DRUG DEVELOPMENT COMMUNICATIONS, 1(4), 259-285 (1974-1975)

INTERACTIONS OF SCIENCE, ECONOMICS AND POLITICS IN DRUG DISCOVERY, DEVELOPMENT & DELIVERY

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Drug discovery encompasses those activities, usually in a laboratory or clinic, that result in identification of a new drug candidate or new use of a known drug. Drug development covers the range of activities from point of discovery or selection of a new drug candidate that appears to merit clinical evaluation, to release of the product for commercialization. Drug delivery includes manufacture, distribution, purchase, and conveyance of the drug to the patient. Science and economics traditionally had been the dominant influences on the relationships among these components; however, in the past fifteen years, political considerations have become a major factor.

Association of the terms Discovery & Development in sequence rather than the usual Research & Development permits some functional distinctions at least as relates to pharmaceuticals. Discovery is the finding of a new thing or a new observation or understanding of an existing thing. Development involves the conversion of a discovery to something useful in the broad sense of utility. There is a great deal of research in development. Delivery includes those activities that make the results of a development available to others than those who develop it. Research is conducted in discovery and development, and to some extent, in delivery.

A distinction frequently is made between basic and applied research. These concepts vary among different individuals. Basic research tends to be looked upon as research directed to the search for knowledge for its own sake; applied research as the search for knowledge directed to creating a useful new product or process. In practice, differences between basic and applied research tend to be more of degree than of kind. In drug discovery and development, the extent of interplay between so-called basic and applied research is related as much to the individual scientist's training, experience, and ability to perceive and associate things that are significant as to the purported purity or utility of the project. Distinctions between pure and applied research can be misdirecting when individuals in positions influencing public policy speak out on such issues with more administrative authority than scientific judgement. An illustration is that of a recent Commissioner of the F.& D.A. who suggested that the decline in new drug product introductions by the Industry was attributable to the greater expenditures on applied and developmental than basic research.

Discovery, development, and delivery of new drugs form a continuum and each cannot thrive isolated from the others. Development has been the least appreciated, if not a denigrated, component of new drug creation. In a relative sense, drug discovery has been glamorized, drug delivery politicized, and drug development unrecognized. The route from discovery to delivery, bridged by development, has been successfully traveled in the past because of feed-back relationships, both scientific and economic, that have provided incentives for passage along the route. Political, social and economic changes which can make this passage unattractive, are appropriate matters of concern.

The title of this article identifies interactions of six broad parameters pertaining to drugs. To permit a manageable discussion of

interactions, these will be treated under headings of Science, Economics, and Politics after a brief historical perspective.

BRIEF HISTORICAL PERSPECTIVE

Pharmaceutical-related activities in the United States could be examined in terms of four historical segments - namely: prior to World War I, between World War I and World War II, from World War II to the early 1960's, and the period subsequent to that time.

Prior to World War I, the U.S. pharmaceutical industry had little influence on innovation and largely provided some supply services to pharmacy. Between World Wars I and II, the U.S. Industry developed modestly but was not a dominant world factor. Natural product drugs, nutritional factors, sedatives, and toxicity-prone chemotherapeutic agents were among the fields attracting research attention.

A stimulus to expanded effort and optimism in new drug research was the observation in the mid-1930's of the chemotherapeutic properties and relative safety of sulfonamides. These drugs ushered in a new era of chemotherapeutics. Shortly thereafter, events associated with World War II and the discovery of antibiotics further stimulated the U.S. industry to expand its pharmaceutical research. The next twenty years was a revolutionary period in new drug discovery and development and provided such major contributions to medicine as antibiotics, corticoids and other steroid drugs, new cardiovascular agents, psychotherapeutic drugs, and novel medicinals in many other areas. During this period government regulatory concern with new drug introductions was principally from the perspective of safety. The path from discovery to delivery occupied a time-lapse of the order of two to three years, and compared to today, was a considerable less expensive one involving perhaps only a few hundred thousand dollars for development costs. During that period, costs leading to a discovery and costs of manufacture and delivery were in a relative sense greater than for development in

comparison with today's distribution of efforts. The majority of new discoveries were patentable, and for a number of years these were largely single source products. Competitive motivations and relatively smaller development costs led to the introduction of more molecular modifications of an initial lead drug. In turn, this increased the probabilities of chance discoveries from use of such drugs in man. Observations of central nervous system activities in man of the anti-tubercular drug, iproniazide, led to research with MAO inhibitors with anti-depressant properties, than sequentially to a type of antihypertensive agent; chemotherapeutic sulfonamides were precursors to analogous diuretics and saluretics useful in hypertension therapy, and to certain oral antidiabetes drugs; and other examples have been cited.

During the early 1950's many could recall the medical consequences of not having the newer medicinal agents that had become recently available and appreciated the discoveries of the 1940's as impressive accomplishments. By the late 1950's, the pace of new product introductions, especially of combination products, had become rather frenetic. At the same time, certain competitive industry practices, such as product promotion and introduction of combination products of questionable merit were beginning to draw criticisms. Subsequently, Senator Kefauver's Subcommittee on Antitrust and Monopoly initiated investigations that resulted in political accusational excesses.

A major fallout from the Kefauver Committee hearings on the pharmaceutical industry, held from 1959 through 1961, were the new Food and Drug laws of 1962, which ushered in an entirely new format under which drug discovery, development and delivery would function. The environment in which we operate in the field of pharmaceuticals in the 1970's results from a continuation and extension of forces that gained momentum during the 1960's. It was during this period that political factors

began to assume increasing influences on delivery, development, and discovery.

SCIENCE

In this context, discovery relates to the process of turning up a possibly useful lead to a new or improved drug, and development is its conversion to a drug product. Drug discovery and development involve scientists from a variety of disciplines and associations. The pharmaceutical industry has been a major source of discovery and virtually exclusive motivator in development. However, substantial background information, or even the foundations of a discovery, may originate in university, government or institutional laboratories. The scientific personnel who may contribute to, or be points of origin for, the discovery process, cover many disciplines with the chemist usually at the point of origin if new compounds are to be prepared, and the biologist helping make if not originating the laboratory discovery of potential utility. The physician-scientist plays a role not only in the evaluation of a new drug candidate for an anticipated application, but can initiate a discovery by observing in man an unexpected response to a new drug that can orient development toward an entirely new indication.

Research directed to drug discovery can be considered in phases of exploration for a lead, followed by exploitation of a lead. The latter includes exercises in molecular modification, which is still part of discovery until a candidate compound is selected for study in depth for development. The search for leads can receive cues from a variety of directions. Historically, nature has provided many of the molecular prototypes for drugs of synthesis - that is, nature's clues from structures such as those of the opium alkaloids, atropine, cocaine, quinine, steroid hormones, antibiotics, etc. Clues from nature also were provided by growth and regulatory factors (vitamins, hormones neurotransmitters) which led to the synthesis of analogs and antagon-

ists. The search for new drugs from nature goes on with its ups and downs in attention. Other sources of leads can be provided by the chemist: who conceives of synthetic model compounds not patterned after natural prototypes, but which incorporate so-called pharmacophoric groups; by exploitation of new synthesis methodology; from availability of certain intermediates for synthesis, etc. Broad screening in the biological laboratories is another source of new leads. This is more feasible with relatively uninvolved testing systems such as in vitro antibacterial screening, mouse behavioral tests, etc. A limitation is the uncertain validity of lab screening model systems in predicting possible utility in humans. Animal model systems frequently are designed as a feedback from drugs with known properties in man, and as a result such animal tests tend to orient discovery in the direction of drugs similar to those already available. There is also the so-called rational approach to the discovery of new drugs, one that fascinates scientists in both industry and academia. The term "rational" as applied to an approach to new drug discovery may imply an understanding of a disease process at a biochemical mechanistic, if not molecular, level; it may imply an approach to design of new drug candidate molecules from basic principles of physical chemistry; it may imply other things to other people - but the rational approach generally is presumed to flow from research that is alluded to as "basic". It is a highly subjective concept. The statement occasionally is made, usually by individuals not in the business of discovering drugs, that a reason the search for new drugs has resulted in fewer introductions is because we have exhausted our store of basic knowledge. At least to the present time there probably have been more contributions to basic science generated by the discovery of new drugs which served as research tools than have advances in knowledge of basic drug mechanisms resulted in major new drug discoveries. In any event, a "rational" approach merits

attention because it leads to a more orderly organization and understanding of existing information in the planning of new research.

A comment about the exhaustion of basic knowledge may by in order. As reflected by dollar figures, between 1950 and 1970 the annual research expenditures of the pharmaceutical industry in the U.S. increased some twelve-fold (from about 50 to 600 million dollars). In a related twenty year period between 1947 and 1967, the Federal Government increased its medical research expenditures some fifty-fold, through both intramural and extramural programs, presumably mostly on basic research. It would have been a remarkable efficiency for the industry's expanded effort to have exhausted the store of relevant basic science during the period in which the Federal Government was adding to it at a rate of increased expenditures some four times that taking place in the industry. Furthermore, the suggestion that the store of basic knowledge is "exhausted" is conceptually ridiculous. It presumes that knowledge is consumed and then is no longer useful. Knowledge is a highly reusable commodity. We probably have at least as great a need to inter-relate and interpret existing information as to generate additional unassimilated observations.

The exploitation of a lead, which is still part of research and is directed toward finding a candidate drug substance that might be worthy of development, is the area where rational approaches of a chemical nature could be particularly valuable. Structure-activity relationships should permit the chemist to make fewer compounds to exploit a lead. This should not only increase the efficiency of the chemical research, but also require fewer compounds to go into the various biological evaluations to permit selection of a candidate for development. Among factors that have contributed to productivity of research chemists in

the laboratory have been the availability of larger numbers of chemical intermediates for syntheses, and the marked improvements in instrumentation and methodology that have permitted more rapid and sophisticated separation, analysis, and structural work.

The relative complexity of some of the drug molecules prepared by synthesis has drawn on the scientific ingenuity of the development chemist to provide methods for larger scale economic production of such drugs. The quality of the research applied in this type of development is inadequately recognized outside of the Industry.

Advances in analytical science and instrumentation have permitted not only more rapid resolution of complex problems but also the solution of problems previously unapproachable. Some peculiar situations and new problems are resulting from this. Non-scientists, or those without historic perspective, may view newer knowledge on older drugs (such as their pharmacokinetics) as corrections of deficiencies in past practices rather than of limitations in the former state of the art. Certain laws, such as the Delaney amendment, have become incongruous and the detection sensitivity of newer methodologies could lead in principle to classification of the human body as a carcinogen.

A beneficial result of the post-1962 drug amendments has been to accelerate the development of better methodologies for the scientific evaluation of efficacy of drugs in humans. Safety assurances, however, remain more elusive and a number of toxicology evaluations are conscience-soothing exercises in the absence of more meaningful methodology.

Advances in pharmaceutical sciences have led to learning more about properties and performances of drug products as distinct from drug substances. With the increase in numbers of multiple source drugs, this has led to confrontations involving science, economics and politics, and will be discussed later.

Scientific methods are becoming applied to more of the components of drug delivery and none too soon. One of the more pressing issues is that of drug utilization - overuse and underuse as the case may be. Certain aspects of drug delivery suffer from deficiencies in factual data, and since delivery is of economic interest to the public, it has become a fertile field for the politician.

ECONOMICS

Although economic factors tie together drug discovery, development and delivery, the diversity of interests and responsibilities associated with these often lead to fragmented or narrow evaluations and judgments. Health service economics has become more political, and discovery and development unavoidably are influenced by this.

Motivations for drug research vary with the setting, but in each there exists a kind of cost-benefit relationship. Academia, government, and most non-industrial institutions that do drug research, largely are motivated to learn more about existing drugs, investigate basic principles, discover or prepare novel substances, or otherwise add to the scientific foundations for drug discovery and development. Both public and private funds have supported such research with the Federal Government assuming a progressively larger role from the early 1950's to the late 1960's, with subsequent plateauing and decline of support. The innovative pharmaceutical industry is the only group whose drug

research has new drug discovery for ultimate development and delivery as its prime objective. Since about 99% of pharmaceutical industry research is supported by its own funds, there must be an economic incentive for such investment.

Annual expenditures identified as in support of R. & D. by the pharmaceutical industry have continued to grow. Between 1950 and 1960, these expenditures as a percentage of sales rose from an average of about 3% to 9% and have continued near the 10% level. From 1951 to 1962 to 1973, the annual R. & D. expenditures for U.S. firms quadrupled in each period from the order of 50 to 200 to 800 million dollars. Proportionally less of the latter increase has been available for expansion of new drug discovery efforts. Added costs resulted from inflation, increased expenditures in clinical studies to learn more about existing products to comply with new regulations, expanded development requirements in toxicology, metabolism, analytical methodology for quality assurance, etc. Inflation has been an impressive consideration since the order of 10% per year increases in budget became required just to maintain the laboratory facilities and personnel already available. Thus, a pharmaceutical company should have the order of a 10% a year profitable increase in sales under these circumstances to stay even in terms of its R.& D. effort. In relating averages it must be appreciated that economic profiles of companies vary from one another and with time. However, as innovative companies market more multi-source products, the added sales from such products is less likely to sustain a 10% of sales allocation to R.& D.

If we attempt to rationalize the present R.& D. expenditures of the research oriented pharmaceutical industry as costs of discovery and development of new and novel products, we would have difficulty in making sound business sense today in terms of expectations of

the 1940 - 1960 period. R.& D. managers recognize and must effectively convey to non-R.& D. people, including fellow management, and to laboratory personnel within R.& D., that the significant changes of the past few years are likely to carry into the future and require certain accommodations. Much of the work in support of existing products has become an added cost of doing business, particularly on the part of those companies that have been innovative and created and developed these new products. Additional costs have been incurred in providing improved methods for quality assurance of existing products - efforts involving development, quality control, and manufacturing innovations. In the past five years, the industry has committed considerable resources to support additional studies on older drugs to meet newer regulatory demands. Such funds in the past would have been available for new drug research. With the need for more metabolism, toxicology and clinical work with drugs, industry resources have had to be increasingly committed to toxicology, biochemistry and medical sciences. In effect, patterns of personnel distributions in the pharmaceutical industry that were established during the 1940's and 1950's have been altered. The limits to total R.& D. expenditures require that justification for personnel allocations in any one discipline must be judged relative to competing needs for personnel among other disciplines. In a relative sense, effort in creative new drug synthesis has become, and probably will continue to be, a smaller proportionate part of the total R.& D. effort of the industry than it was prior to 1962.

Shifts in medical needs and priorities also influence the economics and science of drug discovery and development. The new drug contributions of the past thirty-five years revolutionized the practice of medicine. Since many diseases now can be reasonably well treated, new drugs in several therapeutic categories would have to compete with

relatively good existing ones. However, there remain very important unsatisfied therapeutic needs. Among these are drugs for degenerative diseases of apparent gradual onset that are difficult to quantitate by presently available diagnostic methodologies, and thus also difficult to measure for improvement and establishment of drug efficacy, (atherosclerosis, osteoporosis, connective tissue diseases, etc.) These also are conditions of a chronic nature, would probably require chronic treatment, and thus create more concern with safety. However, with the present regulatory expectations for hard proof of drug efficacy, and decreasing willingness to assume any risks, the economics associated with the development of such drugs becomes quite imposing and less attractive.

The longer time and higher costs of developing products to market are important economic considerations in research program planning. The time lapse in the U.S. for bringing a product to market from point of selection of a drug candidate in the laboratory for development to the point of release for marketing averages about seven years. This can range from a shorter period of time for a new antibiotic or an anti-cancer drug, to longer peiods for a new analgesic, a fertility control drug, etc. The cost for passage through the development route averages about 7 million dollars per drug. Furthermore, only one in five to one in ten that starts under development reaches the marketplace. Something like one in five to seven thousand of the new agents screened in the laboratory becomes a drug product. Not all of those introduced are commercially successful.

A factor that laboratory scientists and administrators must consider in light of present long time and high cost requirements for new product developments, is the relative timing at which events are carried out. In a new drug development, a balance must be struck between the resource-saving but more time consuming approach of carrying out re-

search projects in the sequence of individually justified steps against the time-saving but more costly approach of doing concurrently many of the things that might be required later. In industry, one also should be cautious in diverting resources to do certain kinds of research only because it can be done.

The impression, on balance, is that although we are better prepared scientifically, the economic constraints have increased in new drug discovery and development. New drug R.& D. also carries a benefit-to-risk ratio - whether we speak of risks of supporting expenditures by industry or government. A danger is that either, or both, government and industry, in the future, might consider new drug R.& D. as a less attractive investment.

The end result of successful drug research and development is the delivery of useful medicinal products. If delivery includes the manufacture, distribution, and conveyance to the user, one needs to consider the participation of the pharmaceutical industry, the distribution channels, health professionals such as physicians, pharmacists and nurses, and the economics associated both with the product and the services accompanying delivery of the product. Economic considerations in delivery of the product also can involve the private purchaser, governments (national and local), third party payment groups, etc. It is at the delivery end that the widest range of people and organizations participate in, or are exposed to, the costs of drug products. The concept that emerged in the 1960's - of "health care as a public right", brought greater pressures for more extensive and improved delivery of health care services including drug products.

During the past decade, two phenomena have grown as economic factors. One has been the increased numbers of multi-source products that have appeared as patents expired on drugs introduced during the 1940's and 1950's, the other has been the increase in third party payment

systems for health care, including drugs. This confluence of events resulted in debates as to the quality or equivalence of so-called immitative "generic equivalents" compared to the "original" product. The lower price listings of some "generic equivalents" attracted attention of economy-minded purchasers.

Total product quality and therapeutic equivalence of multi-source drugs is generally admitted to be a scientific-medical issue but economic considerations have made it more of a political issue, (see later section). Unfortunately, even the economics have been only superficially treated. For example, purported savings in government purchases of drugs under the recently proposed Maximum Allowable Cost (MAC) program have been poorly documented and administrative costs not identified.

Although drugs account for a relatively small component of total health care costs, they can exert considerable leverage on need for more expensive services. If we use 1972 figures of $4.32 as average cost per drug prescription and $15 per physician office visit, with hospital costs per day in the vacinity of $100, the quality and performance of the prescription drug product bears a high economic leverage in influencing more or fewer physician calls or hospital days.

In 1973, in the U.S., some $6,787,000 000 consumer dollars were spent for prescription drugs. According to H.E.W., in 1973, of some $19,851,000,000 expenditures under the Public Assistance Program, about $612,000,000 was spent for prescription drugs.

Government as well as private survey data show that prescription drug prices during the past three years have been remarkably stable and inflation resistant.

One would hope that as deficiencies in some immitative products are detected, these either will be corrected and better controlled, or the products removed. The exercise of more uniform production and quality assurance practices will lead to narrowing in price differentials

among suppliers of multi-source products. However, the innovative manufacturer inevitably will bear greater financial burdens. The manufacturer and distributor of only off-patent products does not have to sustain an expensive R.& D. operation, and has the economic advantage of being able to select only those products to market which appear more profitable or less complicated for him to produce, and less costly to service. Furthermore, entry via the less costly abbreviated NDA route is open to him.

Until now, provision for support of new drug discovery and development in the Industry has been made in the cost of the drugs delivered. An economic incentive must be retained if we are not to just benefit from contributions of the past without investing in advances for the future.

POLITICS

This section relates to activities of elected and appointed individuals in public office, of government agencies, and of forces or media influencing or interpreting their operations. As the drug discoveries of the past thirty-five years revolutionized medical practice, the delivery of drug products and attendant services assumed increasing economic and social importance. This inevitably led to greater involvement of political factors.

Political influences on drug discovery, development and delivery have become evident to a larger number of groups and individuals; however the diversity of specific interests involved and differences in the time frame of events have tended to obscure the totality of the changes and their implications.

One can begin with drug discovery and the research leading to it. In the mid-1950's, health sciences research became a politically favored

activity for Federal Government financial support. Individuals such as Senator Lister Hill and Congressman John Fogarty actively championed for increased government support for medical sciences research. The NIH programs, both intra- and extra-mural, underwent rapid expansion from the mid-1950's to late 1960's. Certain criticisms became inevitable. Research support had been sold to Congress in terms of pragmatic expectations, but implemented with little concern for such ultimate accounting. About the time annual NIH budgets reached a billion dollars, the earlier congressional champions were gone, and the political leaders became more interested in delivery of health care than in research. Overall, government support for medical sciences research subsequently has declined.

Neither the rapid rise nor later abrupt retrenchment in government support was conducive to the best utilization of funds for medical sciences research. It is unlikely that support in the future will be as permissive as previously, but recent trends in financing are disruptive.

A more serious concern with NIH research is the greater political interference with its science management and the establishment of priorities on a more politically than scientifically responsive basis.

Government support of medical research has resulted in various contributions through basic sciences that serve as foundations for drug discoveries, and through clinical sciences that are essential to drug development. It is not possible to quantitatively relate benefits of support for basic sciences research to drug discovery. However, the reduction of such research support can only be detrimental.

An unfortunate side effect of the more permissive period of NIH spending was the estrangement of academia from the pharmaceutical industry, a relationship that previously had been mutually attractive. The limitation of government support in the late 1960's resulted in a rapid re-interest of academia in industry support. Unfortunately

this occurred at a time when industry itself was undergoing sharply rising costs of its own research.

Although political issues began to upset academic research support in the late 1960's, the pharmaceutical industry had a 10 year start with its problems. The 1959-1961 excursions of Senator Kefauver into industry practices led to the 1962 New Drug Amendments, and major changes in regulations. Subsequently, political figures periodically have revived old issues and created new ones.

The 1962 statutory changes were generally desirable in principle. The F.& D.A. regulations derived from the law include constructive directives and others that resulted in bureaucratic delays and wastage of resources. It is less the regulations per se that have been onerous than have their interpretation and modes of implementation. Regulatory processes have been applied in a manner inimical to the delivery of new drug advances to the public, and arbitrarily and inconsistently in ensuring compliance with marketed products.

Considerable argument has centered on whether post-1962 regulations have led to the so-called "New Drug Lag". The lag is of two kinds - a reduction in numbers of new drugs introduced, and much longer time intervals from discovery to regulatory approval for delivery. Spokesmen for F.& D.A. have consistently argued that the post-1962 regulations did not lead or contribute to the new drug lag,whereas industry spokesmen, and in more recent years individuals outside the industry, have cited F.& D.A. practices as a major contribution to the lag. It has been stated that the decline in new drug introductions began a year or so earlier than the new drug regulations; however, those familiar with F.& D.A. at that time are aware that its practices were anticipating changed rules. More recently, F.& D.A. has offerred additional arguments - such as the arbitrary separation of drugs into more and less important categories with allegations that there has not been a decline

in introductions of more important drugs. This also has been extended to imply that drugs introduced overseas but not in the U.S. are not particularly important to medical practice. There is no question that fewer new drugs have been introduced, and that the time required for their introduction has markedly increased. There is also no question that F.& D.A. regulations have contributed to this. These are less critical issues than whether a useful purpose is served by the resulting lag.

Individuals outside of Industry and F.& D.A. have little opportunity to directly experience from regulatory practices. Members of Industry hesitate to cite specific situations for fear of retributions that might assume a variety of forms. This results in proliferation of abuses in which F.& D.A. can be either victim or perpetrator. Among more common criticisms of F.& D.A. may be included: uneven and inconsistent exercise of regulations and standards, differences in competence of personnel (particularly medical) among divisions, short terms in office of senior administrators and their unfamiliarity with F.& D.A. practices, inexperience in drug research and use, unwillingness of officials to be exposed to public dialogue on issues, a zero risk philosophy and resistance to taking positive actions on new drug approvals for fear of later criticisms, F.& D.A. demands for immediate responses from others while indulging in long delays on their part, punitive over-reactions to political pressures, interpreting "fair balance" in statements on drugs to result in exaggerations of the negative and elimination of the favorable, peripheral expansion of regulatory scope while inadequate to implement well its prime functions, placing American companies at disadvantage in other countries (many faceted), etc.

Some F.& D.A. actions and inactions may derive from: limited funding for adequate staffing with competent personnel, unreasonable

and unfair criticisms by political figures and for the wrong reasons, threats by dissident employees disrupting normal administrative and corrective practices through pejorative leaks to press and Congressional staffers, lack of recognition for positive actions taken, inconsistent practices and standards among drug companies, etc.

The concentration of attention on the F.& D.A. regulatory impact on drug development has diluted concern with the more recent regulatory constraints imposed by the Environmental Protective Agency (E.P.A.). One can envision adding to the difficulties of new drug development if this agency implements regulations in a manner analagous to the F.& D.A.

The present drug regulatory climate is part of the legacy of political activities started by Senator Kefauver some 15 years ago, and intermittently revived or re-directed later by others. In most Congressional Committee hearings the Chairman, with considerable influence of staff, plays the major role in selecting specific issues and sources of testimony, and directing the lines of inquiry. The purported objectives of hearings invariably are identified such as not to be easily challenged in principle. Major difficulties result from differences among participants in training, experience, motivations, and value judgements.

In 1962, Senator Hubert Humphrey, Chairman of a Subcommittee on Reorganization and International Organizations, became concerned with, and initiated hearings on, the adequacy of drug literature coverage by the Industry. The importance of keeping up with the scientific-medical literature had been not only early recognized by the pharmaceutical industry but innovative steps taken to ensure such coverage. This became evident in the testimony. In 1963, the same Subcommittee held hearings purportedly to review cooperation on drug policies among F.& D.A., N.I.H., V.A. and other government agencies. To an excessive

degree, and with benefit of hindsight, the thrust of the testimony was critical of F.& D.A. and the drug industry.

In 1965, Senator McClellan, Chairman of a Subcommittee on Patents, Trademarks, and Copyrights held hearings on patent policies, possible changes, and the relationships to research, including pharmaceutical. The deliberations provided a fair representation of different views and appeared to objectively search for resolutions in the public interest.

Congressman L. H. Fountain, Chairman of the Intergovernmental Relations Subcommittee of the Committee on Government Operations, and his staff, held a variety of hearings on activities of N.I.H. bearing on health research. The administration of research grants by N.I.H. was subjected to criticism in hearings held in 1967. The censure by that Subcommittee was in sharp contrast to the tenor of the 1966 hearings before Congressman John Fogarty, Chairman of the Subcommittee on Depts. of Labor and Health, Education and Welfare and Related Agencies Appropriations. Health research administration grew as a political issue.

Congressman Fountain and his staff also have criticized specific F.& D.A. decisions and actions. These have included medical science value judgements for which some opposing opinion usually can be found. Criticisms of this kind can result in subsequent regulatory over-reaction as demonstrations of toughness.

For a number of years, Senator Gaylord Nelson, Chairman, Subcommittee on Monopoly of the Select Committee on Small Business, and his staff, have held a variety of hearings on drug prices, product quality, and drug delivery. Criticisms have been made that in its pursuit of issues, the Subcommittee appears to select witnesses in accordance with their value in supporting predetermined conclusions. The Wash-

ington leadership of A.Ph.A. has been particularly close to this Subcommittee.

The most recent venture into hearings on drugs has been that of the Subcommittee on Health of the Committee on Labor and Public Welfare, Senator Edward Kennedy, Chairman. Following a speech at the annual meeting of A.Ph.A. in 1973, largely critical of the pharmaceutical Industry, Senator Kennedy initiated hearings later that year. The Subcommittee has provided an opportunity for various views and positions to be heard; however, in balance,selections have leaned toward witnesses critical of Industry and of F.& D.A.

An encouraging sign was the assignment of the drug product quality and bioequivalence issue to a review by a scientifically competent panel reporting to the Congressional Office of Technology Assessment. The resulting "O.T.A. Report" on Drug Bioequivalence, notwithstanding the imperfections of a rushed job, was a noteworthy approach. Disappointingly, the hearings on the Report were diversionary rather than analytical and its messages may be muffled. Other hearings in the Summer of 1974 also were disappointing. Sessions held purportedly to assess the new drug lag were diverted to harsh attacks on F.& D.A. by dissidents.

New legislation, to-date, has not been enacted from these more recent proceedings. However, the proposed Maximum Allowable Cost (MAC) program of H.E.W. could result in maximum allowable interpretations of drug product quality by F.& D.A., considering its rejection of O.T.A. Committee allegations. The M.A.C. proposal, as it stands, was hastily conceived of political parentage and born with genetic deficiencies in economics and science. It could have a major impact on the future of Industry support for R.& D., the practice of pharmacy, and the quality of drugs delivered to the public.

A most recently proposed F.& D.A. regulation is that covering Freedom of Information. This merits scrutiny not only by Industry, but by all health professionals and scientists. Industry and its scientists may find serious constraints on their future freedom to communicate new information for fear of then permitting F.& D.A. at its sole discretion to divulge considerable other data which in the past has been held to be proprietary. The incentive to create new drugs or improvements becomes blunted when detailed informational results of the investment are made available to anyone else at no expense. Maximum allowable interpretation of these proposed regulations would be highly disruptive.

Drug regulations initiated in the U.S. have been emulated in Canada, but appear to be applied more rationally there. U.S. regulations have resulted in the channeling of some R.& D. overseas. U.S. based companies remain at a competetive disadvantage in that drugs cannot be manufactured in the U.S. for export in compliance with the recipient countries regulations only, but must have F.& D.A. regulatory approval as per U.S. requirements as well.

Among sources of political pressures are consumer advocate groups. These adopt attractive public image group names and pursue matters that are uncontestable in principle. Granting them the best of motives, the temptation to take on all issues and their superficial familiarity with complex problems can do more harm than good. One of the more ill-conceived criticisms and proposals was that of the so-called Health Research Group whose unrealistic recommendations on new drug testing, if implemented, would be disastrous to drug development and clinical research in this country. Another group, called the Council on Economic Priorities, has prepared reports illustrative of how limited understanding of the issues and misinterpreted informational resources can lead to misleading conclusions.

The lay press is the principal vehicle through which the public receives current information. Political figures and self-styled consumer advocates have an overwhelming advantage over others in having their opinions disseminated. The pharmaceutical industry and physicians who were lauded by the press a generation ago for their contributions to therapeutics, today are more likely to be disparaged. Even the scientist is more tolerated than well regarded. The F.& D.A. also does not have a good press. In general, news reports on pharmaceutical issues have been more objective than have columnists featured articles which tend toward the sensational.

With drug products, there also are moral questions involving legal and economic issues that are politically sensitive. Public policy now considers health care as a right. We are still left with the question of how much of this right can any government satisfy with resources that are not limitless. Drug costs per se are a relatively small part of total costs of health care and are unlikely to place a political strain on obligations vs economics. Drug development raises a variety of politically sensitive moral issues. To whom do we administer investigational drugs to determine their safety and efficacy? Are prisoners, corporate employees, medical students - all free agents to volunteer for such studies? How can we prevent abuses, yet retain a system of volunteer testing? Do we interfere with a persons civil liberties by denying him the opportunity to volunteer? How informed can informed consent be? When is it wrong to administer placebos to patients who are treatable? How do we avoid making children "therapeutic orphans" and pregnant women "therapeutic widows" unless they are given new drugs? These are complex problems. The regulatory agencies so far have helped us little in their resolution, and political figures only added confusion. Research for discovery also poses moral questions, such as how limited resources are to

be allocated among programs pointed toward different disease targets. How is the importance of a drug product goal to be determined in relation to economics and the individual?

CONCLUDING REMARKS

The variety of subjects touched on in this article makes it impossible to present details in the text space available. A bibliography is provided from which more information is obtainable on matters discussed, as well as on related issues not covered. References are included to opposing views. Some of the observations are drawn from personal experiences or those of acquaintances.

This article has attempted to identify some currently relevant problem areas in the complex multi-disciplinary drug discovery, development, and delivery processes.

Most of the issues referred to are interdependant to a greater or lesser degree and may appear isolated only when viewed from a narrow perspective of interests or a limited time frame. Individually, we might be well advised to expand our ranges of interests, concern, and actions - after adequate familiarization with the issues.

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