SIGNIFICANT DRUGS OF LIMITED COMMERCIAL VALUE

REPORT OF

INTERAGENCY TASK FORCE

TO THE SECRETARY
OF
HEALTH, EDUCATION, AND WELFARE

JUNE 29, 1979

JUNE 29, 1979

Significant Drugs of Limited Commercial Value

Report of

Interagency Task Force

to the Secretary of Health, Education, and Welfare

June 29, 1979

TABLE OF CONTENTS

FOREWORD i

TASK FORCE MEMBERS AND CONSULTANTS iii

SUMMARY 1

INTRODUCTION 4

1. PROBLEM 7

   A. Immediate Concerns 7
   B. Background 10

2. DEFINITION 19

   A. General 19
   B. Illustrations 21
   C. Updating 22

3. ISSUES 24

   A. Economic 26
   B. Scientific 33
   C. Legal 37
   D. Administrative and Decisional 50

4. INCENTIVES 57

   A. Principles 59
   B. Incentives 62
   C. Summation 73

5. MECHANISM 74

   A. Core Elements 74
   B. Board Structure 74
   C. Concept and Procedure 77
   D. Evaluation 80
   E. Implementation 81

APPENDICES

A. Environmental Protection Agency Pesticide Programs, Federal Register
B. Interim Report of the Committee on Drugs of Limited Commercial Value
C. List of Drugs Deemed of Limited Commercial Value

A. Environmental Protection Agency Pesticide Programs, Federal Register
B. Interim Report of the Committee on Drugs of Limited Commercial Value
C. List of Drugs Deemed of Limited Commercial Value

Foreword

The Interagency Task Force on Significant Drugs of Limited Commercial Value offers this report for consideration, support and action by individuals and associations who are concerned with the public health problem engendered by inadequate resources directed to the research, development, and distribution of drugs of limited commercial value. The Task Force offers concrete suggestions, many of which can be implemented immediately, and others which require new legislation.

This Task Force, voluntarily initiated, consists of members who volunteered their services because of their interest in resolution of the problem. Although all members made significant contributions, special thanks are due to Dr. Irving J. Ladimer who wrote this report in a manner both highly informative and eloquent; the report is based not only on the individual reports compiled by the subcommittees of the Task Force but on Dr. Ladimer's extensive knowledge of the issues. Special thanks are also due to Dr. Peyton Weary, Chairman of the Subcommittee on Incentives, for his many innovative recommendations and his extraordinary enthusiasm in seeking a resolution of the problem.

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs,
Food and Drug Administration

and

Chairman, Interagency Task
Force on Significant Drugs
of Limited Commercial Value

and

Chairman, Interagency Task
Force on Significant Drugs
of Limited Commercial Value

INTERAGENCY TASK FORCE ON DRUGS OF LITTLE COMMERCIAL VALUE

MEMBERS

Marion J. Finkel, M.D., Chairman
Associate Director for New Drug Evaluation
Bureau of Drugs
Food and Drug Administration

John S. Purvis, Executive Secretary
Supervisory Consumer Safety Officer
Division of Neuropharmacological Drug Products
Bureau of Drugs
Food and Drug Administration

John Adams, Ph.D. (Liaison)
Vice President
Scientific and Professional Relations
Pharmaceutical Manufacturers Association

Victor Berlin, Ph.D.
Program Analyst
The Institute of Computer Sciences
and Technology

Bruce J. Brennan, Esq. (Liaison)
Vice President and General Counsel
Pharmaceutical Manufacturers Association

Captain William H. Briner (Consultant)
Associate Professor of Radiology
Department of Nuclear Medicine
Duke University Medical Center

Thomas N. Chase, M.D.
Director, Intramural Research Program
National Institute of Neurological and
Communicative Disorders and Stroke
National Institutes of Health

Anne Harrison Clark
Columbia, Maryland

National Institutes of Health

Anne Harrison Clark
Columbia, Maryland

John S. Crotty, M.D.
Division of Oncology and Radiopharmaceutical
Drug Products
Bureau of Drugs
Food and Drug Administration

Paul Fehnel, Chief
Precedent Regulations and Legislative
Activities Branch
Bureau of Drugs
Food and Drug Administration

Peter L. Frommer, M.D.
Deputy Director
National Heart, Lung, and Blood Institute
National Institutes of Health

Sam T. Gibson, M.D.
Assistant to the Director
Bureau of Biologics and
Director, Division of Biologics Evaluation
Food and Drug Administration

Ronald Kartzinel, M.D.
Director
Division of Neuropharmacological Drug Products
Bureau of Drugs
Food and Drug Administration

Robert Katz, Ph.D.
Metabolic Disease Research
Program Director
National Institute of Arthritis, Metabolism
and Digestive Diseases
National Institutes of Health

Irving Ladimer, S.J.D. (Consultant)
Program Director
Health Services and Medical
Malpractice Program
Research Institute of the
American Arbitration Association

Norman Latker, Esq.
Chief, Patent Branch
Department of Health, Education, and Welfare

Jerome Levine, M.D.
Chief, Psychopharmacology Research Branch
National Institute of Mental Health, Alcohol,
Drug Abuse, and Mental Health Administration

Herbert C. Mansmann, Jr., M.D. (Consultant)
Director, Division of Allergy and
Clinical Immunology
Jefferson Medical College

J. Kiffin Penry, M.D.
Professor of Neurology and Associate
Dean for Neuro-Sciences Development
Bowman Gray School of Medicine

Michael A. Peskoe, Esq.
Associate Chief Counsel for Drugs
Food and Drug Division
Food and Drug Administration

Charles M. Peterson, M.D. (Consultant)
Associate Professor in the Laboratory
of Medical Biochemistry
Rockefeller University

Saul A. Schepartz, Ph.D.
Deputy Director, Division of
Cancer Treatment
National Cancer Institute
National Institutes of Health

Myron G. Shultz, DVM, M.D.
Director, Parasitic Diseases Division
Bureau of Epidemiology
Center for Disease Control

Richard A. Terselic
Director
Office of Planning and Evaluation
Bureau of Drugs
Food and Drug Administration

Peyton E. Weary, M.D. (Consultant)
Professor of Dermatology
University of Virginia
Medical Center

Summary

The development of significant drugs of limited commercial value represents an activity in the public interest calling for the combined support of government, industry, voluntary organizations and others concerned with health care. In our society, it should be possible to provide assistance to small groups of patients as well as to the general population, and to encourage research on medical problems of limited scope which may later have great beneficial effect.

Nevertheless, many significant drugs essential for diagnosis or treatment are not available mainly because research, development and production are deemed too expensive relative to expected economic return. As a result, important groups of patients, some critically ill, and scientific efforts devoted to rare or exotic conditions receive no support from either public or private resources. To assure development of essential drugs which may not be profitable, a voluntary program based on administrative and economic, scientific and legal incentives is proposed.

The program is directed mainly to the private sector to encourage drug development by individual pharmaceutical companies, non-profit organizations or consortia. The federal government, primarily as catalyst, would provide through purchase, loan or contract some financial subsidy or credit under individual negotiated agreements as well as priorities in new drug application review and recognition of suitable organizational arrangements for drug development. Incentives such as tax advantage, patent rights and certain anti-trust exemptions might be later available under proposed legislation where deemed in the public interest. Federal

or credit under individual negotiated agreements as well as priorities in new drug application review and recognition of suitable organizational arrangements for drug development. Incentives such as tax advantage, patent rights and certain anti-trust exemptions might be later available under proposed legislation where deemed in the public interest. Federal

assumption of product liability or payment of insurance costs are also included as available options where deemed essential.

The general principles governing the selection of the incentives include the concept of team effort involving the government as well as all concerned interests; primary emphasis on the private sector; proportionate burden for the patient populations most likely to benefit; administrative simplicity and flexibility; and assurance of capability of performance. Above all, the principle of integrity is stressed:

> "Above all else, no incentive shall be requested or provided to any sponsor which may result in diminishing the safety, effectiveness, adequacy or other integral component of the drug or its application for the purpose and the population for which it is intended. The essential conditions and requirements of the drug approval process must be met, although priority and other assistance may be given to drugs classified and approved as significant, but of small commercial value."

The role of the federal government is seen largely as that of facilitator or " 'broker' with broad powers to negotiate on behalf of the public interest rather than as subsidizer or drug developer."

An independent board, advisory to the Secretary of Health, Education, and Welfare, through the Commissioner of Food and Drugs, would be established to recommend policy. The board would review applications from commercial and non-commercial sponsors. Individual negotiations would result in agreements including specified incentives for the performance of research, development or other activity to assure the availability of drugs which

and non-commercial sponsors. Individual negotiations would result in agreements including specified incentives for the performance of research, development or other activity to assure the availability of drugs which

might otherwise not be produced or distributed. The board would have at least nine members and be fully representative of public and private interests and necessary specialties. It would be supported by the scientific expertise and resources of the Food and Drug Administration and other units of the Department of HEW as well as the cooperation of the drug industry.

Contracts negotiated under this program would be reviewable and subject to renegotiation so that profits or other advantages obtained through the incentives would be in part shared with or returned to the U.S. Government. The board would seek to encourage voluntary industry action as a matter of public interest and would also accord appropriate recognition to firms which participate on the basis of humanitarian concern.

The board's activity and the entire program would be periodically evaluated, in part with the objective of possible relocation of the board to independent auspices.

The Task Force urges immediate initiation of this program to test interest and operation, and to determine how to frame legislation. There is sufficient existing authority to stimulate voluntary action now and to provide essential administrative and selected economic incentives.

Introduction

This Report distills the discussions and recommendations of the Interagency Task Force on Significant Drugs of Limited Commercial Value. This Task Force was originally convened by the Bureau of Drugs of the Food and Drug Administration in March 1978. It was charged to review previous reports by similar committees, such as the Interim Report of the Committee on Drugs of Limited Commercial Value, May 14, 1975 (Appendix B), and to propose a policy, action and means to meet the recognized problem of inadequate resources and motivation for development and distribution of useful drugs deemed to have little or no commercial interest. The Task Force included most of the original members of the Committee on Drugs of Limited Commercial Value which produced the Interim Report of 1975, other interested individuals from various agencies of HEW, representatives of FDA advisory committees, three consultants (scientific, economic, legal) and liaison persons from the pharmaceutical industry. The Associate Director for New Drug Evaluation, Bureau of Drugs, FDA, served as chairperson. Appointed members of the Task Force and its consultant and liaison groups served on specific subcommittees to consider the scope of the problem, incentives, mechanisms, legal issues and general recommendations.

The problems and issues presented by such drugs are long standing, with attention given to them for well over a decade. (Similar issues have been considered with respect to other products and services.) The immediate and critical concerns, however, in part associated with greater

immediate and critical concerns, however, in part associated with greater

public responsiveness, with drug reform and with health consumer activism, call for specific, direct and acceptable action on the part of government, industry, the scientific community and public service and voluntary health agencies. Briefly stated, there is a well substantiated need for drugs and chemical entities, already identified and in various stages of readiness, which are not being made available to meet diagnostic, prophylactic and treatment requirements because there is no discernible profitability at a level commensurate with research, development and marketing costs. But it is equally recognized that there is a general public interest in providing health assistance through drugs as well as other means for relatively small population groups, particularly where the condition or disease may be serious, even fatal. A nation which can call on private and public concern and resources for other needful and significant purposes, whether helping many or few, can and should be able to supply essential drugs.

The Task Force does not consider it necessary to document this premise of need, since other groups and individuals have already done so; accordingly, it concentrates on the means for achieving fair and manageable resolution through reasonable incentives and a workable process for encouraging production of safe and effective drug products.

For the most part, the recommendations emphasize what can be done now, under existing legislative and regulatory authority and administrative structure and with voluntary cooperation, mainly between government and the pharmaceutical industry. The Task Force believes that, despite the

now, under existing legislative and regulatory
structure and with voluntary cooperation, mainly between government and
the pharmaceutical industry. The Task Force believes that, despite the

recognized difficulties, feasible solutions are at hand; and an earnest willingness to proceed, essentially as outlined, can finally make significant drugs of limited economic interest available and helpful.

1. Problem

A. Immediate Concerns

Although there has been interest for many years in problems of inadequate resources and motivation for the development and distribution of useful drugs of limited commercial value, recent requests from patient groups, from scientists and from voluntary and public agencies have created current impetus for action. In the United States, the public voice can be eloquent; and when it speaks of patient need and known but unavailable remedies, such pleas are heard. They are bound to evoke response. Health issues have captured the public's interest, in part because of national concerns for care and cost, and in part because of highly publicized hazards.

Early Interest:

Perhaps the first organized attempt to deal with the problem of special patient need and inadequate resources for development and distribution of useful drugs of limited commercial value was the voluntarily initiated DHEW Interagency Committee on Drugs of Limited Commercial Value. This Committee was established in 1974 and sponsored by the Food and Drug Administration which, for some time, had dealt with these matters on an informal basis. The Interagency Committee in its "Interim Report" of 1975 described the problems, principally those concerned with definition; the availability of governmental and industry support; and legal and insurance issues, and mentioned various potentially useful administrative mechanisms mainly based on economic incentives. Essentially, the report suggested that more definitive study be undertaken. It was not until March 1978, however, that a new Task Force was convened, again voluntarily,

the availability of governmental and industry support; and legal and insurance issues, and mentioned various potentially useful administrative mechanisms mainly based on economic incentives. Essentially, the report suggested that more definitive study be undertaken. It was not until March 1978, however, that a new Task Force was convened, again voluntarily,

composed of most of the original Committee members, other advisors within and outside the agency, representatives of the pharmaceutical industry and special consultants.

Additional Interest:

In 1977 and 1978 considerable interest in this subject became evident through:

1. A report in 1977 by the Office of Technology Assessment (OTA) to the Congress which devoted a chapter to the problem of drugs of little commercial value. That report indicated that the problem had existed for some time but had not received adequate attention, and that the needs of a number of groups would not be effectively met without a systematic study.

2. A report in 1977 by the Commission for the Control of Huntington's Disease and Its Consequences to the Secretary of HEW which recommended the immediate formation of a Task Force to propose solutions. This formal recommendation was and remains similar to those of other voluntary agencies and special disease organizations with small but vocal constituencies.

3. An appeal in 1977 by professional staff in the executive office of the White House to the Pharmaceutical Manufacturers Association to consider incentives in this area. In part, this request was motivated by the need to develop alternative therapies to meet the increasing problem of drug abuse in certain population groups.

4. A survey of its members, begun in 1978, by the Pharmaceutical Manufacturers Association, in response to the White House request and on

problem of drug abuse in certain population groups.

4. A survey of its members, begun in 1978, by the Pharmaceutical Manufacturers Association, in response to the White House request and on

its own initiative, to determine what the firms have accomplished in the area of research and distribution of drugs of limited commercial value and what are their future goals. A final report on this subject is in preparation.

5. Congressional inquiries in 1978 and 1979 to FDA and to this Task Force, largely based on requests from constituents. Also, general Congressional interest in drug reform legislation has included questions concerning the activity of the Department of Health, Education, and Welfare in providing drugs of significant but limited commercial value either through federal production or industry persuasion.

6. Considerable interest, beginning in 1978, by the then Secretary of Health, Education, and Welfare in the form of inquiry to FDA on what was being done to alleviate the problem.

7. Finally, the increasing frequency of articles in both professional and lay publications which have discussed the problem, and, in general, have been critical of the perceived lack of concerted action and purported lack of concern, but also have been constructive in suggesting innovative ways to meet the problem.

This demonstration of current and continuing interest suggests that the matter is no longer one for study. This Task Force has considered the various reports which have been prepared and has taken into account new approaches and particularly the evident interest of the Congress in solutions to the problem. In the view of the Task Force, the problem can be significantly ameliorated by incentives to industry <u>now</u> available and later through legislation specifically directed to this issue.

the various reports which have been prepared and has taken into account new approaches and particularly the evident interest of the Congress in solutions to the problem. In the view of the Task Force, the problem can be significantly ameliorated by incentives to industry <u>now</u> available and later through legislation specifically directed to this issue.

The obvious advantage of this approach is that it marshals interests and resources of all who are concerned and focuses on this problem in proper context.

B. Background

Provision of support to specific or limited enterprise through federal subsidy or promotion on behalf of the entire economy, national security, general welfare or other significant purpose is not new. In fact, it is a recognized policy of our Government to identify and aid small but significant concerns which affect the public interest of our people. Aid may range from direct cash payment to some type of tax advantage or preference, elimination of certain conditions or outright exemptions. Such assistance is rendered in many fields but it must be justified essentially as serving others as well. Any program for a few must be clearly recognized as contributing to many, within our general national purpose. Although the benefit or advantage need not be immediate or direct, the potential must be evident: positively, or protectively, such as maintaining existing activity or policy.

Any proposed program of inducements or incentives to encourage voluntary action for the development of drugs of significant value to small or specific groups must therefore be seen in this framework. Moreover, the establishment of any classification of such drugs as different from other drugs must also come within appropriate legal recognition.

Scope of Problem

A major consideration in justifying such a program is the size, character and implications of the problem. Prior studies conducted

recognition.

Scope of Problem

A major consideration in justifying such a program is the size, character and implications of the problem. Prior studies conducted

under auspices of the Food and Drug Administration, notably the inquiry by the Committee on Drugs of Limited Commercial Value, sought to determine the scope, namely how many patients might be at serious risk because of unavailability of such drugs; how many drugs at various stages of development are in this category; and the significance of these summations.

The Committee confirmed the existence of the problem but not necessarily its boundaries. For instance, extensive lists of drugs and chemicals were compiled on the basis of interviews conducted with representatives of industry, academic institutions and government; literature search; and an assessment of requests and petitions of voluntary health and special disease agencies. The Committee Report did not determine whether these, in total, constitute a public health problem but agreed that solutions were needed for the present and foreseeable future.

One of the major premises, as stated by the Committee, was

> "Although nowhere explicitly set forth, it is recognizable as underlying the thinking and effort on this subject: whenever a drug has been identified as potentially lifesaving or otherwise of unique major benefit to some patient, it is the obligation of society, as represented by government, to seek to make that drug available to that patient. Any qualifications of unstated policy, such as minimum number of potential beneficiaries or an unacceptably high ratio of cost to beneficial result, have not been determined."

not been determined."

This Task Force, although appreciative of the request for such data by earlier study groups, did not consider it absolutely essential to establish quantitatively the magnitude of the problem. All concurred that it would be recognized regardless of its size or scope, because of general understanding, grave implications and potential effect.

The Task Force also agreed on the difficulties of arriving at any meaningful figure. For instance, the 1975 Report notes that such drugs undergo a change of status, that is, may no longer be unavailable or of limited commercial value or may have been replaced by superior drugs. And, relationships between this country and others may permit use of drugs of foreign origin, many of which are customarily listed as of limited economic value in the United States. Further, new health strategies may achieve improvement through prevention or other forms of treatment. Judgments made by clinical investigators and others who are scientifically or therapeutically involved with drugs in this area may not be able to provide correct assessment of their commercial value.

Patients and their needs vary considerably, too. It is clearly impossible to calculate the number of persons who would be potentially benefited by a drug. Although in some instances reasonable estimates of the number of patients with a given uncommon disease may be made, diseases vary in their manifestations and response to therapy; furthermore, demand for a drug is frequently influenced by what is known of its availability and investigational efforts.

Seeking more data about the nature and size of the problem would prolong this study and postpone the critical determinations on policy, required incentives and the mechanism for decision making. Although it is true that certain incentives may be of greater or lesser consequence, depending on the character and breadth of the problem, the management of incentive aid on an individual case basis, as proposed by this Task Force (See Section 5. Mechanism), largely resolves this issue. This entire subject can and should be under constant study to ascertain changes in needs and availability, but basic decisions should not be deferred. Likewise, administration can and should be sufficiently flexible for meeting requests as they arise and providing assistance.* When seen as a dynamic process, it becomes less important to establish definitive facts and figures than to undertake appropriate action leading to a solution.

Past Activity

It should be understood that these studies have not precluded or prevented movement. There has been progress. The Department of Health, Education, and Welfare has informally facilitated the production of significant drugs of little economic value for many years and is still so engaged. For example, the perceived difficulties in obtaining FDA clearances for marketing of such drugs have been variously overcome by the development of a system of classification and the establishment of

* Earlier reports proposed public listings and active solicitation of requests for development of specific drugs. This Task Force concluded that general knowledge and appropriate promotion of the program would encourage petitions.

* Earlier reports proposed public listings and active solicitation of requests for development of specific drugs. This Task Force concluded that general knowledge and appropriate promotion of the program would encourage petitions.

drug group leadership to permit more expeditious negotiation and approval. Also, the FDA has gathered published and unpublished data on drugs of little commercial value and actively sought pharmaceutical company sponsorship of such drugs. In addition, it is possible, through FDA's investigational drug regulations, to employ drugs in various stages of research for therapeutic use. Drugs of this type, developed through Federal funding or facilities, are made available through the National Institutes of Health (NIH), as, for example, in the case of certain anti-cancer drugs, and the Center for Disease Control in the case of drugs for rare tropical or parasitic diseases.

Pharmaceutical firms often supply courtesy or service drugs either under an investigational new drug application or an approved application for marketing.

Program Development

Such prior and continuing actions, although responsive to recognized needs, are, with the exception of the program of the NIH's National Cancer Institute, essentially informal and occasional. Such arrangements do not represent a program based on policy, planning and systematic review and equitable case adjudication. In the case of the FDA its efforts at brokering pharmaceutical industry distribution of drugs of little commercial value are limited by the lack of any incentives to the industry for its participation other than its civic duty or self-image. And in the long run, reliance on this approach may provide a disservice because it deters organized efforts to resolve a basic problem. The

because it deters organized efforts to resolve a basic problem. The

Task Force concludes that the experience and advantages gained through informal arrangement should best be incorporated within a comprehensive and well-formulated program which will receive public recognition, support and promotion.

Pesticides for Minor Use

The only current analogous program of federal assistance to encourage research and development relates to the registration of pesticides for minor use. Under a joint program of the U.S. Department of Agriculture and, as lead agency, the Environmental Protection Agency, registration data requirements and tolerances may be modified to encourage the application of pesticides for special or minor uses.

The Federal Pesticide Act of 1978 amended the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) to permit registration data requirements "commensurate with the anticipated extent of use, pattern of use and the level and degree of potential exposure of man and the environment to the pesticide."* In tailoring registration standards for minor uses, the EPA is instructed to "consider the economic factors of potential national volume of use, extent of distribution, and the impact of the cost of meeting the requirements in the incentives for any potential registrant to undertake the development of the required data."

* Environmental Protection Agency, Pesticide Programs, Minor Uses: Policy Statement and Request for Information, Federal Register Vol. 44, No. 44, Monday, March 5, 1979, p. 12097.

* Environmental Protection Agency, Pesticide Programs, Minor Uses: Policy Statement and Request for Information, Federal Register Vol. 44, No. 44, Monday, March 5, 1979, p. 12097.

The object of the program is to make available previously registered pesticides for new or different uses, generally for minor crops, by adjusting tolerances of pesticide residues in order to stimulate distribution of such products through conventional commercial sources. These uses would otherwise not be considered because of economic reasons, that is, the cost of the research and development is deemed prohibitive for the expected sales volume.

This program has been in effect for a number of years but data of the type and quantity generally required for major use were also expected for minor uses, except that preference was given in terms of time, assistance through research supported by the Government, and waiver of certain fees. The 1978 statute for the first time legislatively recognizes this need, and provides that the required data may be modified essentially on the basis of anticipated use and potential human exposure. By regulation, existing data and studies can and will be applied, to the extent possible, thus largely eliminating additional substantiation. (A special study on this subject due June 30, 1979 will also include recommendations for other incentives such as registration exclusivity for ten year periods and other advantages.) The required research in support of minor uses has been and continues to be undertaken under Inter-Regional Project #4 (IR-4). Funds are supplied by the U.S. Department of Agriculture. This project is headquartered at Rutgers University which conducts research or arranges for its performance by any State Extension University or College or under contract with industry.

Petitions to the EPA are submitted to establish appropriate tolerances and are reviewed by the agency's scientific review staff which considers

Petitions to the EPA are submitted to establish appropriate tolerances and are reviewed by the agency's scientific review staff which considers

regular applications from companies. Scientific advisory councils and consultants are called on for technical advice. The registration, when approved, permits a change in labeling and thus application to new use.

In accordance with standard procedure, companies are required to submit data on effectiveness, adverse effects and certain economic information. However, there is no specific contract or agreement to assure that distribution as intended will be made or that there will be any recoupment by the Government in the event of profit.

In part, these problems are resolved upon renewal of registrations at five year intervals. At such time, the minor use registration may not be continued unless warranted.

Comment

Under this program the subsidy is indirect, that is, through providing support via government funding and through special administrative procedures. There is substantial reliance on industry and agriculture to carry out the intention of the program and thus relatively minor effort to monitor and seek compliance. There is no advisory or policy board or extensive staff for this program. This informality is possible in a comparatively small enterprise in which the major interests know each other and operate essentially through the same network, principally the agriculture extension service.

There is apparently no need under such a program for a series of incentives and for direct financial subsidy. Accordingly, many of the

There is apparently no need under such a program for a series of incentives and for direct financial subsidy. Accordingly, many of the

conditions applicable to drugs for human use and requirements of the pharmaceutical firms that provide such products are not directly relevant. The program, however, does illustrate the place of certain minor incentives for limited activity which can be provided on an administrative basis. It also demonstrates that legislative approval is possible for support of specific limited purposes in the larger public interest.

2. Definition

In order to decide whether a drug is eligible for the special considerations and incentives described later in this Report, it is necessary to establish criteria for acceptance for review.

A. General

The entity would be accorded special status as a significant drug of limited commercial value and its owners or sponsors would be entitled to apply for incentives and receive appropriate support or assistance if

The drug (or chemical) has a demonstrated scientific rationale and (1) is or appears to represent a unique diagnostic, preventive or treatment modality for a specific condition or disease, or (2) although not unique, provides a net advantage over existing agents for a defined patient subgroup

but is either not commercially available or not dependably available from any source because of one or more of the following circumstances:

a. Where there is proven advantage in diagnosis, prevention or treatment of a health condition or rare disease but (1) estimated volume of sale is deemed below the interest of commercial producers or (2) income potential is considered not sufficient to meet current investment criteria for commercial products.

b. Where availability is not due to lack of resources but there is absence of (1) dependable sources of manufacture or (2) assurance of high quality at all times, e.g., as where product has short shelf-life.

c. Where technology or other expertise required for adequate research, manufacture or distribution of the drug is beyond the economic capability of a commercial firm that would otherwise be able to make it available.

d. Where the usefulness of the drug must be further established, but the firm cannot meet the cost or conditions for achieving scientific and therapeutic acceptance, because of complex methodology, scarcity or unavailability to it of the target population, or perceived difficulty of regulatory compliance.

e. Where an interested sponsor or other qualified party cannot obtain legal or ownership rights for production or distribution of the drug.

f. Where manufacture, distribution or application of the drug creates potential liability which cannot be justified on humanitarian or profitability grounds.

Other Conditions

In addition to meeting the criteria for consideration on scientific and economic or related circumstances, as above, a drug, in order to

and economic or related circumstances, as above, a drug, in order to

qualify, must be presented by a responsible proponent or sponsor, such as a commercial pharmaceutical firm engaged in research, development, production, marketing or other distribution; a public health, medical, scientific or research agency; a scientist, physician or health organization capable of contributing to the research, development or distribution of the drug and appropriate use; or a voluntary health association or group which has, or can establish that it can obtain, resources for needed research, development, or distribution of the drug. Interest in a significant drug of limited commercial value, while creditable and commendable, is not sufficient to initiate an application for qualification. The burden is on the applicant for special incentive consideration to demonstrate not only interest and need but capability of meeting requirements for research, production, or distribution.

B. Illustrations

In the course of investigating the problem of drugs of limited economic value with significance for various disease conditions or population groups, several lists of drugs and chemicals were compiled. These are in effect candidates for special incentive consideration as significant drugs of limited commercial value under the definition and process set out in this Report.

The current lists were derived from previous committee reports; responses from public and private agencies concerned with drug research and development; FDA data on drug approvals, applications and investigational drug files; and literature searches of texts, journal articles and compendia (Appendix C). It is recognized that, using various definitions

responses from public and private agencies concerned with drug research and development; FDA data on drug approvals, applications and investigational drug files; and literature searches of texts, journal articles and compendia (Appendix C). It is recognized that, using various definitions

and criteria, many drugs listed may not fit the definition of this Report and, conversely, others not now listed will be added. For example, as noted earlier, the Pharmaceutical Manufacturers Association is developing a similar inventory based on industry reports.

The drugs offered in Appendix C are illustrative of the need for mechanisms to solve the problem of lack of availability of many drugs which might be useful to various patient populations; they are not intended as a list which must be tackled.

Although the drugs on any roster may be organized by stage of development, area of potential use in respect to disease or other health condition and number and characteristics of patients affected, other considerations are noted. Commentary on drugs listed includes such considerations as reported excessive cost for clinical study; lack of interest without better demonstration of effectiveness; interest in special patent protection for a particular entity; production by a single small firm or source without assurance of continued interest.

From such capsule information, it is possible to determine the major reasons offered for nonproduction and incentives requested and to establish categories for consideration of applications under the process later described. Thus, all drugs for which special patent consideration is requested might be reviewed as a group with respect to this issue to assure reasonable consistency in recommending patent or license arrangements or related treatment. Similar study could be given to drugs of foreign origin or use but not available in the United States.

C. Updating

The definition, lists of candidate drugs and the submitted reasons

origin or use but not available in the United States.

C. Updating

The definition, lists of candidate drugs and the submitted reasons

for their status are, of course, subject to constant review and update. The essential characteristic of this problem is change: recognition and inclusion of drugs in partial development for target or new uses; modifications of drugs for special use or particular population groups; use of established drugs for small groups or limited purposes; and changes in needs for incentives as drugs gain or lose profitability. With experience it is anticipated that the principle of seeking to assure availability of drugs for this special objective will be retained and strengthened but the categories and bases for consideration will vary. With this understanding, the means for incentive and mechanisms for consideration become especially important in public policy and administrative management.

3. Issues

Fundamentally, the production of drugs of substantial therapeutic potential which are deemed to be of limited economic value presents a public policy issue in the largest sense. Research, development, distribution and other efforts toward ultimate availability of such drugs require supra-market incentives. Normal competitive motivations must be supplemented by some stimulus or direct advantage beyond that generally expected in the free enterprise arena of pharmaceuticals. Stated otherwise, the economic risk and administrative burdens (costs) are perceived as far greater than that for other products at similar stages, and are likely to far outweigh returns (profits). Thus, something must be done to reduce anticipated costs or to increase estimated profits in order to reach the balance necessary for private sector action. (As discussed below,* the Task Force agreed that private initiative should be paramount, with appropriate public encouragement and limited financial support.)

In our economy, profit (however defined, even as qualified for public service or socially essential activity) is the driving force. The pharmaceutical industry, although especially sensitive and responsive both to general health needs and special or unusual requirements, nevertheless proceeds--and can only proceed--with some expectation of profit to assure continuing contribution. The problem presented by drugs of low or no economic gains must be viewed in this context, since there are admittedly no contemporary alternatives to drug development in the public or non-profit sectors, i.e., the latter do not offer the totality of scientific and managerial talent, facilities, risk capital and other

* See also Section 4. Incentives (Principles, No.4).

public or non-profit sectors, i.e., the latter do not offer the totality of scientific and managerial talent, facilities, risk capital and other

* See also Section 4. Incentives (Principles, No.4).

resources of comparable quantity or quality. (This is not to say, however, that public and non-profit organizations cannot contract for these services and become eligible for incentives to develop drugs of limited economic value, but it is logical to recognize that the pharmaceutical industry has all of the appropriate mechanisms in place.)

The issue is:

To permit the play of the market place to achieve availability of such drugs in due course (by virtue of change in profit estimates or requirements; better conditions for production; more favorable individual competitive advantage or financial support from special sources; or other options)

or

To provide specific, deliberate incentives to assure research, development and production of such drugs.

This is a policy decision to be made in the public interest, jointly devised by all concerned, ratified by elected officials and appointed representatives, and executed in government and in the private and non-profit areas. The public interest is, in this case, not alone general or universal; it also includes, most particularly, those special interests which contribute to and support society, and for which society may wish to provide special support. So seen, the issue calls for weighing the cost of scientific, economic, legal, administrative and decisional considerations against the societal benefits to be derived. The equation includes not only (a) known factors of research and medical requirements,

to provide special support. So seen, the
cost of scientific, economic, legal, administrative and decisional
considerations against the societal benefits to be derived. The equation
includes not only (a) known factors of research and medical requirements,

health needs and therapeutic gains and (b) economic requirements, but also (c) unknowns, such as capability of specific incentives, and effectiveness in actual use. Most of all, any policy decision here bears mightily on similar problems in our society of special need and limited resources or insufficient incentives. When and how does Government step in and, equally, how does it step out, when the problem can be otherwise resolved?

The Task Force, considering components of this issue, as described below, decided to recommend a comprehensive effort to achieve availability of drugs by encouraging sponsorship of such drugs by private industry and voluntary, non-profit enterprise and by providing carefully defined incentives, mainly through negotiated contract, to assure production in return for stipulated direct or indirect financial and other advantage. Government's role would be largely catalytic, managerial and supportive, with limited monetary or credit aid.

A. Economic

Assuming the economic premise that, in response to stockholder interests, a drug manufacturer will engage in the development, manufacture and marketing of a product line only when profitable*, the incentive to do otherwise must be based either on an expectation of future profitability or some contribution toward humanitarian or patriotic interests. These social purposes are, of course, well-known and often served, but cannot be considered significant, since companies cannot reasonably be expected to act in a systematic fashion in response to such appeals. It is too expensive to produce drugs mainly for psychic rewards.

* Individual items or services may not be profitable, but will contribute to a larger product series or program.

since companies cannot reasonably be expected to act in a systematic fashion in response to such appeals. It is too expensive to produce drugs mainly for psychic rewards.

* Individual items or services may not be profitable, but will contribute to a larger product series or program.

Pharmaceutical market:

Thus, the strict economic incentive remains as the principal consideration. The economics of the drug industry, while similar to those of other industries in the critical relationship between revenues and costs (i.e., profit sought is essentially the difference between gross sales and production cost), is substantially different in other ways.

First, drugs for human uses are produced to meet recognized or anticipated needs associated with the diagnosis, prevention or treatment of a disease. These needs do not always arise in orderly or regular series, nor do they remain over predictable periods. Accordingly, the industry must be prepared to act quickly and specifically "to save lives" or prevent serious injury, often without regard to any immediate economic consequences, in order to meet social requirements. This response may lead to substantial short-term economic loss or gain, which must be considered in terms of average return over a long period of time.

Second, the industry is not wholly independent in respect to other factors. For example, the number of physicians, the number of hospitals, advances in technology, growing awareness by physicians of the need to treat definitively certain diseases, as well as political and scientific changes have a very direct influence on the volume and type of drugs needed

treat definitively certain diseases, as well as political and scientific changes have a very direct influence on the volume and type of drugs needed

and thus developed and marketed. Also, the industry is dependent on outlets which it cannot govern or control such as pharmacies, hospitals and public programs.

In essence, although economic policy may reflect social policy, economic values do not necessarily reflect social values. That is, socially desirable activities to encourage health wherever possible and to prevent or cure disease, no matter how many or few may be involved, will not necessarily be commensurate with dollar return for such efforts.

Finally, the overriding problem faced by the large and progressive drug company today is the risk capital or "up-front" cost of research and development, regulation and monitoring. Today, no drug can be produced at small cost. Therefore, most drugs are produced for the mass market rather than the specialized interest. Low-profit drugs for uncommon diseases or for narrowly defined populations will rarely be the subject of research or study, will generally not be produced and, if available, will often not be distributed.

To some extent, these drugs are the ones most needed by disadvantaged groups who have the least economic market power. Thus, the drug of small economic value is also the drug which is associated with a type of discrimination.* In consequence, such drugs cannot be priced at a level high

---

* This refers generally to unavailability of a drug due to the inability to pay directly or indirectly, influenced in part by the handicap of disease, rather than to discrimination due to the customary ethnic, geographic or social differences, although these may present some parallel. Thus, victims of some diseases may become impoverished thereby and present social but not economic demand.

nation.* In consequence, such drugs cannot be priced at a level high

---

* This refers generally to unavailability of a drug due to the inability to pay directly or indirectly, influenced in part by the handicap of disease, rather than to discrimination due to the customary ethnic, geographic or social differences, although these may present some parallel. Thus, victims of some diseases may become impoverished thereby and present social but not economic demand.

enough to yield a balanced profit, since that would preclude any reasonable volume of sales. An alternative is to provide government payment or special third-party payment, such as already accomplished for patients requiring kidney dialysis and transplantation or for victims of black lung disease. (These are exceptions to the accepted economic principle that conventional demand creates supply; here the demand was to some extent politically supported and subsidized to achieve supply.)

Regulation; Information and Promotion

Associated with the up-front costs are the particular problems of regulation and information. The drug industry is directly and strictly regulated from the technical standpoint because of the nature of the product and the facilities used. Because of government reimbursement for prescriptions under Medicaid indirect regulation of prices of drugs is achieved under HEW's Maximum Allowable Cost (MAC) Program; in addition, Medicare utilizes the MAC Program as a guideline in its reimbursement policy.

The ethical drug industry, unlike others, is highly dependent on intermediaries: the scientific and medical professions, hospitals and public and voluntary agencies, among others. Drugs and pharmaceuticals are not sold directly to the public, the ultimate consumer, but must be prescribed. Their bulk purchases are often controlled by formularies and local or institutional regulation. Thus, drug companies must spend a disproportionate amount on specialized education, information and advertising to assure effective use and sale.

local or institutional regulation. Thus, drug companies must spend a disproportionate amount on specialized education, information and advertising to assure effective use and sale.

Despite such requirements and consequent high cost, the industry is highly competitive. Thus, each company must be essentially opportunistic, move rapidly and effectively and yet be prepared for erratic and uncertain demand. Marketing in the drug field is extraordinarily complex and must take into account possible and probable demand based on all of these factors as well as the considerable problems of distribution, inventory maintenance and control (e.g., packaging, dosage forms, substitutions, shelf-life), possible recalls and, today, special legal and liability problems.

Changing the Marketplace:

In light of all of these considerations applicable to the pharmaceutical economy, it is only reasonable that drugs which are not considered profitable by the marketing specialists would rarely be produced in any substantial volume. They certainly will not be available, without incentive, on a regular basis even in response to recognized significant (but relatively small) therapeutic need. The fact that a drug will "save a life" will not markedly change the situation. This attribute is no substitute for direct or indirect dollars, absent some subsidy or method of selling so that "the price is right" for every needed drug.

An alternative inducement suggested would allow some type of anti-trust exemption for companies willing to produce significant drugs of small

trust exemption for companies willing to produce significant drugs of small

or no profit. Or should other perceived restraints be lifted? In other words, would the priority for significant drugs of small economic value justify changing the pharmaceutical marketplace? And, if so, how could this be circumscribed so that it meets the national interest but does not run counter to that interest?

If some priority is given to such drugs, from what source will resources for development come? At present, all reasonable or available resources are presumably used for commercially profitable drugs. What company would therefore wish to sacrifice present profit for a questionable undertaking, even in the higher public interest? What circumstances would induce a company to assign a scientist, a facility or a distributor for the production of a low economic drug unless there were some prospect of future advantage? And, if a future advantage were recognized, with subsidy, would resources have to come from an existing pool, or would there be another source? Specifically, more federal dollars do not produce more skilled manpower nor are they sufficient to provide for the additional facilities needed for production.

Within this economic framework, is it still possible to meet the need for the development and distribution of significant drugs of limited economic value?

Yes.

economic value?

Yes.

First, there is flexibility within a single company and, even if this is not available, cooperative arrangements among companies not otherwise possible might be justified. (See Section 4. Incentives, Principle 10).

Second, because of benefit/risk considerations, requirements for development and scientific clearance, such as toxicologic and clinical testing which are now very expensive for staff, technology, facilities and other resources, might be made less encompassing.

Third, involvement of other interests such as voluntary agencies and special government assistance can add dimension and support which are not usually available in the conventional drug development process. These are resources not drawn from the companies and thus should not limit their concern and investment in other drugs.

Finally, since, under the Task Force proposal, drugs of limited economic value will be developed in response to specific, small but certain demand, there is virtually no likelihood of market failure. If there is change, it should be in the direction of profit gain.

In sum, with special incentive consideration as recommended by the Task Force, the development of drugs of limited economic value can be maintained as a private enterprise within the pharmaceutical marketplace.

maintained as a private enterprise within the pharmaceutical marketplace.

The role of government would be essentially catalytic and cooperative but not preemptive or disruptive of any recognized industry function.

Planning, production and other contributions by private industry representatives or associations or by individual companies would likewise be supportive. If successful, the Task Force proposal would phase in a system of assistance for important but low-income pharmaceuticals which, in time, would become part of the standard productive capacity of the industry. In turn, their success would permit a regular flow of similar beneficial drugs.

B. Scientific

There can be no consideration of drug development, with or without inducements, unless there is in fact some assurance that drugs deemed significant for these special purposes actually exist or that the current stage of research, development or application clearly indicates that the drugs can be produced. The need for a therapeutic agent obviously does not produce it.

In this area, certain groups of patients, generally through their special health organizations, have claimed that there are potentially helpful drugs which are not available to them. Or scientists who have

special health organizations, have claimed that there are potentially helpful drugs which are not available to them. Or scientists who have

promising leads maintain that they cannot obtain support for further research or development because the market for the drug is too small to warrant such support. In the same vein, drugs used abroad are sometimes not available in the U.S. despite an apparent market because it is asserted that the clearance processes of the Food and Drug Administration are too time-consuming and costly.

Regulatory Requirements for Investigation and Marketing

It is often stated by proponents of drugs that are not available, whether for economic or other reasons, that the difficulties of meeting FDA's Investigational New Drug or New Drug Application requirements are too great. The argument is made that a drug of limited application need not be (and often cannot be) submitted to the extensive pharmacologic and clinical studies mandated for standard products. Since the target is a small, specialized population, opportunities for extensive clinical trials or for comparative studies may be impossible.

The proponents urge that the scientific requirements be made more flexible and substantially less demanding. This plea often comes from scientific investigators and other professional advocates. They suggest that such drugs should be made available not so much at the cost of less therapeutic efficacy or greater possible toxicity, but rather on the basis

of minor risk, if any, based on fewer tests or shorter, less extensive, developmental and evaluative processes. In short, it is submitted that the importance and significance of the drug may justify a change in procedure. This parallels the concept that the greater the possible benefit, the greater the allowable risk. (The target populations for the drugs, i.e., the patients themselves, and their representatives, have yet to express themselves on whether they would be willing to accept an increased risk, e.g., an uninvestigated potential for carcinogenesis, for the benefit of immediate therapeutic gain from the drug.)

Whether such modifications in philosophy and scientific procedure can be rationalized on the ground of the public interest remains a basic policy question which perhaps can only be addressed in individual cases. The Task Force agreed that <u>fundamental</u> scientific requirements could not be impaired or abridged because of the relative cost of studying such drugs. Benefit/risk considerations in the treatment of serious diseases, however, do warrant some <u>modifications</u> of the requirements that must be met for marketing approval of drugs for these conditions. For example, the realities of the situation are such that limited patient populations are available for study of the drugs at issue. Thus, the smaller the number of patients involved in the clinical investigations the lesser the certainty of degree of risk involved in taking the drugs. The advantage of use of drugs in life threatening or very seriously disabling diseases may, however, offset any potential disadvantage that, after

the certainty of degree of risk involved in taking the drugs. The advantage of use of drugs in life threatening or very seriously disabling diseases may, however, offset any potential disadvantage that, after

prolonged use, for example, the drugs might prove to pose a certain risk of malignancy, a risk which had not been adequately studied prior to marketing because it was felt that release of the drug was more important than delay to seek support for and to conduct tests for potential carcinogenicity in animals. (It is not necessary, nor is it desirable, for scientists alone to make benefit/risk decisions based on data which are less extensive than those gathered for drugs intended for widespread use. When significant drugs of limited commercial value are released for marketing without certain tests, or with postponement of such tests, ordinarily required under FDA's policies and guidelines, the conveying of such information to patients or their representatives will permit them to participate in the decision to use such drugs.)

In addition to some pragmatic modification of requirements for approval of drugs of limited commercial value for treatment of serious diseases, steps can be taken to accord such drugs administrative priority. This would recognize the special concern of the Government and others in promoting their development and distribution as soon and as effectively as possible. Several steps, now available, can be taken which would reduce clearance and follow-up costs: early discussions between FDA staff and sponsors; careful tailoring of documentary requirements to the purposes and claims of the drug; expeditious handling within the FDA; and, where possible, use of prior data and pertinent studies.

The Food and Drug Administration has in the past promoted and currently advances special consideration for drugs of primary concern, either because of major therapeutic significance or public health interest. The legislation, regulations and administration are sufficiently flexible to permit reasonable latitude. It is known to a certain segment of industry, particularly to that segment which has sought marketing approval for humanitarian purposes of drugs of limited commercial value (or which has been approached by FDA to market such drugs after FDA has independently gathered the scientific data available to establish safety and effectiveness), that FDA accords priority review and tailors requirements for marketing to the circumstances in which and the indications for which the drug will be used. Nevertheless, because this is not widely known and because specific guidelines are not available on when such modifications will be entertained, the Task Force considers it desirable that FDA publicize, perhaps through a regulation, the technical requirements which are needed for research and marketing approval of drugs of limited commercial value.

C. Legal

Legal considerations encompass two broad areas: (1) potential liability in the development and marketing of these special drugs and (2) options now available or to be sought to provide legal protection for some type of exclusivity (e.g., patents, data) or exemption (e.g., disclosure).

available or to be sought to provide legal protection for some type of exclusivity (e.g., patents, data) or exemption (e.g., disclosure).

Liability:

The potential legal liability or even threat of suit based on the development, distribution or use of significant drugs of limited commercial interest would seem at this time to be essentially similar to that of other drugs. No distinction under case law or statute is made by type of drug or sponsor, although there are differences, as always in this country, based on jurisdiction and, in some respects, based on sponsor, i.e., private versus public. The only significant federal intervention has occurred in the case of swine flu legislation (P.L. 94-380, 1976) which applies to a mass immunization, basically different from the essentially conventional process intended for significant drugs of limited commercial interest. Under this law, the Federal Government stands as defendant in claims filed under the Federal Tort Claims Act, as amended, with right to proceed against manufacturers for their negligence or failure to comply with certain provisions. The Government bears the burden of explaining risks and obtaining consent.

Burden of Demonstrating Difference

To develop a special protection plan for the drugs subject to this program might raise major administrative, legal and doubtless legislative problems as well as policy and political issues.

problems as well as policy and political issues.

Among others, a difference in treatment in this respect (such as acceptance of liability in whole or in part by the Government or limiting recovery under a type of no-fault plan or some form of exemption) would have to be justified by a showing of likely greater vulnerability or greater cost (insurance, investigation or other expense) for such drugs. Even if these could be shown, it would further have to be demonstrated that the difference constitutes an impediment of such magnitude or potential that it serves to discourage industry from consideration of non-economic drugs, with resultant public detriment. Relative to other industry disincentives, professional or product liability or its implications would have to be substantial. In effect, it would be necessary to find that, no matter what other changes were made or incentives offered, the issue of liability remains as a serious obstacle.

It is entirely reasonable to require a very grave justification, well supported, since the solution would likely involve some form of government participation, waiver or special consideration on behalf of manufacturers, distributors and perhaps others. Any such advantage, whether through Federal assumption of liability, sharing in insurance cost, indemnification or tax write-off (to mention several options), would have to be reviewed in light of general policy to assist particular groups deemed to be serving the public interest. Inevitably, there would be the argument that such action would invite similar requests for other special or worthy interests in health or in other fields.

the public interest. Inevitably, there would be the argument that such action would invite similar requests for other special or worthy interests in health or in other fields.

Legal and Legislative Problems

The liability problems thus fall into two classes:

(1) Establishing a sound basis for special treatment of this risk.

Constitutional cases have clearly established the need for justifying on emergency, special public interest, or non-discriminatory grounds any legislation or administrative action that would treat one category of legal action differently from others in the same class. Whether the bases for difference with regard to the drugs at issue are such as to support a general distinction is, at this stage, doubtful. If accepted in principle, there are other issues. For one, members of this class of drugs are not constant or definite; new entries and changes are possible at any time. For another, they do not present equal or even similar liability problems even though comparable in other respects.

(2) Applying, by regulation or interpretation, the special coverage or protection afforded defined drugs and parties eligible for protection.

Assuming that a special classification is established and supported, there will still be questions of definition, as described below. The

there will still be questions of definition, as described below. The

series of legal actions and appeals that may be encountered, to set a precedent or example, may well undo any possible gain, because of time, costs and publicity and general impact on problems of this type.

Administrative Problems

Assuming good grounds for providing special, perhaps unique, protection for this class of drugs, two administrative problems arise:

(1) Defining the drug and its product family entitled to such protection, and those associated with it who may enjoy any special legal status or limited liability.

Problems of application, coverage or scope are bound to arise in complex areas of alleged medico-legal fault or negligence and causal relationships. These would be compounded when related entities of the defined drug are implicated and where there are stages involving a number of individuals between research and ultimate use. To whom and how far protection may extend may pose especially difficult problems.

(2) Justifying and administering special courses of action or different bases for recovery for injuries attributed to the defined drug.

bases for recovery for injuries attributed to the defined drug.

The corollary to special protection for providers obviously is special vulnerability (or different treatment) for consumers. Despite any special patient labeling, physician explanations or other consent agreement, a claim based on injury or death will be filed in the forum or in the manner expected to yield the best and highest recovery. Any limit will likely be contested and, as in the special swine flu legislation, there will doubtless be preliminary litigation to test whether users of drugs of little commercial value should be subject to less advantageous legal or administrative provisions.

The argument for special liability treatment must stand or fall on the gravity of the problem as viewed by the potential producers and the government, representing the public interest. In testimony before the Task Force as well as in other submissions on this subject, product liability was listed as a risk area for which an incentive was desired, but it did not receive high priority. In the first place, conventional drug companies cover their entire line of products under a comprehensive insurance program. The additional premium, if any, for this special group of drugs for a limited period would ordinarily not be significant unless these drugs were produced under less stringent qualifications and were therefore more likely to create adverse effects which could generate claims.

Second, the problem of identifying the drugs and the associated effects would create more administrative and insurance difficulties than might be

Second, the problem of identifying the drugs and the associated effects would create more administrative and insurance difficulties than might be

warranted. Special liability treatment might be appropriate where the drug sponsor or producer is a research center or a university which is concerned solely with the development of various types of special drugs. Even in such instances, however, the liability problem can be met, and usually is, by provision for insurance premium or other type of coverage expense under the grant or contract.

A third special consideration, however, might apply if all such drugs were pooled either under federal or industry auspices. In other words, if the drugs developed or marketed under this program were identified and maintained as a separate pooled resource, then appropriate liability status might result and coverage be accorded.

The Task Force, however, has made no such recommendation and, in fact, contemplates that individual companies will be responsible for the development and management of these drugs in standard fashion, except for the requirements of reporting in accordance with the contract, subsidy, or other assistance or incentive provided for their development and use.

The Task Force also considered the relevance and application of the recommendations concerning compensation of injured research subjects. The HEW Secretary's Task Force on the Compensation of Injured Research Subjects concluded that there should be a compensation program for those injured in

HEW Secretary's Task Force on the Compensation of Injured Research Subjects concluded that there should be a compensation program for those injured in

the course of participation in biological and medical research but did not specify a particular form.* Emphasis, however, was placed on a non-fault arrangement to eliminate the need for claiming and proving negligence in these situations.

If compensation for patients injured through use of limited profit drugs were made available under the Federal Employee Compensation Act (no-fault) or under a state law similar to it, there would be, generally, lower recovery than under standard customary personal injury litigation. The Task Force, however, concluded that the liability problem for drugs of limited economic interest was closer to that of the standard product liability maintained by drug firms and thus could be best incorporated in such systems. This arrangement, of course, would not preclude the payment of all or part of the costs by the government but would not change the form or amounts available to potential claimants.

---

* For intramural research, conducted by HEW, coverage under the Federal Employee Compensation Act was recommended; for HEW sponsored research any equivalent of F.E.C.A. was recommended. The amounts would be commensurate with "excess" injury, i.e., injury caused by the research, and to the extent that it exceeds the illness or treatment generally associated therewith. See HEW Secretary's Task Force on the Compensation of Injured Research Subjects, January 1977 (HEW Publication No. OS-77-003).

any equivalent of F.E.C.A. was recommended. The amounts would be commensurate with "excess" injury, i.e., injury caused by the research, and to the extent that it exceeds the illness or treatment generally associated therewith. See HEW Secretary's Task Force on the Compensation of Injured Research Subjects, January 1977 (HEW Publication No. OS-77-003).

Recommendations on Liability

In light of the relatively low priority of the liability problem and the difficulties associated with providing general statutory protection or some type of administrative exemption for significant drugs of small commercial interest, it is the Task Force position that:

> Liability protection should not be made generally available by new federal statute or administrative action under current law, but should be provided for particular situations, on a showing of unusual liability potential, to individual sponsors who have undertaken development of significant drugs of limited commercial value.

Any liability aid would be granted as part of an integrated plan of assistance to a firm or sponsor under the program of incentives to develop drugs of limited use.* This aid could consist of one or more of the following elements:

(1) Federal assumption of all legal liability through purchase of the drug and all rights and obligations, including explanation of risks and benefits, labeling conditions and legal aspects, under Federal tort or contract law.**

---

* Any application for liability aid, as part of a total plan to assistance for a firm, would be subject to reconsideration and negotiation, at request of applicant or the Government, based on actual experience compared with original risk estimates. (See Section 5. Mechanism; C. 4. Reconsideration and Appeal).

**This option is least likely to be sought since the liability issue is hardly sufficient for surrender of ownership to the Government.

of applicant or the Government, based on actual experience compared with original risk estimates. (See Section 5. Mechanism; C. 4. Reconsideration and Appeal).

**This option is least likely to be sought since the liability issue is hardly sufficient for surrender of ownership to the Government.

(2) Federal payment of insurance premium attributable to risks of the defined drug for a specified period (5-10 years). (This would, of course, permit coverage for an indefinite time as long as the claimant's injury occurred during the specified period.)

(3) Federal reimbursement of liability loss attributable to risks of the defined drug, not due to (a) negligence in research, production, distribution or (b) failure to comply with Federal regulations or contract conditions.

(4) Grant or contract for production of drug including agreed estimated costs of potential liability.

These options should not change the basis for recovery on the part of the injured patient claiming malpractice or product fault, since establishment of special or lesser indemnity might tend to restrict drug use, especially where needed, and create problems of definition and possible unconstitutional discriminatory classification. As framed, these incentives do not require legislation (as would be required for tax exemption or special depreciation allowance) and thus could be offered now.

Exclusivity:

A major incentive for producers might be provision of special patent protection or rights or license availability. The Federal Government has developed policies for granting patents under certain conditions to encourage research and development or to reward contributions to research and development provided by industry or academic institutions when

has developed policies for granting patents under certain conditions to encourage research and development or to reward contributions to research and development provided by industry or academic institutions when

essential work in the public interest would not otherwise be performed. In general, the government has sole or specified rights to inventions, products of research and development or publications which are supported in whole or in part by Federal funds, staff, facilities or other resources. Where these are shared or pooled, the Government may create a proportionate or greater share to the participant or contributor in accordance with established policy.

Patents

The use of this mechanism is generally regarded as beneficial to the Government since it does not involve a further direct financial contribution, may allow some rights to the Government, as negotiated, and provides a significant incentive to the grantee which may yield immediate or later financial return. Although, in general, such grants are considered to be exceptions to the encouragement of competitive activities (since patents wholly owned by the Federal Government are freely available to all), it has also been argued that the grant of another patent in this fashion actually stimulates or facilitates free enterprise. So regarded, patents become a competitive rather than an anti-competitive tool.

In the drug field, patents have generally been recognized as extremely valuable assets, since it is well-understood that pharmaceutical firms reap their greatest profits shortly after introduction of a successful drug and thus during the time of original patent protection. The effective and imaginative use of patent rights as an incentive has been amply demonstrated. For example, such an approach was used in the case of sodium valproate, a drug which was widely known but not available in the U.S.

reap their greatest profits shortly
drug and thus during the time of original patent protection. The effective and imaginative use of patent rights as an incentive has been amply demonstrated. For example, such an approach was used in the case of sodium valproate, a drug which was widely known but not available in the U.S.

The Government contributed to the development of this drug, thus providing a certain amount of the risk capital and waived its rights to the patent or license. In this instance the U.S. company was the exclusive licensee of a French firm and was permitted to retain these rights without sharing.

Experience at the National Institutes of Health indicates that certain drugs will not be developed further by industry unless some of the risk taking or "up-front" investment is absorbed by the Government. In addition, it may be necessary to provide some limited market protection to the developer through the transfer of specified patent rights or data rights to assure a certain profit or time advantage over potential competitors. Stated otherwise, this is a technology transfer process in which the same elements and judgments generally associated with industrial development must be considered in Government-industry negotiation. To do so, however, the Government must have the ability, by statute or inherent right, to transfer or grant such exclusivities.

Patents may escalate the price of drugs and therefore increase the cost of health care. The use of patents as an incentive, therefore, must be balanced against the public interest in cost containment wherever possible, including drug prices. This problem is less significant with respect to patent allocations to non-profit organizations such as universities which have less influence on pricing. But the granting of patents or similar rights to only one group of developers raises questions of equity and fairness and may encourage private companies to funnel their work through universities.

universities.

Since, in general, the drug of small commercial value is unlikely to be profitable, the allocation of the patent will not generally create unjust enrichment or deprive the public of a recoupment of investment. Restrictive use of patents for such drugs through retention in the public domain would suggest that incentives of this type are not desirable and may dampen the interest of potential producers who regard such rights as integral aspects of participation. The strategic use of the patent incentive appears appropriate, if available under Federal policy.

Protection of Marketing Exclusivity

Under the proposed Drug Regulation Reform Act being developed by members of the Congress and under intended regulations announced by the Food and Drug Administration, after a certain number of years of marketing of a drug (the figure varies but is less than ten) another potential manufacturer can obtain marketing approval for that drug by submitting an abbreviated new drug application which need not contain animal and clinical data to establish safety and effectiveness of the drug. Although this is eminently sensible from the standpoint of the public in that repetitive studies need not be performed when it has already been well-established that a drug is safe and effective, in the case of a drug of little commercial value such a policy might serve as a disincentive to development of such a drug, since the original marketer may not have recouped his investment in the few years of exclusivity that he has been permitted. Therefore, for such drugs it may be justifiable to extend the time until acceptance by the FDA of an abbreviated new drug application.

permitted. Therefore, for such drugs it may be justifiable to extend the time until acceptance by the FDA of an abbreviated new drug application.

Recommendation and Comment

Both patents and a reasonable time for exclusive marketing represent significant assets in drug development which may, along with other incentives, motivate companies. The Task Force takes the position that they should come within the scope of negotiation as allowable incentives. Whether such incentives are essential in a field of relatively small profit, if any, is difficult to tell. In individual cases, however, the availability of such incentives, wisely used, may well make the difference between action and inaction.

On the other hand, it may not be possible to reserve these rights solely for this program, since there are development needs for other health products of equal or greater public concern. A suggested compromise may be limited licenses on some type of formula basis so that exclusivity can be granted to companies for a period sufficient to amortize specified research and development or similar costs. In other words, the element of exclusivity would be employed solely to safeguard reasonable return but not to provide a profit. Such flexible arrangements are possible and have been used in certain programs such as for drugs in the cancer chemotherapy programs. Any such policy would require a case by case review to assure a granting of rights commensurate with expected performance.

D. Administrative and Decisional

With acceptance of the principle of according incentive aid to industry for the development of drugs of limited economic interest, through case-by-case negotiation with government, the Task Force necessarily directed its attention to the means for considering applications, particularly

industry for the development of drugs of limited economic interest, through case-by-case negotiation with government, the Task Force necessarily directed its attention to the means for considering applications, particularly

the decision-making process. There was agreement on three major points:

1. Determinations should be the responsibility of a board or commission which would, by its composition, reflect the public interest and represent all those directly concerned: government, industry, health agencies, the scientific/medical community.

2. Such a board or commission should be free of political, partisan or administrative influence to the greatest extent possible, but assured of financial, scientific and managerial support.

3. In view of these considerations, the board or commission should, at the outset, be located where it would have the required resources, necessary advice and guidance, and relationships within and outside Government.

Location and Structure

The location and line of administrative responsibility, the Task Force agreed, should be determined on these principles: (a) neutral environment, with due regard to accommodation of all pertinent interests; (b) access to scientific, technical and administrative resources; (c) adequate staff and ability to conduct independent studies and surveys; (d) direct relationship to executives responsible for determinations (direct or by delegation) under applicable statute; (e) relative freedom from bureaucratic constraints, and (f) adequate funding for a reasonable period.

Above all else, the board or commission should be accorded reasonable autonomy and the capacity to act with authority, even though determinations

period.

Above all else, the board or commission should be accorded reasonable autonomy and the capacity to act with authority, even though determinations

would, by law, have to be advisory to a government official. Some of the incentives would require the grant or award of federal funds or credit and thus would have to be approved and enforced under appropriate statutes. The Task Force concluded that the significance of the board's activity, its prestige and the broad support anticipated would, for all practical purposes, assure a substantial degree of independence in case decisions and in policy formulation.

Placement Issues

In light of these considerations, the Task Force recognized that the board or commission, although expected to be independent in its judgments, could not responsibly be established in its early stages as a free-standing agency either within or outside the government structure or as a quasi-federal organization. Ideally, an independent body would best reflect and maintain the independence in action desired for such a board; but such status might render the organization financially vulnerable, and could create problems of access to industry and governmental data and expertise. If the board, after some years of successful activity, garners widespread support and recognition, it may then be feasible to consider revising its charter to render it independent.

The location of the board or commission in an existing independent agency such as the National Academy of Sciences would similarly require assurance that the Academy would be in a position to provide administrative and maintenance support at reasonable cost and would itself not become unduly involved in operations. The Task Force noted that, even though the Academy or similar agencies might not be suitable as hosts, they might and should be called upon for advice in the selection of members, management and administrative arrangements.

unduly involved in operations. The Task Force noted that, even though the Academy or similar agencies might not be suitable as hosts, they might and should be called upon for advice in the selection of members, management and administrative arrangements.

Establishment of the commission or board, even as proposed, by industry or largely supported by company contributions poses problems of creating a financial pool, suitable location and, frankly, appropriate insulation from perceived influence. Reliance on industry for this purpose as well as for managerial, scientific and other guidance might, in the view of some who are equally concerned, endow pharmaceutical firms with potential ability to direct or influence policy.

In some contrast, the Task Force considered the placement of the board in a scientific agency or department such as the National Institutes of Health or National Science Foundation. The former would have the advantage of already acknowledged interest, experience in meeting many of these problems (i.e., through the Cancer Chemotherapy Program and the grants and contracts operations) and standing within the Department of Health, Education, and Welfare, along with the F.D.A. with which it would closely cooperate. The National Science Foundation, although not part of DHEW, maintains close relationships, can provide scientific resources and managerial talent, while offering relative autonomy. These options clearly present some of the significant benefits of federal support--research, administrative, financial and legislative--but do not, as of this time, consist of lead agencies with well defined dedication to the interests at issue.

Finally, a proposal that the board might be closely associated with the new National Center for Drug Science to be established by the proposed

Finally, a proposal that the board might be closely associated with the new National Center for Drug Science to be established by the proposed

Drug Regulation Reform Act being developed by members of Congress was deemed inappropriate. According to the proposed Act this Center will provide financial support for the development of drugs to treat diseases of low incidence. Placement of the board in the Center could subject it to the influence of the particular research interests of the Center.

For reasons described below the Task Force concluded that the board or commission should be associated initially with the Food and Drug Administration but that this positioning might be subject to later change following the developmental stages of the program.

Administration and Management

The board or commission involved in negotiation and recommendation would be the core of the program which would, of necessity, also include (a) development of policy through contributions from all sources; (b) promotion of the concept of support for drugs of this nature; (c) initiation and direction of studies to determine scientific potential, therapeutic need, economic requirements and the general state of the art and other conditions. In this strategic locus, the board would be at the center of discussions concerning the social and public policies associated with federal aid, and the impact of such aid on the pharmaceutical industry, on health agencies and on competing interests.

health agencies and on competing interests.

The authority of the board, its determinations and its needs would also, at various stages, be reflected in legislation, regulation and procedural guidelines. These would be essential to assure a legal basis for action, and for efficient as well as equitable management. It was the strong conviction of the Task Force, however, that the board or commission should not become a bureaucracy and itself add another obstacle to effective drug development. The advisory board, whether composed of full time or part-time members, must have the freedom and opportunity to act in accordance with its mandate, and not be burdened with the customary requirements of federal or large industrial officialdom. It was recognized that the board's operations and activity would have to be reviewed; but the Task Force expressed the hope that there might be a minimum of audit, reports and accounting, yet that these be adequate and sufficient to assure responsible management.

First Position and Evaluation

In view of the innovative character of the proposed board or commission, coupled with its significant responsibility, it was generally agreed that initially the board might best be placed within the Food and Drug Administration as advisor to the Secretary of Health, Education, and Welfare through the Commissioner of Food and Drugs. This position would at once provide scientific and administrative resources through a lead agency but with direct access to the most appropriate decision-maker, the Secretary.

through the Commissioner of Food and Drugs. This position would at once provide scientific and administrative resources through a lead agency but with direct access to the most appropriate decision-maker, the Secretary.

Such placement would also assure immediate funding and staffing of the program and that appropriate action would be undertaken by the agency most concerned and directly sympathetic to its mission.

Nevertheless, the Task Force agreed that the board's activity and influence should be carefully watched and evaluated and that its role and location might be changed in the future. For example, if it were able to establish a constituency and appropriate resources, it might become an autonomous agency, either within the federal government or outside, or based within another department. Or the commission form might be changed to one of administrator, once policy were firmly established.

Accordingly, the Task Force recommended that within three to five years, an independent study should consider how this program might best be continued, and where the commission or board might best be situated. Such an evaluation team might include distinguished leaders aware of public policy and its impact, as well as persons skilled in management and administration.

4. Incentives

The underlying rationale of this report is that heretofore unavailable drugs will become available through appropriate incentives offered chiefly by the federal government but also by industry and the professional community, with public endorsement and support through legislation and societal recognition. In effect, a cooperative program is proposed to meet the needs of selected patient groups within the resources and interest of government, industry and other concerned groups.

The program contemplates that applications for aid in research, production or distribution of drugs, based on the incentives, will be made by:

a. commercial sponsors, such as pharmaceutical firms, consortia or groups, or associations;

b. non-commercial sponsors, such as (1) voluntary health agencies, (2) academic or research institutions or coalitions of such institutions, established for this purpose or otherwise, (3) individual researchers, scientists, physicians or groups, similarly established for this purpose or otherwise, or (4) local or

individual researchers, scientists, physicians or groups, similarly established for this purpose or otherwise, or (4) local or

national public health, research or scientific/medical organizations or agencies, such as health departments, environmental agencies or special units.

Any sponsor or applicant will have the same burden of demonstrating (1) the scientific basis or therapeutic merit of the candidate drug and its significance in accordance with the definition, e.g., uniqueness or, alternatively, net advantage over existing agents and (2) unavailability because of specified conditions (Section 2. Definition).

The commercial sponsor will have to specify the limitations on potential profit based on estimated market problems, sales volume, commercial or legal risks. Further, the commercial sponsor will have to show capability of performance if incentives are provided.

The non-commercial sponsor will have to specify any similar limitations regarding potential for payment or reimbursement or other conditions for research, development, production or distribution where all or some of these functions are provided by contract or similar arrangement with a commercial firm or other agency capable of required performance. The non-commercial sponsor will have to show capabilities under contract and participation through distribution or other service, if incentives are provided.

In sum, the conditions for application for special incentive consideration are (1) presentation of a drug deemed significant but of small economic value and (2) demonstration of ability and capacity, if incentives are granted.

A. Principles

The following general principles govern the selection of the particular incentives.

1. Team Effort: The program of drug development, incentive creation and mechanism for providing assistance must be a team effort involving the federal government, private industry, academic and research community, medical practice and voluntary health agencies.

2. Multi-faceted approach: Incentive combinations and flexibility are required since no single incentive will likely suffice.

3. Board Authority and Responsibility: The board, commission or unit created or designated to administer the mechanism for special incentive consideration and recommendation must have broad and strong authority to negotiate and utilize the options best serving the public interest in order to meet the responsibilities proposed under this program.

strong authority to negotiate and utilize the options best serving the public interest in order to meet the responsibilities proposed under this program.

4. Private enterprise: New drug development contemplated under this program should be based in the private sector, since the pharmaceutical industry has demonstrated its willingness and capacity to respond, has assembled the required multi-disciplinary talent and can effectively participate. Accordingly, incentives to encourage private industry action are most appropriate.

5. Proportionate benefit and burden: Although the general public must bear some of the costs of this program, mechanisms for consideration and recommendation of incentives should ensure that, where possible, patient populations that stand to benefit most should bear a proportionately larger, but not prohibitive, share of the burden.

6. Profit return: Sponsors aided through this program who realize a profit must be willing to share such profits, currently or retroactively, to repay in whole or in part any subsidy or other incentive granted.

7. Federal assistance: Although some public-fund subsidization or similar incentive will be required, the role of the federal government must be primarily that of facilitator, catalyst or "broker" with broad powers to negotiate on behalf of the public interest rather than that of subsidizer or drug developer.

broad powers to negotiate on behalf of the public interest rather than that of subsidizer or drug developer.

8. Administrative simplicity and flexibility: To assure maximum private industry cooperation, administrative and managerial aspects should be simple, minimal and non-bureaucratic, offering the least potential for abuse or arbitrary action. Accordingly, to the extent that this program may require financial, market, trade secret and liability information, there must be full protection against unauthorized disclosure and assurance of confidentiality.

9. Risk-Benefit ratios: Priority in the consideration and recommendation of incentives must be given to drugs with greatest possibility of approval under the Federal Food, Drug and Cosmetic Act. Risk-benefit ratios must be developed, considering such factors as scientific and therapeutic validity, on the one hand, and disease incidence, severity, and alternative therapy, on the other hand. This approach will establish a sound basis for selection and avoid any "politicization" of the approval process for drugs under this program.

10. Competition: Incentives advancing the free competitive system must be preferred but, where the public interest is best served through consortia, patent exclusivity or other non-competitive arrangements, they should be given favorable consideration.

11. Reviewability: Negotiations and agreements for incentives must recognize the changing needs and developments and must therefore allow for reasonable review and modification on behalf of the sponsor and the government.

12. Capability: Incentives should be considered and recommended only where there is early and clear indication that the sponsor can in fact complete the research, development and distribution if appropriate assistance is given.

13. Integrity: Above all else, no incentive shall be requested or provided to any sponsor which may result in diminishing the safety, effectiveness, adequacy or other integral component of the drug or its application for the purpose and the population for which it is intended. The essential conditions and requirements of the drug approval process must be met, although priority and other assistance may be given to drugs classified and approved as significant but of small commercial value.

B. Incentives

The recommended incentives to be offered under this program fall into two main categories:

two main categories:

1. Administrative and organizational: relating to priority under drug approval regulations; and structure or organization, such as cooperative arrangements, consortia and contract relationships.

2. Financial and commercial: relating to Federal financial aid through purchase, loan, grant, contract or service; and profit aids, as through tax, patent or legal liability arrangements.

   The latter category requires authorization or special appropriation under existing law or under new laws created for the specific purpose of providing aid to promote availability of drugs of limited economic value.

In addition, there would be the incentive, under either of these categories or through cooperation without specific incentive aid, of:

3. Recognition: service awards and other public appreciation of contribution.

Administrative and organizational

A. Special consideration -- Candidate drugs approved for special incentive consideration under this program would have the advantage of priority treatment under a regulation under current study by the Food and

A. Special consideration -- Candidate drugs approved for special incentive consideration under this program would have the advantage of priority treatment under a regulation under current study by the Food and

Drug Administration. This regulation would inform sponsors of the type of information required to obtain approval for marketing of drugs under this program, or otherwise recognized as significant drugs of limited commercial value for which the only incentive is priority rating. Such status would ensure that priority action would be given through scientific assistance and other service offered to clarify and speed conditions for approval under investigational or new drug application processes. (It may be noted that administrative and procedural difficulties have been offered as justification for not prosecuting drugs of limited commercial value or for estimating excessive time, cost and staff requirements. This perception is obviously not warranted in view of the many examples of special consideration based on a showing that a drug is of major therapeutic value or public health importance.*) The willingness of the FDA to promote this program, the present flexibility and proposed regulation should be sufficient.

B. Structure and organization of sponsors -- Any suitable arrangement undertaken to permit effective research, development and distribution of the drugs at issue which does not conflict with antitrust laws or non-competitive activity contrary to the public interest would be encouraged and protected. Such arrangements solely for the purpose of research, development, distribution or application of a drug under this program could

---

* For example, see Drug Classification, FDA Bureau of Drugs Staff Manual Guide (BD 4820.3, 8/31/76) under which drugs of potentially important therapeutic gain receive certain priority processing.

* For example, see Drug Classification, FDA Bureau of Drugs Staff Manual Guide (BD 4820.3, 8/31/76) under which drugs of potentially important therapeutic gain receive certain priority processing.

include but would not be limited to (1) voluntary consortia of (a) companies or (b) research agencies and universities involving either domestic or foreign firms or institutions, in order to share certain risk, cost, liability, facilities, expertise and patent rights, and similar burdens or resources; (2) contract or other arrangements between non-commercial and commercial organizations, in order to share sponsorship, support and productive efforts and resources under mutually advantageous conditions; (3) partnership, sharing, exchange or staff assignment relationships among commercial, non-commercial and public organizations whether federal, state or local under existing legislation, in order to provide the respective expertise, scientific and commercial economies and advantages of such management; (4) exchange of rights of ownership of patents, licenses or other assets, on a limited basis, in order to share or obtain resources for a specified period.

All such or similar arrangements would be subject to approval as permissible under pertinent federal or state statutes or international agreement as not conflicting with any law or policy relating to competition, trade, protection of rights or disclosure of information. The Department of Health, Education, and Welfare, as facilitator interested in promotion of this program, would provide legal and other assistance and intervention with appropriate public agencies to effect or obtain approval for arrangements deemed to serve the public interest.

deemed to serve the public interest.

Financial and commercial

A. Purchase--The Federal government, for specific and limited public health programs involving special conditions or target populations, could purchase on a non-profit or limited profit basis any drug approved under this program and may enter into agreements for purchase before, during or after any stage of research, development or production. This incentive, probably joined with other incentives including those in category 1 (administrative and organizational) may be sufficient to stimulate and achieve availability.

B. Loan--The Federal government could negotiate loan or loan guarantees in any of the following forms or with similar conditions: (1) low interest; (2) variable interest; (3) long term; (4) variable term; (5) minimal security; or (6) cost-sharing or stipulated forgiveness. All such options, depending on the request and need of the sponsor, might be negotiated within the principle of lending funds or providing credit solely for the purpose of research, development, distribution or application of an approved drug under this program. For the most part, loans would be made to commercial sponsors, probably small pharmaceutical firms, based on their general fiscal situation and estimate of profit loss or yield for the drug under consideration. The particular form, such as low interest or right to repay at the option of the firm or other features would be subject to initial negotiation and renegotiation at the request of either party, based on monitoring of the approved drug project.

at the option of the firm or other features would be subject to initial negotiation and renegotiation at the request of either party, based on monitoring of the approved drug project.

The Task Force recommends that legislation for this incentive establish a revolving fund with periodic support of public and private dollars or credit to cover losses through reduced interest, delayed payments, loan forgiveness or inflation effects. There is ample precedent for federally created and subsidized loan funds (international monetary fund, international reconstruction and development, federal housing) employed to stimulate programs of major public interest.

The loan arrangements possible under this incentive might permit a commercial firm to accept a project calling for initial research and development outlays that would not be feasible without special terms.

To illustrate: a loan to cover the initial research and development cost of $8,000,000 for a drug of modest commercial value which could yield an average gross profit of 10 percent per year, could be amortized at ten percent interest in about 22 years. (See Table I.)

Thus, with a federal loan program, drug firms requiring such reasonable opportunity and assistance to proceed, with other assurances such as acceleration, deceleration, or partial forgiveness, could undertake critical service in the public interest. Although, in general, loans may not be major inducements or be justified for large firms, even those firms may have to take advantage of this option for projects of low profitability or

major inducements or be justified for large firms, even those firms may have to take advantage of this option for projects of low profitability or

possible loss. The loan option, wisely if not widely used, can be a significant stimulus. Legislation under which the Department of Health, Education, and Welfare (perhaps with the advice of other agencies) would be able to establish and maintain a loan program can be relatively simple, in view of other examples and the advantages of well-defined and responsible applicants.

C. Grant--The Federal government could, under any of its current grant programs of the Department of Health, Education, and Welfare or other department or agency or under the Congress' proposed National Center for Drug Science, make a grant for research or other approved purpose to a sponsor applying under this program. To provide information and expedite such applications, the board responsible for this program would regularly assemble and disseminate information regarding pertinent grants-in-aid and requirements for application and, as appropriate, provide endorsements or justifications for special consideration. Also, by statute, grant authority might be provided for grants directly in furtherance of this program.

Grants for clinical study are, in general, chiefly available for non-commercial organizations, but other sponsors are not precluded. Their major federal support in this respect derives from contract, joint enterprise or sharing of facilities or staff. The grant mechanism, however, is available to all qualified applicants who meet program requirements. Funding generally is available only on a timed or scheduled basis, often requiring application a year in advance, so that this mode is likely to prove feasible mainly for limited and specialized purposes.

basis, often requiring application a year in advance, so that this mode is likely to prove feasible mainly for limited and specialized purposes.

D. Contract--The contract, usually let on the basis of competitive bid, is the simplest and generally most easily employed form of assistance. As its name implies, it is a negotiated agreement under which the sponsor, replying to a proposal offered by the government, subscribes to the terms and conditions for delivery of specified service or product. The Department of Health, Education, and Welfare has ample contract authority under several statutes to effect such agreements. As the program matures, the Department will require appropriations to cover the cost of such contracts, and may also consider it appropriate to obtain specific statutory authority for the type of contract deemed suitable.

Elements which could be incorporated into negotiated contracts include but are not limited to: (a) cost-sharing or joint-venture arrangements with other sponsors or the government, (b) automatic payback for drugs which prove to be profitable or for which no further financial incentive is needed, (c) patent arrangements (See H., below) and (d) cost pass-through subsidy.

The cost pass-through option (d, above) would be attractive to non-commercial organizations, such as voluntary health agencies. They could purchase, at cost, alone or with other private or public funds, specific drugs from a manufacturer so as to subsidize research or development. Thus, the drug could be sold to patients at an affordable price and the manufacturer could be assured of at least partial support. This approach would give high visibility to voluntary health agencies and should enhance their ability to raise additional funds. It would serve as an ideal mechanism for those who stand to gain most from drug development to contribute directly toward such efforts.

would give high visibility to voluntary health agencies and should enhance their ability to raise additional funds. It would serve as an ideal mechanism for those who stand to gain most from drug development to contribute directly toward such efforts.

The contract, as a versatile and comprehensive instrument, may also include allowances for insurance premiums to cover liability, for contingencies and for cancellation or renegotiation under specified notice and conditions. Moreover, the contract can and should include provisions for forfeiture in cases of non-delivery or other failure to comply with its terms.

E. Shared Service and Testing--A special form of contract, perhaps most helpful, would be the provision of Federal assistance through special service, expertise, use of facilities or access to government data or methodology under proper control. The service provided would not constitute drug development or production on the part of any federal agency, but could provide technical aid, technological resources, testing and evaluation and various administrative aspects to assure compliance and to minimize the burden of meeting federal fiscal and regulatory requirements. In such cooperative arrangements, the federal project officer would have to be permitted access to information, certain rights of inspection and authority to recommend sanctions based on progress reports and investigations.

The most direct service would be testing in government facilities or under government sponsorship. This would be a useful option for some drugs or firms, and should be offered, although most would not desire or require such aid. The Task Force generally favors private sector effort, with federal help as needed only for very specific purposes. Moreover, federal testing would likely add to the already high cost of drug development.

F. Pooled Funds--Under arrangements among companies which would be authorized as an incentive (B, above), there could be pooling or

F. Pooled Funds--Under arrangements among companies which would be authorized as an incentive (B, above), there could be pooling or

matching of funds through creation of a fund for the purpose of financing research, development or distribution leading to production of significant drugs of limited commercial value. Money or credit, undesignated or designated for specific purposes or drug groups, would be contributed by industry, health agencies, and philanthropic organizations to such a fund (which would have to be created by statute, if federal funds were also joined or matched). Contribution of public money would encourage donations to such a fund by private sources. In effect, like a revolving fund for loans, this fund would provide direct subsidy, subject to recovery where feasible.

Applications for fund aid would be considered by a special advisory committee or a subcommittee of the board established to operate the program (Section 5, Mechanism).

G. Tax Incentives--The Federal income tax laws are often used to encourage investment in enterprises deemed to have substantial public interest and advantage to the general economy. Thus, provision might be made for special tax treatment of funds invested or profits realized in research, development, distribution or sale of significant drugs of limited commercial value.

The Task Force notes certain possibilities from such an approach which suggest that tax incentives be carefully defined and limited to preclude windfall profits; avoid fraud, waste or expensive methods; and, principally, to severely restrict such an incentive to properly qualified sponsors and activities. Otherwise, this attractive option will become

preclude windfall profits, avoid fraud, [illegible]
principally, to severely restrict such an incentive to properly qualified
sponsors and activities. Otherwise, this attractive option will become

the subject of pressure for extension and possible abuse. Properly framed and monitored, a tax incentive could be helpful to firms which might not otherwise be able to participate.

H. Patents and Licenses--By negotiated contract, certain patent or license rights which might be held by the Government could, under Federal patent policy, be awarded to or retained by sponsors of significant drugs of limited commercial value. Such rights would constitute an exchange for the expected loss or nonprofitability associated with research, development, production or distribution. This option has the advantage to the government in that no direct or present federal funds would be required. On the other hand, it would require special approval since it involves certain non-competitive aspects. (It would also require profit disclosure if incorporated in a cost recovery contract.) This approach represents an anti-competitive incentive which may be in the public interest (see A. Principles, 10). This option would not be suitable for a drug with no profit potential but would be useful for a marginal-profit entity where cost could be recovered over an extended period. Table I illustrating loan amortization also illustrates a negotiated formula under cost recovery contract for recoupment of development costs in exchange for patent or license rights.

I. Liability--Without special statute, cost of premiums for insurance to cover potential liability where such an obligation may be unusual or substantial, may be included in any federal grant, contract, loan or other subsidy as part of the negotiated agreement. Any arrangement to render the federal government primarily liable, as under the swine

loan or other subsidy as part of the negotiated agreement. Any arrangement to render the federal government primarily liable, as under the swine

flu legislation, would require a specific law. Such legislation does not seem warranted for the relatively small risk and small population group at risk for whom these drugs would be provided.

J. Recognition--Along with any other incentive and, in a sense, the most significant and most meaningful award, must be public recognition for the efforts of any commercial or non-commercial organization on behalf of this program. There are many creative ways to credit deserving sponsors for outstanding or unusual work and dedication.

These might include ceremonies explaining their achievement and their response to need; visible awards or citations to firms and employees; or participation in certain governmental activity such as board memberships or eligibility for specified positions; or permission to cite such recognition in advertising or promotion. In general, the serious and appropriate recognition which may be accorded must be viewed as a genuine and significant incentive which, by itself, can stimulate participation.

C. Summation

Incentives are the foundation of this voluntary system to achieve availability of drugs of limited commercial interest. This approach, the Task Force urges, should be tried before any imposition or sanction is considered, even for this important social purpose. But the voluntary method will succeed only with dedicated cooperation on the part of all concerned. This program should be considered as part of a larger, more comprehensive effort to improve the national drug reservoir which is filled by industry, research and academic sources and public agencies.

concerned. This program should be considered as part of a larger, more comprehensive effort to improve the national drug reservoir which is filled by industry, research and academic sources and public agencies.

5. Mechanism

A. Core Elements

The mechanism accepted by the Task Force for the program to provide incentives toward the production and availability of significant drugs of limited commercial value comprises: (1) an independent board, advisory to the Secretary of Health through the Commissioner of Food and Drugs; (2) a procedure for consideration and approval by the board of applications for incentives leading to a negotiated agreement to provide research, development, distribution or other service to achieve availability of approved drugs and (3) a procedure for surveillance, review and renegotiation.

In addition, the board would be expected to recommend implementing legislation and regulations and to conduct or fund studies or research for improved management of the program and to evaluate its progress.

All the above functions are seen as essential for a comprehensive program. As the program proceeds, certain functions will become relatively more important and may call for substantial expansion, i.e., review and evaluation. Others, such as legislative-regulatory design should be completed and become less significant. But, including all within one general purpose and structure assures coordination, balance and rational modification, as required.

B. Board Structure

The program, at least at the outset, would be the responsibility of an advisory board consisting of at least nine members representing

The program, at least at the outset, would be the responsibility of an advisory board consisting of at least nine members representing

government, industry, professions, public and recognized special interests, e.g., organizations for research or care of persons with rare or untreated disease. The membership should be large enough to include needed disciplines or experience in law, economics, administration as well as the medical, scientific and public policy interests. A small expert and technical staff as well as support personnel (which may be relatively large) would be required, subject to and provided by the organization responsible for the board. No new statute is needed.

The board should be placed under the Secretary of the Department of Health, Education, and Welfare but located in and serviced by the Food and Drug Administration. The advice and support of other federal agencies, private and non-profit interests and consumer groups, should be provided to the Secretary in selection of members for assurance of independent action. Similarly, such advice should thereafter be available to the board and the FDA.

This board would have to be advisory to the appropriate decision-maker, the Secretary of HEW, since its opinions or determinations would affect public actions, funds and policy. Under present law, it appears that only the Secretary of HEW, or the FDA Commissioner in certain respects, can so act on behalf of the Government.

As an advisory body it can be fully representative of public and private interests and necessary specialties. This size also permits subdivisions for specific tasks and part-time rather than full time

subdivisions for specific tasks and part-time rather than full time

assignment. As proposed, it would also be large enough to have members serve as liaison to counterpart industry or scientific committees.

The board would be expected to advise on and to recommend to the Secretary or Commissioner: (a) initiatives to promote and assure the success of the program, (b) proposals on general matters brought to its attention through applications for incentives, (c) research studies on program issues and (d) primarily, appropriate action on individual applications presented to it for review and evaluation.

The need for and performance of the board should be reviewed in light of its purpose and fulfillment of such purpose. Accordingly, the Task Force proposes that, not earlier than three or later than five years after establishment, an independent review of the board's work, structure and responsibility should be undertaken, in part with the object of determining whether it can be constituted as a non-governmental agency or more suitably placed within federally-related auspices, e.g., the National Academy of Sciences, in order to operate with maximum independence, objectivity and neutrality, free of political or bureaucratic influence. Any such change, of course, would require financial support from public and private funds for administration, studies and other functions. But the Task Force specified further that any such change should not deprive the board of access to federal and other public sources of expertise and data, as may be needed for effective operation.

C. Concept and Procedure

The core of the program for which this mechanism is proposed, consists of: (a) encouraging and requesting members of the pharmaceutical or health aid industry to develop drugs on an individual, partnership or consortium basis, (b) recommending incentive aid as stipulated by statute or regulation and (c) reviewing progress.

1. Information

The board will by notice and regulation announce the availability of the program of incentives to encourage production of significant drugs of limited commercial value. It would issue rules for approval of candidate drugs on application from any of the defined sources.

2. Promotion

The board's first task therefore would be to encourage voluntary industry action as a matter of public interest, with due recognition for such participation. The board would as soon as feasible advertise broadly and selectively, i.e., to the firm or firms most directly interested, for applications leading to required development, production, distribution or other action to achieve availability of specific drugs. Similar and parallel promotion would be undertaken cooperatively by and with industry, professions and others.

3. Consideration of Applications

The board would consider, within the shortest possible time, applications for incentives under this program to reach an approved agreement under

3. Consideration of Applications

The board would consider, within the shortest possible time, applications for incentives under this program to reach an approved agreement under

which the drug would become available. Applications would include requests for incentives as proposed in Section 4 (available at present or proposed), along with justifications, in accordance with specifications set by the board.

As indicated in Section 2, Definition, justifications for requested incentives may include: (a) current economic hardship, precluding normal production without subsidy or assistance; (b) estimate of expense incurred and to be incurred for scientific and administrative work relative to expected return within a reasonable period, e.g, ten or fifteen years, as negotiated; (c) special or unusual circumstances, e.g., unpredictable legal liability; personnel facilities or material shortages; need for expensive consultation, review or tests; packaging, shipment, storage or other distribution problems; (d) need for collaborative work requiring exemptions from antitrust laws or foreign trade regulations or similar restrictions; (e) prior experience under this program resulting in economic loss or competitive disadvantage.

Based on the application, the board would negotiate to develop an advisory agreement with one or more applicants to provide incentives deemed essential as conditions for required action. The board's negotiated agreement would provide for reduction or removal of incentives or return of some or all gains based thereon, if net profits in excess of a specified percentage, as negotiated, e.g., ten percent, accrue within the contract period, provided that no agreement would obligate either party for more than the contract period, that is, after such date, no incentives will be provided and no review of profit, loss or other result of the agreement

than the contract period, that is, after such date, no incentives will be provided and no review of profit, loss or other result of the agreement

will be considered. However, before such date, new agreements may be developed, based on amended applications or requests by the government for reconsideration.

The board's advisory agreement would be considered final when approved by the Secretary or designee. It would then be converted into a contract stipulating the work to be done by the qualified sponsor(s) for the approved incentives and the terms of performance, e.g., time, facilities to be used, approvals required, progress and fiscal reports, delivery and other conditions.

4. Reconsideration and Appeal

The Secretary, on request of a party to a negotiated agreement, may review the terms and, with the concurrence of the board, amend the agreement because of: (a) serious error in calculation or projection during negotiation; (b) unanticipated contingency or condition likely to result in unexpected profit loss; (c) change in circumstances affecting need for the drug, or (d) change in circumstance of sponsor, i.e., dissolution, merger, sale or other change precluding continuation of agreement. Unless reconsideration or appeal is timely requested, the sponsor would be obligated to meet the terms of agreement, with standard penalty for nonperformance.

5. Review and Surveillance

To assure proper and effective performance, the board would be authorized to establish simple review, audit, inspection and reporting

To assure proper and effective performance, the board would be authorized to establish simple review, audit, inspection and reporting

procedures. This process could be used to provide assistance where needed as well as to effect compliance.

The described procedure for fulfilling the functions of the board parallels existing investigational and new drug application procedures of the Food and Drug Administration in requiring advance approval for specified action, except that the sponsor would be given incentives (based on justification) for achieving results and thus is obligated, under a negotiated agreement, to perform as specified. Changes would be allowed, if appropriately requested. Relatively short-term agreements, in general, are contemplated. Thus, later profits would accrue to the drug firm; and, also, later losses would not be recoverable. The incentives allowed include those already available and some requiring statutory authorization.

D. Evaluation

Evaluation of this program should be by the Secretary and the agency responsible for the board's performance and service, aided by independent consultants.

Without a specific evaluation requirement, this program might proceed in unproductive ways or be operated in a less than optimum environment. Since it depends largely on voluntary participation, the constituency served or involved may not be significant critics; other means, objective and independent, are needed.

E. Implementation

1. Legislation

This program may be implemented immediately despite the fact that without new legislation the incentives that can be offered are limited. To broaden the incentives, statutory provisions will have to be enacted. These include: (a) authorization for loans; (b) amendment of the Internal Revenue Laws to provide tax advantage (allowances, depreciation, deductions) for costs and expenses incurred in participating under a negotiated agreement; (c) amendment to patent laws to allow exclusive or modified patents or licenses, with exemptions from Federal rights, for five or ten years; (d) amendment to anti-trust laws to permit limited exchange of data, pooling and other collaboration to meet terms of a negotiated agreement; (e) amendment to FDA law to provide grants and contract authority where not now available. In addition the Congress' proposed National Center for Drug Science would have grant authority for support of research and development of drugs for uncommon diseases.

Other incentives which may be proposed may require additional statutory authority. The principal Congressional action, however, could be for additional appropriations to HEW to adequately support the program.

2. Regulations

Four regulations under present statute are sufficient to initiate this program: (1) explanation of the program and establishment of the board* to conduct the program; (2) listing of incentives such as

* An independent body would require statutory authorization.

Four regulations under present statute are sufficient to initiate this program: (1) explanation of the program and establishment of the board* to conduct the program; (2) listing of incentives such as

* An independent body would require statutory authorization.

contracts and grants and special consideration under FDA procedures available for drugs subject to the program; (3) justifications required for application for support, and (4) provision for review and appeal of board actions. Other aspects may be adequately handled by instructions, guidance and arrangements for cooperation with industry and others.

3. Voluntary Action

The involvement and participation by industry is essentially voluntary under this program. As for other programs, the trade and professional associations, individual firms and leaders can be enlisted to publicize and provide participation and help develop guidelines and procedures under the proposed mechanism.

This series of implementing steps suggests that a viable program can be instituted at once, based on regulation and voluntary action, to be followed, as needed, by legislation. The Task Force believes that the federal government should make a firm commitment to undertake appropriate action, in an expeditious manner, to make available significant drugs of limited commercial value, through conventional means or otherwise, if necessary. The Task Force emphasizes immediate action, in part to test interest and in part to determine how to frame legislation. There is sufficient existing authority to mount this relatively modest proposal.

TABLE I

FORMULA FOR A DRUG OF MODEST COMMERCIAL VALUE WITH ESTIMATED YEARLY INCREASE IN GROSS PROFITS OF 10%

INITIAL R & D COST	$8,000,000
DEBT SERVICE	10%/YR.
AMORTIZATION FORMULA APPLIED	25% OF NET PROFITS/YR.

GROSS PROFIT	DEBT SERVICE COST	NET PROFIT	25% OF NET PROFIT	REMAINING BALANCE
700,000	800,000	(100,000)	0	8,100,000
770,000	810,000	(40,000)	0	8,140,000
847,000	814,000	33,000	8,250	8,131,750
931,700	813,175	118,525	29,631	8,102,119
1,024,874	810,212	214,658	53,664	8,048,455
1,127,357	804,845	322,512	80,628	7,967,827
1,240,093	796,782	443,310	110,828	7,856,994
1,364,102	785,699	578,403	144,601	7,712,393
1,500,512	771,239	729,273	182,318	7,530,075
1,650,563	753,007	897,556	224,389	7,305,686
1,815,619	730,569	1,085,050	271,262	7,034,424
1,997,181	703,442	1,293,739	323,435	7,671,099
2,196,899	767,110	1,429,789	357,447	7,313,652
2,416,589	731,365	1,685,224	421,306	6,892,346
2,658,248	689,234	1,969,014	492,253	6,400,093
2,924,073	640,009	2,284,064	571,016	5,829,077
3,216,480	582,907	2,633,573	658,393	5,170,684
3,538,128	517,068	3,021,060	755,265	4,415,419
3,891,941	441,542	3,450,399	862,600	3,552,819
4,281,135	355,282	3,925,853	981,463	2,571,356
4,709,249	257,136	4,452,113	1,113,028	1,458,328
5,180,174	145,833	5,034,341	1,258,585	199,743
5,698,191	19,974	5,678,217	1,419,554	0

94 x

3,538,128	517,068	3,021,060	755,265	4,415,419
3,891,941	441,542	3,450,399	862,600	3,552,819
4,281,135	355,282	3,925,853	981,463	2,571,356
4,709,249	257,136	4,452,113	1,113,028	1,458,328
5,180,174	145,833	5,034,341	1,258,585	199,743
5,698,191	19,974	5,678,217	1,419,554	0

94 x

