than investment strategies. Second, the examination should

emphasize the benefits of the drug regulations as opposed to a more expansive treatment of the cost of regulation, usually expressed in time delays, reduced flow of NCE's and increased expenditures for research and development.

We believe that clarification of these issues must precede the design of changes in the regulatory framework of new drugs. Contrary to the views of some economists and physicians, we are unable to conclude from the available evidence that the 1962 Amendments have caused a decline in drug innovation in the United States or that the social costs of the Amendments have exceeded their benefits. Before these issues can be addressed in a meaningful way, additional research focused on the innovation process in individual therapeutic areas is needed.

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