SUMMARY OF RECOMMENDATIONS

Drug Users

1. The Social Security Administration should expedite the completion of its detailed studies on program financing, program administration, and reimbursement methods for several alternative approaches to the inclusion of prescription drugs under Medicare. (Page 19)

Drug Makers

2. The Department of Health, Education, and Welfare should conduct a continuing survey of drug costs, average prescription prices, and drug use. (P. 36)

3. The Secretary of Health, Education, and Welfare should call one or more conferences with representatives of the drug industry, pharmacy, clinical medicine, and consumer groups to consider--

   (a) Provision of incentives to the drug industry to invest more research effort in products representing significant improvements to therapy and less in duplicative, noncontributory drug products and combinations. (P. 48)

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(b) Development of a registration and licensing system under which no drug product would be permitted in interstate commerce unless produced under quality control standards set by the Secretary of Health, Education, and Welfare. (P. 48)

(c) Limitation of free drug samples to those specifically requested by prescribers, by industry agreement or legislation. (P. 48)

(d) Development of more effective methods for ascertaining actual acquisition costs of prescription drugs. (P. 48)

4. The Secretary of Health, Education, and Welfare should call for a joint study by the Department of Health, Education, and Welfare, the Department of Commerce, the Department of Justice, the Federal Trade Commission, and other Federal agencies to consider--

(a) The substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and government agencies. (P. 49)

(b) The substantial differences in the prices at which drug products are offered to American and foreign purchasers. (P. 49)

(c) Revision of current patent and trademark laws on prescription drugs. (P. 49)

Drug Distributors

5. The Congress should enact legislation requiring that the containers of all dispensed prescription drugs be labeled with the identity, strength and quantity of the product, except where this is waived upon specific orders of the prescribers. (P. 53)

6. Encouragement should be given to the wider use of prepackage dispensing, in which manufacturers prepare and pharmacists dispense tablets and capsules in precounted form, in sealed, pre-labeled containers, and in such numbers as conform to those most frequently prescribed by physicians. (P. 53)

7. The National Center for Health Services Research and Development should develop and support research to improve the efficiency and effective-

ness of community and hospital pharmacy operations. (P. 54)

8. The Bureau of Health Manpower should support--

   (a) The development of a pharmacist aide curriculum in junior colleges and other educational institutions. (P. 58)

   (b) The development of appropriate curricula in medical and pharmacy schools for training pharmacists to serve as drug information specialists on the health team. (P. 58)

   (c) A broad study of present and future requirements in pharmacy, adequacy of current pharmacy education, and the educational changes which must be made. (P. 58)

9. The Health Services and Mental Health Administration should support studies of State laws, regulations, and codes, with priority given to the establishment of model State licensing laws, uniform reciprocity standards, and provisions for the utilization of pharmacy aides. (P. 59)

Drug Prescribers

10. The Department of Health, Education, and Welfare should provide expanded support to medical schools, enabling them to include a course in clinical pharmacology as an integral part of the medical curriculum. (P. 65)

11. The Department of Health, Education, and Welfare should establish or support a publication providing objective, up-to-date information and guidelines on drug therapy, based on the expert advice of the medical community. (P. 70)

12. The Department of Health, Education, and Welfare should support the efforts of county medical societies, pharmacy and therapeutics committees, medical foundations, and medical schools in taking the responsibility for providing continuing education to physicians on rational prescribing. (P. 70)

13. The Secretary of Health, Education, and Welfare should be authorized to publish and distribute a drug compendium listing all lawfully available prescription drugs, including such information as available dosage forms, clinical effects, indica-

tions and contraindications for use, and methods of administration, together with price information on each listed product. (P. 71)

Drug Quality

14. The present clinical trials to determine the biological equivalency of important chemical equivalents should be continued by the Department of Health, Education, and Welfare on a high priority basis. (P. 79)

15. Adequate financial support should be provided to the Food and Drug Administration for necessary educational and inspection operations so that acceptable quality control methods can be instituted and properly maintained in all drug manufacturing and packaging establishments. (P. 81)

16. The Food and Drug Administration should be authorized to provide additional support, including grants-in-aid, to State and local agencies in order to improve quality control of prescription drugs in intrastate commerce. (P. 82)

Ongoing Programs

17. The Federal Interdepartmental Health Policy Council should concern itself with the coordination of all ongoing Federal prescription drug purchase and reimbursement programs. A special subcommittee of the Council should be appointed for this purpose. (P. 103)

Classification and Coding

18. The Department of Health, Education, and Welfare, the Department of Defense, and the Veterans Administration should test the proposed drug classification system to determine the feasibility of its eventual use in all public and private drug programs. (P. 105)

19. (a) An appropriate identifying code number should be made part of all drug labels, package inserts, catalogs and advertising. (P. 107)

(b) An appropriate coding system should be developed and tested by government and industry for this purpose. (P. 107)

(c) After consideration of the results of this test, appropriate legislation should be introduced to require coding of all drug

products in interstate commerce. (P. 108)

20. The drug code adopted by government and industry should be utilized in the National Drug Code Directory. (P. 108)

Utilization Review

21. The National Center for Health Services Research and Development, in cooperation with State and local medical groups, community pharmacies, hospitals, and consumer groups, should support pilot research projects on prescription drug utilization review methods. (P. 110)

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TERMINOLOGY

The term generic equivalents is not used in this report. It has been widely used, but has been given so many different interpretations that it has become confusing.

Instead, the following terms are utilized:

Chemical equivalents - Those multiple-source drug products which contain essentially identical amounts of the identical active ingredients, in identical dosage forms, and which meet existing physico-chemical standards in the official compendia.

Biological equivalents - Those chemical equivalents which, when administered in the same amounts, will provide essentially the same biological or physiological availability, as measured by blood levels, etc.

Clinical equivalents - Those chemical equivalents which, when administered in the same amounts, will provide essentially the same therapeutic effect as measured by the control of a symptom or a disease.

The following terms are also utilized:

Generic name - The established or official name given to a drug or drug product.

Brand name - The registered trade-marked name given to a specific drug product by its manufacturer.

Molecular "manipulation" - A minor modification in the molecular structure of a chemical, yielding a new and patentable product.

"Me-too" or "duplicative" drug - A new drug, often made by means of molecular manipulation, which offers no significant therapeutic advantage over a related drug already on the market. (Chemical equivalents, since they are chemically identical, are not considered to be "me-too" products.)

Rational prescribing - Prescribing the right drug for the right patient, at the right time, in the right amounts, and with due consideration of relative costs.

INTRODUCTION

Since the Task Force on Prescription Drugs was formally established in June of 1967, members of the Task Force staff in cooperation with many governmental and nongovernmental consultants have examined various important aspects of drug production, distribution, and use.

These studies have included the health needs and prescription drug use of the elderly and other groups, the prescription drug industry, the drug distribution system, the prescribing patterns of physicians, drug quality, ongoing drug insurance programs in the United States and other countries, drug classification and coding, and drug utilization review.

Findings from these studies have been considered by the Task Force, and are summarized in the following sections, together with recommendations for action.

These proposals are not concerned with any specific drug program. They are directed toward producing the highest possible quality of health care, at the lowest practical cost, for all people.

THE DRUG USERS

The elderly in the United States--those aged 65 or more--represent only a relatively small proportion--about 10 percent--of the total population of this country.

But their inordinate health needs, their high health care costs in general and high drug costs in particular, and their limited financial resources combine to create a serious and sometimes a devastating medical and economic problem far out of proportion to their numbers.

For many elderly people, illness serves as a major cause of their poverty by reducing their incomes, while poverty serves as a major contributory cause of illness by making it impossible for them to obtain adequate health care.

Yet it is not only the totally impoverished or the totally incapacitated who are in a precarious position. There are many elderly men and women who have some income and some savings--who may even have sufficient Medicare or other insurance to protect them against the bulk of hospital and medical costs of a brief illness--but who cannot pay for the out-of-hospital drugs and other costs of a long-continuing chronic illness without

seeing their financial assets eroded or totally dissipated.

Numbers and Health Needs of the Elderly

There are now more than 19 million Americans over the age of 65. Among them, about 57 percent are women and 43 percent are men. This disproportion in sex distribution has been increasing steadily since about 1930--a trend of importance in any prescription drug study, since the use of these drugs by women is significantly higher than that by men.

In connection with the elderly, the term aging has often been considered synonymous with illness. There is, in fact, no necessary relationship between the two, but it is undeniably a fact that illness strikes the elderly far more frequently than it does younger age groups.

Approximately 80 percent of the elderly--in comparison with 40 percent of those under 65--suffer from one or more chronic diseases and conditions.

Arthritis and rheumatism afflict 33 percent; heart disease, 17 percent; high blood pressure, 16 percent; other cardiovascular ailments, 7.5 percent; mental and nervous conditions, 10.5 percent; hearing impairments, 22 percent; and visual problems, 15 percent.

Many of these conditions can be controlled or alleviated by modern medical care, especially by the proper use of drugs. This is reflected in the heavy expenses of the elderly for health care, and particularly in their heavy expenses for drugs.

Health Expenditures

Between 1950 and 1966, total national expenditures for health services and supplies--including hospital costs, physicians' fees, and drug costs--rose from $11.9 billion to $41.8 billion. (Per capita expenditures increased from $78.20 to $212.47.)

In that same period, expenditures for out-of-hospital prescription drugs rose from $1.0 billion to $3.2 billion. (Per capita expenditures increased from $6.85 to $16.05.)

The increase in drug expenditures has resulted in part from a greater number of prescriptions per individual--an average of about 2.4 acquisitions per capita in 1950 and 4.6 in 1966--as well as from a significant rise in the average cost of prescriptions.

In 1950, a number of independent surveys reported the average cost of all prescriptions at the retail level was between $1.66 and $2.03. In 1966, independent

surveys estimated the average was between $3.26 and $3.59. A special study conducted for the Task Force showed that the average prescription cost for the elderly in 1966 was even higher--$3.91.

Distribution of Drug Expenditures

If drug use were equally distributed among all groups--that is, 4 to 5 prescriptions per year at a cost of $3 to $4--there would be no major problem for the elderly. But this is far from the actual situation.

Although the elderly represent slightly less than 10 percent of the total population, they account for about 23 percent of all prescription drug expenditures.

A nationwide study by the National Center for Health Statistics in fiscal year 1965 showed the following (see Table 1):

-- The average number of acquisitions--i.e., the number of prescriptions or refills--for the elderly was more than twice that for the total population, and nearly three times that for those under 65.

-- The average number of acquisitions for elderly women was nearly 50 percent more than the number for men.

Table 1

Average Number of Acquisitions and Annual Cost of Prescribed Drugs, per Person by Selected Characteristics, Fiscal Year 1965

Characteristics	No. of Acquisitions [a]			Annual Cost		
	All Ages	Under 65	65 and Over	All Ages	Under 65	65 and Over
All persons	4.7	4.0	11.4	$15.40	$12.77	$41.40
Sex						
Male	3.7	3.1	9.3	12.00	9.88	34.70
Female	5.6	4.8	13.1	18.60	15.49	46.70
Color						
White	4.9	4.2	11.5	16.40	13.62	42.60
Nonwhite	3.1	2.7	10.2	7.80	6.57	26.90
Geographic Region						
Northeast	4.4	3.8	10.6	13.30	10.80	37.00
North Central	4.4	3.8	10.9	15.00	12.37	39.90
South	5.3	4.5	13.6	17.50	14.64	47.40
West	4.3	3.7	9.7	15.30	12.93	40.00
Disability - Men						
None				14.80		19.40
Mild				33.50		40.90
Moderate				33.60		40.80
Severe				71.70		71.00
Disability - Women						
None				23.20		34.00
Mild				50.00		64.40
Moderate				63.40		67.60
Severe				101.40		94.70

a/ New prescriptions or refills.

-- The per capita expenditure for prescription drugs for the elderly was almost three times greater than that for the total population, and more than three times greater than that for those under 65.

-- The per capita expenditure for elderly women was more than one-third higher than that for elderly men.

-- The per capita expenditure for the elderly with severe disabilities was nearly three times greater than that for those with no disabilities.

In general, the survey showed, total prescription drug expenditures in all age groups were higher for women than for men, for whites than for nonwhites, and for those in the South and West. The higher expenditures for whites appear to be a reflection of their greater affluence--their greater ability to seek medical care and to afford drugs rather than greater health needs. The high cost in the South appear to be related to exceptionally heavy utilization, while in the West they reflect lower utilization but much higher costs per prescription.

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Similarly, although the burden of drug costs falls most heavily upon the elderly, it does not fall evenly upon these individuals.

A 1968 estimate, for example, indicates that 20 percent of the elderly will have no drug expenses, while the costs will be less than $50 for 41.5 percent, between $50 and $99 for 19 percent, between $100 and $249 for 15.5 percent, and $250 or more for 4 percent.

A recent investigation, carried out on a limited group in Pennsylvania, indicated that, among the elderly who actually obtained prescription drugs, about 2 percent accounted for about 21 percent of the total cost, and about 10 percent of the individuals accounted for about 47 percent of the cost.

Financial Resources of the Elderly

The size of drug bills for the elderly represents only one phase of the problem. Intimately related is their ability to pay those bills.

Since July 1, 1966, implementation of the Medicare program has substantially increased the ability of many elderly men and women to meet their doctor and hospital bills, not entirely but in large part. Expenditures for

out-of-hospital prescription drugs, however, are not covered by the present Medicare law, and it has been necessary for elderly patients to utilize other sources.

Income. In 1966, half of the families headed by an elderly individual had total incomes--including Social Security payments--of less than $3,645, or $70 a week. For elderly men and women living alone, or with someone not a relative, more than half had incomes of less than $1,500, or about $30 a week.

Assets. Recent studies have shown that the average per capita amount of savings and other assets held by the elderly is about $15,000.

But 30 per cent of the elderly have assets of less than $1,000 apiece. For them, a serious illness could wipe out their meager savings in a few months.

Health Insurance. Health insurance through Blue Cross, Blue Shield, commercial insurance companies, group practice plans and other organizations is available to many of those over the age of 65, but provision of prescription drugs--except to hospitalized patients--is limited.

Where out-of-hospital drug expenses are covered, these are generally included in major medical policies involving deductibles of $100, $250, or $500--useful only in so-called "catastrophic" illnesses.

Recently, drug insurance programs have been developed to provide adequate coverage of out-of-hospital drug costs, but membership in the plans is usually limited to members of employed groups, and few of these are in the older-age group.

Tax Relief. To the extent that expenses for drugs are included as deductions on income tax returns, reduced income tax payments represent a source of payment for these drugs.

For the elderly, such relief obtained through Federal income tax deductions has been estimated to represent about 9 percent of drug expenditures. But these savings benefit only those elderly individuals who receive enough income to require income tax payments, and would be of little importance to those with low incomes.

Free Drugs. From the 1964-65 study of the National Center for Health Statistics, it appears that about 3 percent of the elderly received their drugs at no cost

from their physicians.

Public Assistance. About 6 percent in 1964-65 obtained prescription drugs from State or local welfare agencies or similar sources. The provision of free drugs through welfare agencies--under Medicaid or other Federal, State or local programs--may solve the problem as it directly affects some of the elderly. The basic economic problem is not solved, however, but merely shifted from the elderly to the taxpayers.

Out-of-Pocket Costs. In enabling the elderly to meet their out-of-hospital prescription drug expenses, the combined impact of insurance coverage, tax relief, free drugs, and public assistance does not seem to be substantial, covering only about 20 percent of total costs.

The remainder--about 80 percent--must be met by out-of-pocket expenditures from income and assets. For those over 65, these financial resources are rarely substantial.

Thus, the elderly, with limited income, limited savings, and minimal protection from health insurance and other sources, are obliged to face the burdens of drug costs which are far heavier on a per capita basis than those which weigh on their fellow citizens, who in most

cases are younger, healthier and wealthier.

Patterns of Drug Use by the Elderly

Essential for an effective attack against the drug problems of the elderly are detailed, objective data on the drugs they actually use and the costs of these prescriptions.

In 1966, for example, the elderly obtained about 198 million out-of-hospital prescriptions from community pharmacies at a total retail cost of $852 million, involving many thousands of different drug products. a/ But this knowledge is not enough.

It is necessary to know--

--which drugs, by brand or generic name, were dispensed for the elderly.

--which were utilized most frequently;

--which diseases accounted for the greatest drug utilization;

--which drugs were most frequently involved in long-term maintenance therapy;

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a/ An additional 26.9 million prescriptions, at a cost of $104.7 million, were obtained from hospital and mail order pharmacies and other sources.

--how much each of these drugs cost at the wholesale level, and at the retail level; and

--to what extent drug costs could be reduced if low-cost chemical equivalents were used wherever they were available.

To obtain the needed information, the Task Force requested the Public Health Service to undertake a special study, with major responsibility assigned to the Health Economics Branch of the Division of Medical Care Administration, and assistance provided by other agencies within the Bureau of Health Services, and by the Food and Drug Administration.

This project--probably the first of its kind ever undertaken--was aimed at developing a master list of the drugs which were most frequently prescribed and dispensed for the elderly in 1966, a/ and which would account for about four-fifths of their drug use during that year.

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a/ 1966 was selected as the study year, since it represented the most recent period for which essentially complete data were available for Task Force analysis beginning in June 1967.

The Task Force Master Drug List. As developed for the Task Force, the Master Drug List (MDL) contained the 409 most frequently prescribed drugs dispensed to the elderly in 1966. These accounted for 174.7 million, or 88 percent, of all prescriptions dispensed by community pharmacies for the elderly in that year, and for $682.3 million, or 80 percent, of their prescription drug costs at the retail level. a/

The complete MDL, with a variety of analyses, will be presented in a separate background paper.

Included among the 409 products were 379 which were dispensed under their brand names. These accounted for more than 90 percent of the total number of MDL prescriptions, about 90 percent of the total acquisition cost to retailers, and 95 percent of the total retail cost to the patients.

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a/ It should be noted that insulin, which has figured prominently in many drug insurance programs, is not included in these tabulations, since it is generally dispensed without a prescription. In 1966, it was estimated that insulin dispensed to the elderly cost about $3 million at the retail level.

Among these were 87 products which were dispensed under their brand names, but for which chemical equivalents were available--often but not always at lower cost--and could have been prescribed under generic names. They accounted for about 29 percent of the total number of prescriptions, 27 percent of the total acquisition cost to retailers, and 27 percent of the retail cost to patients.

Also included were 30 drugs which were dispensed under their generic names. They accounted for about 10 percent of the number of prescriptions, 10 percent of the total acquisition cost, and 5 percent of the total retail cost.

Average Prescription Cost. For all 409 MDL drugs, the average cost per prescription was $3.91. For the 379 drugs dispensed under brand name, it was $4.11. For the 30 drugs dispensed under generic name, it was $2.02.

Most Widely Used Drugs. The 10 most frequently used products--headed by an oral antidiabetic agent, and including two tranquilizers, two diuretics, an analgesic, an anti-arthritic agent, a cardiac drug, and two sedatives--accounted for 20 percent of the total number of MDL prescriptions, 21.6 percent of the total acquisition cost to

retailers, and 20.7 percent of the total retail price to consumers.

Only two of these were available from several manufacturers under a generic name.

Approximately 50 percent of the total cost to patients was represented by the top 29 drugs, which also represented 53 percent of the total number of prescriptions and 49 percent of the total acquisition cost to retailers. Among these were 18 drugs which could be obtained only under a brand name from a single supplier, eight which were dispensed under a brand name although a chemical equivalent was available, and three which were dispensed under generic name.

Therapeutic Category. Cardiovascular preparations--including vasodilators, digitalis and its congeners, and hypotensive drugs--accounted for 38.9 million, or 22 percent, of the total prescriptions, and $157.8 million, or 23 percent, of the total retail cost to consumers.

Tranquilizers, with 16.9 million prescriptions at a total cost of $78.9 million, rated second, followed by diuretics, with 16.0 million prescriptions at $62.6 million; and sedatives, with 15.1 million prescriptions at $32.3 million.

These four categories together represented about one-half of all prescriptions for products in the MDL, and 49 percent of the total cost to patients.

Antibiotics ranked fifth, including 13 million prescriptions at a retail cost of $64.3 million.

Diagnostic Category. About 66.2 million, or 38 percent, of the total prescriptions, at a cost of $244.3 million, or 36 percent, of the total retail cost, were used for the treatment of heart disease and hypertension.

An additional 17.3 million prescriptions, at a retail cost of $65.4 million, were applied for the control of arthritis and rheumatism.

About 11.6 million prescriptions, at a cost of $47.4 million, were dispensed for the treatment of mental and nervous conditions.

Together these groups accounted for 95.1 million, or 54 percent, of the total MDL prescriptions, and $357 million, or 52 percent, of the total cost to consumers.

Maintenance Therapy. A sizeable proportion of out-of-hospital drugs prescribed for the elderly are so-called long-term maintenance drugs, used primarily for the control of chronic diseases. Few of these --

at least at the present state of knowledge--can be cured, but in many instances appropriate drug therapy will enable the patient to live a reasonably comfortable and productive life.

Among the 409 drugs in the MDL, 71 were prescribed for 30 to 59 days during the year, 42 of them for 60 to 89 days, and 78 of them for 90 days or more.

These last 78 accounted for only about 20 percent of all MDL products, but they represented 59.6 million, or 34 percent, of all MDL prescriptions, and $242 million, or 35 percent, of total costs to the consumer. More than half of them were for the control of cardiovascular disease.

We find, therefore, that the requirements for appropriate prescription drug therapy by the elderly are very great--far greater, in fact, than those of any other group--and that many elderly men and women are now unable to meet these needs with their limited incomes, savings, or present insurance coverage. Their inability to afford the drugs they require may well be reflected in needless sickness and disability, unemployability, and costly hospitalization which could have been prevented by adequate out-of-hospital treatment.

With steadily increasing prescription expenditures, this problem is destined to become increasingly serious.

The Task Force therefore recommends that the Social Security Administration should expedite the completion of its detailed studies on program financing, program administration, and reimbursement methods for several alternative approaches to the inclusion of prescription drugs under Medicare.

The Task Force defers any definitive recommendation on the possible inclusion of out-of-hospital prescription drugs under Medicare until the completion of these studies.

THE DRUG MAKERS

The Industry

Total drug sales--prescription and nonprescription drugs alike--have increased substantially in the last decade, rising from nearly $3 billion in 1957 to about $5 billion in 1967 at the manufacturer's level. Prescription drugs accounted for about two-thirds of this volume.

Foreign drug sales by American companies exceeded a billion dollars in 1967.

Approximately 95 percent of the prescription drug sales were made by the 136 member companies that comprise the Pharmaceutical Manufacturers Association (PMA). Members of the PMA produce and sell both brand name and generic name products. Just as they account for the overwhelming proportion of sales, they conduct essentially all of the industry's research, they control the overwhelming proportion of drug patents, they conduct the most vigorous promotion of their products, they compete vigorously--usually on the basis of innovation and quality and rarely on the basis of price--for the favor of the medical profession, and they achieve the industry's highest rates of profit.

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The drug industry's research and development program is now nearly $500 million a year, almost all conducted by about 70 of the PMA members.

The industry's research effort has been noteworthy in many respects --

--New drugs developed through research have given physicians remarkable weapons for the improved treatment of infections, metabolic disorders, arthritis, heart disease, high blood pressure, and a host of other crippling or deadly diseases.

--Based on percentage of sales, the drug industry's investment in research is about three times greater than that of any other major industry.

--The number of new products has been impressive. For example, between 1957 and 1968, 311 products introduced on the market were described as important new single entities. They represented about 15 percent of the 2,131 new prescription drug products introduced during that period. Also included were 1,440 products containing two or more older drugs in a new combination, and 380 drugs which were essentially duplicates or minor modifications of products already in use.

--The annual number of important new entities, those which represent significant advances, reached a peak in 1958--four years before the Kefauver-Harris Drug Amendments of 1962--and decreased steadily until 1967, when the number started to rise again.

Also impressive is the vigor and frequency with which industry spokesmen have said that any government interference in their operations may force them to reduce their research programs.

The Task Force is convinced that the directions and quality of some industry research programs deserve careful consideration.

We have noted the serious and increasing concern expressed by practicing physicians, medical educators, pharmacologists, and economists--and even some industry leaders--at the number of molecular modifications of older drugs introduced each year. Some of these modifications undoubtedly represent significant advances, but most appear to be so-called "me-too" drugs--substances which are not significantly different from other drugs, nor significantly

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better, and represent little or no improvement to therapy, but which are sufficiently manipulated in chemical structure to win a patent.

We have noted the comparable concern expressed at the number of new fixed combinations of old drugs introduced each year. Although these combinations may offer some convenience to elderly patients in particular, clinicians and pharmacologists have cautioned that they also involve obvious hazards and combine drugs in a "locked-in" proportion which may or may not fill the needs of individual patients.

The numbers of duplicative and combination drug products introduced in recent years have been decreasing, but they still represent the great majority of all so-called new drugs.

It is evident that these duplicative products, along with combination products, are used widely by some physicians, perhaps on the basis of the industry's exceedingly effective marketing and promotion activities. But it is also evident that the need for this over-abundance of drug products has not been convincing to some medical experts.

In many of the Nation's leading hospitals, when expert physicians have served on pharmacy and therapeutics committees to select the drugs needed for both inpatient and outpatient therapy, they have generally found many if not most of these duplicative drugs and combinations to be unnecessary. These products have been found generally unnecessary by physicians providing medical care to the armed forces. They have been found generally unnecessary by leading clinical pharmacologists.

If these items were offered at prices substantially lower than the products they duplicate, they would provide at least an economic advantage, but in most instances they are introduced at the same or even higher prices.

The development of such duplicative drugs or combination products cannot be considered an inexpensive fringe benefit. Each requires laboratory research, clinical trials, and the accumulation of sufficient data to demonstrate to the Food and Drug Administration that the new product--although it may not represent any significant therapeutic advance--is at least safe and efficacious.

Since important new chemical entities represent only a fraction--perhaps 10 to 20 percent--of all new products introduced each year, and the remainder consists merely of minor modifications or combination products, then much of the industry's research and development activities would appear to provide only minor contributions to medical progress.

The Task Force finds that to the extent the industry directs a share of its research program to duplicative, noncontributory products, there is a waste of skilled research manpower and research facilities, a waste of clinical facilities needed to test the products, a further confusing proliferation of drug products which are promoted to physicians, and a further burden on the patient or taxpayer who, in the long run, must pay the costs.

A solution to this problem requires joint efforts on the parts of industry and the Federal Government (see page 47).

Quality Control

Any company, large or small, brand name or generic name producer, can institute and maintain an effective

quality control program, and most companies have apparently done so. The cost of such a program has been estimated to be about 2.4 percent of sales for a large company, but may be somewhat more for a smaller firm.

On the other hand, not all companies have maintained adequate quality control, and their products have had to be recalled--either voluntarily or by government order--for such defects as mislabeling, subpotency, or contamination. These recalls have involved both large and small firms, and both brand name and generic name products.

Several hundred such violations are reported each year. Investigations have often indicated that these are related to the failure of a manufacturer to comply with what are known as Good Manufacturing Practices, including such factors as plant sanitation, personnel surveillance, equipment maintenance, raw material standards, record keeping, and quality checks at every appropriate stage of manufacture and packaging.

The Task Force believes that this situation may be substantially improved by the intensified inspection program now being developed by the Food and Drug

Administration. At the same time, it believes that further study is warranted of the alternative proposal that a registration and licensing system be established under which no drug product would be permitted in interstate commerce unless produced under quality standards set by the Secretary of Health, Education, and Welfare, (see page 47).

Marketing

For those major companies which have presented any data, marketing expenses--including particularly those for advertising and promotion--represent from about 15 to 35 percent of sales. Such expenses for generic name products appear to be substantially lower than those for brand name products.

Industry spokesmen have claimed that marketing is an accepted part of any business activity; that their marketing costs are reasonable; and that their marketing efforts--including advertising, direct mailings, and personal visits by detail men to physicians--are primarily educational in nature. They have claimed that the promotional aspects of drug marketing are a mark of the intense

competition in the industry.

On the other hand, critics have asserted that intensive promotional efforts may be acceptable to sell such products as detergents, beer and used automobiles, but not for such vital necessities as prescription drugs; that the expenses for drug marketing are excessive and add needlessly to the cost of prescriptions; that prescription drug advertising and other promotion has reached the proportions of supersaturation; and that some has been --at least until recent regulations were established by the Food and Drug Administration--inaccurate, unscientific and biased.

It appears evident to the Task Force that drug promotional activities are related to the particular type of competition which unquestionably exists in the prescription drug industry, among others--an intense competition between companies, with the promise of a greater share of a relatively limited market and richer profits for the successful competitor--but that these activities have little to do with normal price competition in the

retail marketplace--with the promise of eventual price savings to the consumer.

The Strategy of Names. Intimately related to marketing, and the competition between brand and generic products, is the subject of brand and generic names.

In the past, whether fortuitously or by design, most generic names--though certainly not all of them--have been relatively long, complicated and difficult to pronounce and remember.

During the past year, this situation has improved somewhat as the result of new policies established by the U.S. Adopted Names Council, but more improvement is needed.

The Task Force commends the Council for its efforts toward simplifying generic names and urges that these efforts be continued and strengthened.

Advertising and Promotion. Included among the promotional activities of some major prescription drug companies have been the support of scientific or medical conferences or symposia totally unrelated to any commercial product; the publication of educational materials for the public on such subjects as prevention of narcotic and drug abuse,

immunization campaigns, and school health; the establishment of scholarships and fellowships, especially for the benefit of underdeveloped countries; and the no-strings-attached support of some scientific and medical societies.

These and similar activities are held in high esteem in the scientific and medical community, and are recognized as significant contributions to the improvement of public health.

Also included among promotional activities is the drug advertising in medical journals, direct mailings, throw-away publications, and others which has long since reached astounding proportions. It is estimated that the major drug companies together now spend some $3,000 per physician annually to reach each of the nearly 200,000 physicians who represent the target audience--those who will decide for which drug product their patients should pay.

Significantly, this advertising rarely if ever mentions price.

Unquestionably, much of this material is accurate and educational. The frequency of biased, inaccurate drug

advertising has apparently been reduced since the enforcement of new advertising regulations by the Food and Drug Administration began in 1967. But the overall value of such advertising volume continues to be seriously questioned.

Similarly, the potential impact of these large advertising expenditures on the editorial policies of the journals which are supported in large part by drug advertisements appears to deserve careful study.

Detail Men. Major brand name manufacturers--and a few generic name companies--employ about 20,000 representatives to call on physicians, hospitals, and pharmacists, and provide information on their products.

Whether such activities may be described as primarily promotional or primarily educational is difficult to determine. It is doubtful, however, that physicians can expect such detail men to give invariably unprejudiced and objective advice.

Significantly, the presentations of detail men rarely include mention of price.

Free Samples. Free drug samples have customarily been distributed to physicians without request to induce them to try a product and test its advantages on their own patients. But few physicians are able to undertake any serious trials of this nature. Furthermore, if a physician does try a drug, in most instances he can do so with only a very few patients; the possibility that such a limited study can serve as a basis for a scientific judgment seems to be small.

Free drug samples have made it possible for physicians and hospitals to supply drugs at no cost to some indigent patients. This need, however, has been modified by the advent of Medicaid and other programs under which Federal and State welfare funds may be used to provide drugs to eligible patients.

It has been reported that free samples have been involved in accidental poisonings, drug abuse, and black market activities.

Some major drug manufacturers have reacted to this problem by distributing free samples only to those prescribers who have specifically requested them. It

appears that further steps in this direction call for joint efforts by the industry and the Federal Government (see Page 47).

Industry Prices

Few aspects of the drug industry are more confused--or more confusing--than its pricing structure. Ostensibly, wholesale prices are listed in company catalogs and price lists, but these generally represent maximum prices. These serve merely as an umbrella beneath which actual prices are set by quantity discounts, hospital discounts, government discounts, two-for-the-price-of-one deals, rebates, and other special arrangements.

With many Federal, State and private drug programs now using reimbursement formulas based on wholesale costs to the vendor, there is need for developing an efficient system to ascertain actual acquisition costs. This calls for cooperation among manufacturers, wholesalers, vendors, insurance companies, and governmental agencies (see page 47).

Price Indices. Particular confusion has resulted from the comparison of various indices intended to indi-

cate the trend of drug costs.

From the Consumer Price Index of the Bureau of Labor Statistics, it is obvious that retail drug prices have been decreasing steadily since about 1958.

From three independent surveys, it is equally obvious that these prices have been increasing during the same period.

The disparity is based on the fact that the indices are measuring different things.

The BLS index is aimed at measuring the change in a relatively fixed "market basket" of about a dozen selected drug products. During the past decade, the prices of these items have, on the average, decreased. The items selected for the "basket," however, do not accurately represent the most widely used drugs, and they do not reflect the changes in consumer expenditures which constantly occur when new and more costly products are introduced on the market and replace less costly products.

On the other hand, the independent surveys are not concerned with the price changes of any individual drug products, but instead are aimed at determining the average

price of the prescriptions which people do purchase. All three of these surveys show a definite upward trend in the average cost of these prescriptions, but they do not agree in the extent of increase because of different sampling methods.

We find there is need for information on actual drug costs, expenses and utilization by the elderly and other groups.

Accordingly, we recommend that the Department of Health, Education, and Welfare should conduct a continuing survey of drug costs, average prescription prices, and drug use.

Hospital and Government Discounts. Many drug manufacturers customarily offer their products to hospitals at prices substantially lower than those available to community pharmacists. The savings are not necessarily reflected in lower drug prices to hospital patients.

To a considerable extent, these hospital discounts represent a subsidy to hospital patients--or, more often, to the hospitals themselves--at the expense of non-hospitalized patients.

Spokesmen for some pharmacy associations have urged that wholesale prices to hospital pharmacies and community pharmacies be kept at the same level--a move which would lower prices moderately to community pharmacies, but raise them substantially to hospital pharmacies. Hospital spokesmen have declared any such action would raise hospital per diem rates still higher.

Similar differences are apparent between the prices of drugs sold to community pharmacies and those sold to Federal and State agencies.

The Task Force finds that the substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and governmental agencies deserve further examination (see page 49).

Foreign Prices. Many American companies offer their products for sale in foreign countries at prices substantially below those available in the United States, primarily to meet price competition which does not generally exist in this country.

During the past few years, there has been mounting insistence that these companies should price their

products essentially the same in all countries.

The drug companies have countered that any increase in their foreign prices would drive them out of the foreign markets, not only reducing their earnings but upsetting still further this country's unfavorable balance of trade. On the other hand, any attempt to reduce American prices to the level of prices on foreign markets could be catastrophic to their total financial structure.

The Task Force finds that further study is required on the different prices at which drug products are offered to American and foreign purchasers (see page 49).

Patents, Trademarks and Competition

In the case of most commodities, rival companies compete vigorously on the open market on the basis of both quality and price, with the consumer having the right to make the final judgment. In most instances, the results have been steadily increasing quality and decreasing price.

In the case of drugs, there are distinct differences. The competition is based almost entirely on real or presumed therapeutic advantages. The patient, who must pay for the drug, rarely has any voice in its selection. The

decision on which product the patient must buy is made by the physician. Although moderate or even enormous price differences may exist between products of comparable quality, this is seldom brought to the physician's attention.

Some have attempted to justify this situation by describing the physician as the patient's expert purchasing agent. In the view of the Task Force, this concept is not valid; in most situations, a purchasing agent who purchased without consideration of both quality and price would be unworthy of trust.

In what has been described as this "new competition" in the drug business, patents and trademarks have played key roles.

On the one hand, industry supporters have insisted that the present patent and copyright system makes possible the incentives and rewards that are essential for the industry's large research and development effort, the flow of new products to which it leads, the subsequent benefit to health, and the ready identification of brand name products.

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On the other, it has been asserted that drug patents, combined with multi-million-dollar drug advertising campaigns, can keep new or small companies out of the high-profit circle, and effectively stifle price competition in the marketplace.

Various proposals to modify the patent system have been considered by the Task Force.

Abolition of Drug Patents. Removal of all patent protection from new drugs, it appears, would be a destructive move. Virtually all the important new drugs of recent years have come from countries providing patent protection. Few, if any, have come from Eastern European nations which offer little or no patent protection. Several important drugs have originated in Italy, which does not provide patent protection, but these have been quickly patented in foreign countries.

Restricted Patent Life. It has been estimated that a company will usually recoup all its research and development costs within about three years after it reaches the market. Accordingly, it has been proposed that the patent on a drug should be reduced from the

present period of 17 years to a much briefer period--such as 10 years, 7 years, or even 5 years.

It has been shown, however, that requirements to establish the safety and efficacy of a new drug may take many years of effort--perhaps as many as seven years. Where such testing continues after a patent is issued, the period of actual patent protection may be less than the statutory 17-year period.

Co-Terminal Patents and Trademarks. It has also been recommended that the patent life on a drug be maintained at the present 17 years, but that exclusive rights to the trademark should last no longer than the patent. Thus, at the end of the 17-year period, any qualified manufacturer would be free to market the drug under its original trademark or brand name.

Generic Name Only. A related proposal is that new drugs should be marketed only under a generic name--exclusively by the inventor until the patent expired, and then by any manufacturer who desired to produce it. Used with the generic name would be the name of the manufacturer, to identify the source of the product. This would

clearly tend to minimize the confusing multiplicity and complexity of names put before physicians and would better identify the nature of the drug.

Compulsory Licensing. Unlike the United States, many countries have provisions under which the government may require the patent holder to license other manufacturers through a suitable royalty system. These provisions have rarely been enforced, perhaps because realistic price competition exists in the marketplace and lower prices may be invoked through negotiations.

Proponents of such legislation in this country have argued that if licensing were required after the first three years of a product's market life--i.e., after major recovery of research and development costs--other firms could enter that product market by paying royalties, and price competition might then occur among these rivals. Beneficial results to consumers would be possible only for those products with a commercial life longer than three years. For such products, the patent holder would continue to earn an innovator's profits, though perhaps at lower rates than before, and consumers possibly could

purchase prescriptions at lower price levels.

Make-or-Sell Licensing. As yet another approach, it has been proposed that the patent holder should not be permitted to monopolize both the manufacture and the sale of a new drug, but should be required to license either other producers or other sellers.

We note that these and other proposals to amend patent and trademark laws on drugs have been considered in the United States and other countries, and believe further study is necessary (see page 49).

Profits and Risks

In a free enterprise system, it is obvious that a company must make a profit. Unless it achieves this primary objective, it cannot stay in business.

Ample evidence is available to demonstrate that the drug industry has been able to stay in business. It has maintained an annual profit rate based on net worth which is substantially above that of the average of major American industries.

--One study of 41 industries has shown that, between 1956 and 1966, the drug industry never

ranked lower than third on the basis of after-tax income as a percentage of net worth. In six of those years, it ranked in first place.

--Another study showed that, among 31 major industries, drug makers have averaged an 18.1 percent return on capital, as compared with 9.7 percent for the whole group.

A similar high rate of profit for the drug industry is indicated on the basis of profits calculated as a percentage of sales.

Spokesmen for the drug industry have agreed that its profitability is above average. They say, however, that this high rate is necessitated by the high degree of risk in the industry, and the need to attract the capital to finance further growth.

The Task Force has been unable to find sufficient evidence to support the concept of the drug industry as a particularly risky enterprise.

There is abundant evidence that the development of an individual drug may be associated with a high degree of risk, and that any such development is an economic as

well as a scientific gamble. There is, however, no evidence that this kind of risk characterizes a typical major drug company with a substantial line of drug products. When such a company undergoes a painful loss in this kind of a gamble, the record would seem to show, it generally covers it by substantial profits on other drugs.

The record would also tend to show that--at least during the past 20 years--losses of this nature have driven few if any major pharmaceutical manufacturers into serious financial straits.

In recent years, some major American drug manufacturers have diversified their operations by moving into other operations. In some instances, this has been described as an attempt to minimize risks. At the same time, however, it is apparent that other companies are diversifying their operations by moving into the drug field.

The Chief Economist of the Federal Trade Commission has testified that, on the basis of advice given by investment analysts, there is no reason to conclude that the drug industry is a uniquely risky industry. In fact,

it appears that large drug companies should have little difficulty obtaining adequate capital for growth should they choose to go into the market for it. Actually, however, their earnings are large enough to preclude the frequent need for equity capital.

If new Federal regulations concerning drug safety, drug efficacy, and drug advertising have had any significant effect in reducing drug profits, this is not evident in recent drug company profit statements.

The "Reasonableness" of Drug Prices

Whether prescription drug prices set by the major manufacturers are "too high," "reasonable," or "too low" is obviously a problem which cannot be resolved to the mutual satisfaction of all manufacturers and all consumers.

It appears, however, that current drug prices at the manufacturer's level are marked by these characteristics:

1. They reflect research and development costs which are relatively high in comparison with other industries, and which include a substantial degree of effort yielding only duplicative or "me-too" drugs and combination products that

contribute little to the improvement of health care.

2. They reflect promotion efforts which are high and are directed primarily to physicians.

3. They reflect a high degree of competition based essentially on quality and innovation, rather than the normal competition based on quality, innovation, and price.

We find, therefore, that the exceptionally high rate of profit which generally marks the drug industry is not accompanied by any peculiar degree of risk, or by any unique difficulties in obtaining growth capital, and that industry profits have not been significantly reduced by new governmental regulations concerning drug safety, drug efficacy, or drug advertising.

It is also evident from this study that there are certain problem areas which call for cooperative study and action by the drug industry, private groups, and the Federal Government.

Accordingly, the Task Force recommends that the Secretary of Health, Education, and Welfare should call

one or more conferences with representatives of the drug industry, pharmacy, clinical medicine, and consumer groups to consider--

(a) Provision of incentives to the drug industry to invest more research effort in products representing significant improvements to therapy and less in duplicative, noncontributory drug products and combinations.

(b) Development of a registration and licensing system under which no drug product would be permitted in interstate commerce unless produced under quality control standards set by the Secretary of Health, Education, and Welfare.

(c) Limitation of free drug samples to those specifically requested by prescribers, by industry agreement or legislation.

(d) Development of more effective methods for ascertaining actual acquisition costs of prescription drugs.

Similarly, it is evident that certain other areas of concern require detailed analysis by appropriate agencies of the Federal Government.

The Task Force therefore recommends that the Secretary of Health, Education, and Welfare should call for a joint study by the Department of Health, Education, and Welfare, the Department of Commerce, the Department of Justice, the Federal Trade Commission, and other Federal agencies to consider--

(a) The substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and government agencies.

(b) The substantial differences in the prices at which drug products are offered to American and foreign purchasers.

(c) Revision of patent and trademark laws on prescription drugs.

THE DRUG DISTRIBUTORS

Between the manufacturers who make drugs and the patients who purchase them is a large, complex distribution network.

Included in this network are the major drug vendors--independent pharmacies, chain drugstores, prescription pharmacies, mail order pharmacies, hospital pharmacies, dispensing physicians, and others. Considered with them in this section are the drug wholesalers.

Of the average prescription drug dollar paid by the consumer, about 50 cents is now taken by the manufacturer, 10 cents by the wholesaler, and 40 cents by the retailer.

During the past three decades, the operations of this system have undergone significant changes. For example, before World War II, most of all the drug products handled were in bulk form, and were compounded into tablets, capsules, powders, solutions or other dosage forms by the pharmacist. Now about 95 percent are furnished by the manufacturer in final dosage form, ready for consumption.

Formerly, wholesalers handled the overwhelming proportion of drug products. Now, with manufacturers tending to sell directly to hospitals and the larger independent pharmacies and chains, the wholesalers handle only about 48 percent of the dollar volume of the market.

In the years to come, other changes in the number and nature of both wholesale and retail outlets will undoubtedly occur as the result of continuing economic pressures, health manpower shortages, the expansion of new types of careers in pharmacy, and the introduction of innovations enabling drug distributors to respond more effectively and efficiently to the health needs of patients.

Prescription Price Information

There is an obvious need for patients to be able to determine readily the prices charged by the various pharmacies in their community. This appears to be particularly important in the case of long-term maintenance drugs.

The Task Force recognizes the difficulties in making such information easily available. Many patients are not told which drug has been prescribed for them--or are unable to decipher the physician's prescription. In many States,

laws or regulations forbid pharmacies to advertise; even without such rules, however, advertising current prices on many thousands of different drugs and dosage forms would pose formidable practical problems. Physicians, especially those in large cities, are likely to be unaware of the different prices which may be set at different pharmacies.

The Task Force also recognizes that the retail price of the prescription includes not only the cost of the ingredients, but also in some instances the availability of home delivery and 24-hour-a-day operations, as well as the professional services of the pharmacist--and that different pharmacists may wish to place different values on such services.

It recognizes that many or most patients may wish to select a pharmacy more on the basis of convenient location than on the basis of price.

Nevertheless, if the patient is to maintain the right to select a pharmacy, he also has a right to know the prices it charges and to compare these with other prices.

The Task Force finds there is a need for medical associations, pharmacy associations and consumer groups, working together at the local level, to develop mechanisms

whereby patients may obtain information on local prescription prices, especially for long-term maintenance drugs.

Prescription Label Information

It is frequently necessary for a physician to determine the nature and amount of a prescription drug which a patient has been taking. In some instances--as in the case of a suspected adverse drug reaction, or accidental or deliberate overdose--the rapid identification of a drug may be a matter of life and death.

As a step in improving the quality of health care, the Task Force recommends that the Congress should enact legislation requiring that the containers of all dispensed prescription drugs be labeled with the identity, strength and quantity of the product, except where this is waived upon specific orders of the prescribers.

To promote efficiency and minimize errors, the Task Force recommends that encouragement should be given to the wider use of prepackage dispensing, in which manufacturers prepare and pharmacists dispense tablets and capsules in precounted form, in sealed, prelabeled containers, and in such numbers as conform to those most frequently prescribed by physicians.

The New Role of Pharmacy

The pharmacy profession currently faces a dilemma which is partly though not entirely of its own making.

Many other aspects of health care--the practice of medicine and surgery, hospital operations, and particularly drug manufacture--have developed and adopted new devices and techniques which have remarkably improved the provision of health services. In contrast, the number of important new methods introduced to enhance the efficiency of retail pharmacy operations, at least during the past two or three decades, has not been noteworthy.

The Task Force recommends that the National Center for Health Services Research and Development should develop and support research to improve the efficiency and effectiveness of community and hospital pharmacy operations.

The role of the pharmacist is viewed by many people as simply transferring pills from a large bottle to a small one--counting tablets, typing labels, and calculating the price. Much of his time is seen as devoted to routine merchandising of cosmetics, shaving supplies, stationery and other commodities which have little or no relationship to health care.

This has raised doubts concerning the relevance of modern pharmacy education. As with other members of health professions, on the one hand, it would seem that much of the traditional education is not utilized, since a nonprofessional pharmacist--working under the supervision of a licensed pharmacist--can effectively perform many of the routine tasks of counting, labeling, and pricing. At the same time, many pharmacists are seeking a new role as a drug information specialist, and thus it would appear that their formal education has not taken this into account.

These problems regarding what the role of the pharmacist properly is--or should be--deserve careful consideration.

Pharmacist Aides

Experience in numerous pharmacies--military and nonmilitary Federal installations, nongovernmental hospitals, and others--has demonstrated that individuals without formal pharmacy education can effectively undertake many of the routine activities of pharmacists, under the supervision of a licensed pharmacist.

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Such activities offer the possibility of developing the career of pharmacist aide, comparable to the nursing aide, the orthopedic aide, the pediatric aide, the obstetrical aide, and similar paramedical positions.

Drug Information Specialists

At the other end of the spectrum, it is also becoming evident that appropriately trained pharmacists may become new and vital members of the total health team by serving as drug information specialists.

Some community pharmacists are already providing such services. They do not prescribe, but they discuss practical details of drug administration, possible side-effects, and other facets of drug use with each patient to whom a prescription drug is dispensed. They maintain patient or family records which contain data on drugs which have been dispensed to each patient, allergic responses, and adverse reactions. They call to the attention of the physician any prescriptions which may have been written for the same patient by other physicians, and they refer to him any prescriptions which may involve drug-interaction, synergism, or similar effects.

Some hospitals--especially teaching institutions and those in major medical center complexes--are already using pharmacists as consultants on drug therapy. They serve not only as drug distributors, but also as sources of drug data for physicians, interns, residents, and nurses. They may participate in ward rounds with the staff, providing valuable drug information on both old and new drug products. Although they do not prescribe for patients, they enable the physicians who do prescribe to keep up more effectively with drug information.

While some pharmacists are already serving as drug information specialists, and others are probably competent to do so, not all pharmacists have adequate competency in this field. Some licensed pharmacists have received five or even six years of formal college training, but about 15 percent of those now in practice have received two years or less of formal pharmacy education, and nearly half of these have had courses lasting only about six months.

Pharmacy Education

The manner in which pharmacists, pharmacy associations, pharmacy schools, and the pertinent State pharmacy agencies respond to increasing demands for pharmaceutical services will unquestionably determine in large measure how the

pharmacy profession will evolve during the years to come.

The Task Force commends the efforts of those pharmacy schools and State pharmacy associations which are already stressing continuing postgraduate education.

As a guide to the responses which should be made, there is a clear need for a broad study of pharmacy education similar to the famed Flexner study of medical education made half a century ago.

The Task Force therefore recommends that the Bureau of Health Manpower should support--

(a) The development of a pharmacist aide curriculum in junior colleges and other educational institutions.

(b) The development of appropriate curricula in medical and pharmacy schools for training pharmacists to serve as drug information specialists on the health team.

(c) A broad study of present and future requirements in pharmacy, adequacy of current pharmacy education, and the educational changes which must be made.

Pharmacy Laws

The present patchwork of State pharmacy laws, regulations, and codes of ethics obviously reflects attempts to cope with a variety of pharmacy problems on a piecemeal basis. Whether they are aimed at the protection of the public health or the prevention of competition--fair or unfair--is not clear in all cases.

Many of these rules seem to have derived from periods of manpower excesses. They block efforts to cope with the present shortages of skilled manpower, the need for mobility to meet rapidly changing health needs, and the probable development of new careers in pharmacy.

The Task Force recommends that the Health Services and Mental Health Administration should support studies of State laws, regulations, and codes, with priority given to the establishment of model State licensing laws, uniform reciprocity standards, and provisions for the utilization of pharmacy aides.

THE DRUG PRESCRIBERS

In the modern use of drugs, important roles are played by the drug researcher, the manufacturer, the distributor, the pharmacist, and the official who carries the legal responsibility for drug safety, efficacy and quality. But the most strategic role is that of the physician who prescribes the drug.

It is the physician who has major responsibility for the welfare of the patient.

It is the physician who is constantly faced with an awesome assortment of competitive and often duplicative products.

It is the physician who is the target of a barrage of advice, information, guidance, and promotion from detail men, advertisements, medical articles, pamphlets, bulletins, and throw-away journals.

And it is the physician who--with or without adequate training and competent advice--must make the decision on which drug or drugs to prescribe.

On his decision may well depend the health or even the life of his patient. On it will depend, at least

in part, the quality, cost and effectiveness of any drug insurance program, governmental or nongovernmental. And on it will depend the economic well-being of a drug company.

Rational Prescribing

The appropriate selection of a drug--the right drug for the right patient, in the right amounts at the right times--is generally defined as rational prescribing, and any significant deviation is considered to be irrational prescribing.

Rational prescribing is obviously the result of judgments on many points--the safety and efficacy of the drug for the clinical problem at hand, the advantages or disadvantages of alternative forms of therapy, the most appropriate dosage form, the length and intensity of treatment, the possible side-effects or adverse reactions, and the possibility of drug interaction.

To these may be added judgments concerning relative costs.

Rational prescribing is clearly a major goal for the welfare of patients. It is likewise a major goal for any drug insurance program. Here, emphasis has been placed not directly on achieving rational prescribing but rather

on preventing some of the more serious or costly forms of irrational prescribing. Among the latter are these:

--The use of drugs without demonstrated efficacy.

--The use of drugs with an inherent hazard not justified by the seriousness of the illness.

--The use of drugs in excessive amounts, or for excessive periods of time, or inadequate amounts for inadequate periods.

--The use of a costly duplicative or "me-too" product when an equally effective but less expensive drug is available.

--The use of a costly combination product when equally effective but less expensive drugs are available individually.

--The simultaneous use of two or more drugs without appropriate consideration of their possible interaction.

--Multiple prescribing, by one or several physicians for the same patient, of drugs which may be unnecessary, cumulative, interacting, or needlessly expensive.

We find that some patients may be receiving as many as a dozen different drugs simultaneously, prescribed either by one or several different physicians, and that often physicians may not be aware that their patients are receiving drugs prescribed by others.

We find no reason to believe that any or all of these types of irrational prescribing can be effectively prevented--or that rational prescribing can be effectively induced--merely by rules and regulations. Instead, we believe the objective of rational prescribing can be reached most effectively through improving medical education--particularly in the area of clinical pharmacology--at both the undergraduate and postgraduate levels, supplying practicing physicians with objective data on which they can base their individual prescribing decisions, and supporting those in hospitals, clinics, medical societies and health insurance programs who are seeking to achieve rational prescribing by their fellow practitioners.

The Teaching of Pharmacology

In most American medical schools, the principal course in pharmacology is given during the second year. Generally, this is the only formal exposure of the student to the subject.

The nature of the pharmacology instruction has been a matter of much debate but little change. Although it is in reality a clinical as well as a basic science, it is taught primarily as a basic subject, with emphasis on the principles of drug action, a review of specific drug groups, examples of drug applications, and the broad fundamentals of prescription writing.

After the usual course in basic pharmacology, most medical students are given no formal training in the applied aspects of this field--in clinical pharmacology--but left to acquire what practical training they can absorb from a variety of courses in the several fields of clinical medicine.

Perhaps the most serious criticism of this informal exposure is that it fails to equip the soon-to-be physician with the essential scientific and critical attitudes towards the use of drugs and the evaluation of drug promotion--probably the most intensive promotion to which he

will be subjected for the rest of his professional career.

The Task Force has noted that some medical schools have responded to such a deficiency by establishing courses in clinical pharmacology or pharmacotherapeutics. In these courses dealing with the practical aspects of drug prescribing, emphasis is generally placed on such subjects as the design of comparative clinical drug trials, and the techniques of statistical analysis. Also included in some courses is the evaluation of drug advertising and promotional material, and the importance of drug costs.

Many who participate in these and related programs have received a major part of their training in the Section of Clinical Pharmacology in the National Heart Institute of the National Institutes of Health.

The Task Force recommends that the Department of Health, Education, and Welfare should provide expanded support to medical schools, enabling them to include a course in clinical pharmacology as an integral part of the medical curriculum.

Postgraduate Education

Upon entering private practice, the average physician, knowingly or unknowingly, becomes the key figure in drug marketing strategy.

--He must choose from a very large number of competitive and often duplicative products.

--He must deal with a very large amount of advice, biased or unbiased, from detail men, advertisements and other forms of promotion.

--Substantial efforts are made on his behalf by the drug industry and others to prevent any interference with his right to prescribe as he sees fit.

--Finally, it is assumed that he has the training, experience, and time to weigh the claims and available evidence, and thus to make the proper selection.

Everything, of course, hinges on the validity of this final assumption.

We find that few practicing physicians seem inclined to voice any question of their competency in this field. We have noted, however, that the ability of an individual

physician to make sound judgments under these quite confusing conditions is now a matter of serious concern to leading clinicians, scientists, and medical educators. A distinguished pharmacologist, for example, has stated that lack of knowledge and sophistication in the proper use of drugs is perhaps the greatest deficiency of the average physician today. Other medical leaders have pointed to the wide discrepancy in the prescribing habits of the average physician as compared to the prescribing methods recommended by panels of medical experts. Still others have commented on the continued use by the average physician of products which have been found unnecessary or unacceptable by specially qualified therapeutics committees in hospitals and clinics.

We note that the most widely used source of prescribing information is essentially a compilation of the most widely advertised drugs.

The responsibility for these and other deficiencies has been placed on various factors:

--Inadequate training in the clinical application of drug knowledge during the undergraduate medical curriculum.

--Inadequate sources of objective information on both drug properties and drug costs.

--Widespread reliance by prescribers for their continuing education upon the promotional materials distributed by drug manufacturers.

--The exceedingly rapid rate of introduction and obsolescence of prescription drug specialties.

--The limited time available to practicing physicians to examine, evaluate, and maintain currency with the claims for both old drugs and newly marketed products.

--The constant insistence on the idea that the average physician, without guidance from expert colleagues, does in fact possess the necessary ability to make scientifically sound judgments in this complicated field.

Information Sources

Several significant approaches have been attempted to cope with this problem. In the United States, a small number of independent publications--which do not publish advertising--seek to present objective evalua-

tions of the efficacy, safety, rationality, and occasionally the costs of specific drugs. These have relatively limited circulation, but are highly esteemed by medical leaders.

Many American hospitals and clinics utilize pharmacy and therapeutics committees to develop formularies which serve as guidelines to the staff members of the institutions. These, too, appear to contribute significantly to rational prescribing.

Other approaches to the problem of communicating objective and updated drug information have been proposed. These include, among others, closed-circuit television programs originating in medical centers; the development of community pharmacy and therapeutics committees; and the utilization of existing regional medical programs to sponsor continuing drug information programs; and the use of hospital pharmacies as drug information centers.

Several foreign drug programs--notably those in Great Britain, Australia, and New Zealand--provide all physicians with prescribing guidelines prepared by panels of independent medical experts. Such publications--frequently updated to meet changing conditions--have been widely accepted by the medical profession in those countries.

In consideration of these factors, in view of the unfilled informational needs evident in this country, and as a major contribution to improving the quality of health care, the Task Force recommends that the Department of Health, Education, and Welfare should establish or support a publication providing objective, up-to-date information and guidelines on drug therapy, based on the expert advice of the medical community.

We recommend that the Department of Health, Education, and Welfare should support the efforts of county medical societies, pharmacy and therapeutics committees, medical foundations, and medical schools in taking the responsibility for providing continuing education to physicians on rational prescribing.

The Bureau of Health Manpower, the Division of Regional Medical Programs, and the National Library of Medicine in particular should assign high priority to the support of such efforts.

Finally, we affirm our interim recommendation that the Secretary of Health, Education, and Welfare should be authorized to publish and distribute a drug compendium listing all lawfully available prescription drugs, including such information as available dosage forms, clinical effects, indications, and contraindications for use, and methods of administration, together with price information on each listed product.

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DRUG QUALITY

During the past several years, the clinical equivalency of generic name products has been the center of particularly heated controversy.

This issue may be presented as follows:

--Given two drug products containing essentially the same amount of the same active ingredient--that is, two chemical equivalents--will they give essentially the same clinical effects?

This question, of increasing interest to both physicians and patients, is now under careful consideration by the scientific community. Objective research has shown that in certain instances the clinical effects may not be the same.

The Task Force has found, however, that lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health. Where low-cost chemical equivalents have been employed--in foreign drug programs, in leading American hospitals, in State welfare programs, in Veterans Administration and Public Health Service hospitals, and in American military operations--

instances of clinical nonequivalency have seldom been reported, and few of these have had significant therapeutic consequences.

Even though such cases are few, and others may well be reported in the future, these cannot be ignored, and the problem deserves careful consideration because of the medical and economic policies which are involved.

The interrelation of medical and economic factors is especially obvious in the case of two chemically equivalent products, both containing the same amount of the active ingredient and both meeting legal standards, but priced at different levels.

If the physician can be given reasonable assurance that two such competitive products will, in fact, give predictably equivalent clinical effects, then his choice between the two may well be based on relative costs. Under such conditions, there would be little justification for prescribing a relatively expensive brand of a drug when an equally effective counterpart is available at substantially lower cost. Similarly, there would be little justification for a Federal drug program to provide for reimbursement of such an expensive brand.

But if the physician cannot be given this assurance, his clinical judgment would dictate that he use only the product which can be expected to yield the desired clinical effects--regardless of cost or any other nonmedical factor.

The physician should be given assurance--not in the form of advertising, promotion, or the established image of the manufacturer involved, but in the form of objective, scientific data. In view of the thousands of drug products on the market, the accumulation of such data might seem to be monumental. But, with the exception of a few drugs for which adequate analytical methods are currently unknown, the Task Force has found that the problem is by no means insoluble.

Clinical Equivalency and Biological Equivalency

For the direct determination of clinical equivalency, it would be necessary to compare drug products containing the same active ingredient, in the same tablet or capsule or other dosage form, in the same amounts, and measurement of their relative effects in human patients in the alleviation of symptoms or the control of a specific disease.

Except perhaps in rare instances, such a comparison appears to be impractical at this time. It would be time consuming and costly. It would be complicated not only by individual human differences but by differences in the symptoms or diseases under consideration.

Clinical equivalency studies could be conducted in experimental animals, but the nature of specific diseases and the nature of drug absorption and action in animals and human beings may not be directly comparable in all cases.

Instead, attention has been directed to the use of biological equivalency--or relative biological or physiological availability--measured in normal subjects as a proxy for the direct measurement and comparison of therapeutic effects.

This is based on the general agreement among pharmacologists that with most drugs--certainly those taken orally for their effect on internal tissues and organs--their therapeutic effectiveness will be closely related to the absorption of the active ingredient into the blood stream.

Thus, it is assumed that if the active ingredient in two or more chemically equivalent products reaches the blood (or other fluid or tissue)--and becomes biologically or physiologically available--at the same time and in the same amounts, their therapeutic effects will be essentially the same.

Among the formulation factors which may be involved here, and involved in any possible nonequivalency of orally ingested products, are particle size; crystal form; the pressures and other conditions used in tablet-making; and adjuvants, such as substances incorporated as fillers, lubricants, binders, coatings, flavorings, colorings, and tablet-disintegrating agents.

Attention has also been directed toward physico-chemical tests which might be used to indicate biological equivalency--and, in turn, clinical equivalency. Perhaps the most important of these is the dissolution rate. Once a drug is dissolved in the gastrointestinal fluid, absorption is usually rapid. It is not surprising, therefore, that reported instances of clinical nonequivalency are rare among drugs which are highly soluble or administered in solution but most frequent among drugs

of inherently low solubility which are administered in solid dosage forms such as tablets and capsules.

Biological Equivalency Trials

In consideration of the foregoing, the Task Force initiated a program in the fall of 1967 to determine scientifically the biological equivalency of a number of chemical equivalents.

A major phase of the investigation was an attempt to determine whether any observed differences in biological equivalency could be related to differences in the physical or chemical characteristics of the products.

It was recognized at the outset that such trials were urgently needed for relatively few drugs. For example, among the 409 products most widely used by the elderly--and which accounted for about 88 percent of all prescription drugs dispensed to this group, there were only 89 which were dispensed under brand name but could have been dispensed under generic name from one or more additional suppliers. An additional 30 were actually dispensed under generic name.

Among these, the priority for clinical trials was determined on the basis of the following criteria:

1. The product is generally considered as a "critical" drug--that is, required for the control of a disease, rather than for the alleviation of temporary symptoms.
2. It is generally dispensed in solid form--as a tablet or capsule.
3. The active ingredient is relatively insoluble.
4. Particular attention should be given to those drugs which had previously been the subject of reported or suspected nonequivalency or therapeutic failure.

A number of drugs meeting these criteria were selected by the Task Force in consultation with representatives of clinical medicine, pharmacology, pharmacy, brand name and generic name manufacturers, the Food and Drug Administration, and other governmental agencies. Biological equivalency studies on these products in human volunteers began late in 1967 in the FDA laboratories; at Georgetown University, under an FDA contract; and at the Public Health Service Hospital in San Francisco.

(Detailed results of these investigations are not presented in this report. Since they obviously may be of practical concern to physicians and scientists, the data are being announced as quickly as they become available in the usual medical and technical publications.)

As an important part of these trials, attempts were made to determine whether any observed differences in biological availability could be correlated with differences in any physico-chemical characteristics of the product. Such physico-chemical differences could presumably be utilized in developing new and approved specifications for drug quality testing.

Although complete data are not available, it appears noteworthy that all instances of biological nonequivalency found in the first phases of the trials were, in fact, marked by differences in dissolution rate.

The Task Force recommends that the present clinical trials to determine the biological equivalency of important chemical equivalents should be continued by the Department of Health, Education, and Welfare on a high priority basis.

Drug Standards

In the United States, the two most important official compendia of drug standards and specifications are the U.S. Pharmacopeia (USP) and the National Formulary (NF). Both have long and distinguished histories, and are highly regarded by physicians and scientists.

Although both publications have clearly stated that they cannot guarantee it, their standards and specifications have been widely presumed to assure the clinical equivalency of chemical equivalents.

The recent finding that some chemical equivalents are not biologically equivalent, even though they conform to existing USP and NF standards, has shown that certain of these standards may require revision.

During the past year, representatives of both USP and NF have been cooperating closely with the Task Force to meet this challenge. It is expected that existing specifications will be tightened where indicated and possible, and that these modifications will be incorporated in the revised USP and NF editions now in preparation.

The Task Force commends the U.S. Pharmacopeia and the National Formulary for their prompt and responsible approach to the problem of clinical equivalency.

Quality Control

The establishment and enforcement of product standards and specifications represents one important approach to the problem of drug quality and clinical equivalency.

Another is the establishment and rigid enforcement of appropriate quality control standards in all aspects of drug production and packaging. The Task Force has already recommended that a registration and licensing system be considered under which drug producers and packagers would be required to conform to a code of Good Manufacturing Practices and other criteria. (See Page 48)

We likewise recommend that adequate financial support should be provided to the Food and Drug Administration for necessary educational and inspection operations so that acceptable quality control methods can be instituted and properly maintained in all drug manufacturing and packaging establishments.

We recommend that the Food and Drug Administration should be authorized to provide additional support, including grants-in-aid, to State and local agencies in order to improve quality control of prescription drugs in intrastate commerce.

The enforcement of an acceptable quality control program may be expected to have these effects:

--Many reputable manufacturers, both large and small, already maintain acceptable quality control programs, and will merely be obliged to continue them.

--Some manufacturers may elect not to institute such programs, and their products would therefore be found unacceptable for shipment in interstate commerce.

--Other manufacturers will elect to institute and maintain acceptable quality control methods. This may result in slightly higher production costs, which the manufacturers would most probably cover by setting slightly higher prices on their products.

The Task Force in strongly convinced that the added investment of Federal funds to require acceptable quality

control methods, and the slightly higher drug prices that may result in some instances, would be more than justified by the improvement in drug quality that would be achieved.

We have given careful consideration to proposals for the placement of fulltime Food and Drug Administration inspectors in every drug manufacturing plant--large and small--but believe this would involve unjustifiably heavy expenses and inappropriate use of skilled manpower.

We have also considered proposals for the extension of batch certification--now applied mainly for insulin, antibiotics and biologicals--to all drugs, requiring FDA testing and approval at the manufacturer's expense before any batch may be released for distribution. We feel this would place an unnecessarily heavy and costly burden on manufacturers which would be reflected in unnecessarily higher prices to consumers.

Instead, we find that further study is needed on the use of self-certification, with each manufacturer instituting and maintaining a quality certifying program approved by FDA.

ONGOING PROGRAMS

The provision of out-of-hospital prescription drugs through governmental or private insurance programs has been undertaken in one form or another for nearly a century. Many of these include techniques and approaches which deserve consideration in any out-of-hospital program that might be designed under Medicare.

Accordingly, the Task Force has examined a wide variety of ongoing programs--all of the major drug programs conducted by the Federal Government, a number of selected State programs, six of the leading private programs in this country, and the major programs in eleven foreign countries.

These programs are not directly comparable. In some foreign countries, for example, national economic and social structures lend themselves to controls and methods of operation which are probably not suitable in the United States. Certain aspects of military drug programs may not be adaptable for civilian programs. Other approaches utilized in private programs may be impractical for a government operation.

Nevertheless, a study of these diverse systems has proved to be illuminating. It has clearly indicated

that out-of-hospital prescription drugs can be provided under programs that are medically acceptable and economically sound.

Federal Programs

Through direct purchase or reimbursement, the Federal Government is now concerned with the provision of prescription drugs through several major programs. As shown in Table 1, expenditures for drugs in these programs totaled more than $491 million in fiscal year 1967.

DOD Military Procurement. The largest direct drug procurement program is that of the Department of Defense, with its responsibility for supplying about 3,000 military establishments in this country and overseas.

A major characteristic of the DOD operation is its testing and inspection program to assure drug quality and the ability of the products to withstand prolonged exposure to climatic extremes. DOD sets its own drug specifications, maintains its own manufacturing plant inspectors, and operates its own testing program. Manufacturers must undergo stringent pre-award surveys of their facilities as well as testing of their products

Table 1

ESTIMATED FEDERAL EXPENDITURES FOR PRESCRIPTION DRUGS (Fiscal Year 1967)

	(million)	
Direct Purchase		
Department of Defense	$ 111.0	a/
Public Health Service	4.1	b/
Veterans Administration	39.5	c/
Federal Supply Schedule Contracts	6.2	d/
Total Direct	$ 160.8	
Reimbursement Programs		
CHAMPUS	$ 0.2	
VA Hometown Pharmacies	2.9	
Public Health Service	0.7	
Medicare In-Hospital	230.0	e/
Medicaid	96.5	f/
Total Reimbursement	$ 330.3	
Total all Federal Drug Expenditures	$ 491.1	

a/ Includes $92.4 million purchased through Defense Supply Center Philadelphia, Pa. and approximately $15.7 million purchased through Federal Supply Schedule Contracts; remainder purchased locally.

b/ Includes $1.3 million purchased through PHS Supply Service Center, Perry Point, Md., and $2.8 million from other sources including the Veterans Administration.

c/ Includes $14.6 million purchased through Federal Supply Schedule contracts administered by VA for General Services Administration.

d/ Includes purchases for miscellaneous Federal agencies.

e/ Includes $115.0 million for overhead drug expenses of hospitals and extended care facilities.

f/ Includes other Federally-supported State Public Assistance Programs; excludes $85.5 million, which was the State portion of the total drug program expenses.

in DOD laboratories. After drug contracts are awarded, both the plant facilities and the stored products are continuously spot-checked, and DOD actively solicits reports from military hospitals and physicians on drug quality, therapeutic efficacy, and adverse reactions.

About 240 of the 1,200 drugs currently stocked are purchased under generic name.

The DOD policy is to purchase drugs under contract from the lowest "responsible bidder." It may buy foreign-made drugs where the acquisition cost is at least 50 percent less than "responsible" domestic bids. The same pre-award standards and continuing surveillance imposed on domestic firms are applied to foreign manufacturers with DOD contracts.

As a Federal purchasing agency, DOD may purchase patented products from unlicensed manufacturers.

DOD Military Medicare. Through its Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), the Department of Defense provides out-of-hospital prescription drugs through hometown pharmacies to some 6.5 million eligible retired military personnel and military dependents. Various carriers are used for program administration.

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Any pharmacy willing to meet CHAMPUS requirements may participate. The pharmacist is reimbursed for the acquisition cost of the drug plus a dispensing fee which has been set for each State.

Each eligible beneficiary must first meet a deductible requirement of $50 per year--or $100 per year per family--and pay a co-insurance charge of 20 or 25 percent, depending on beneficiary status.

No formulary requirements are involved.

The average prescription price in 1967 was reported to be about $4.15.

Veterans Administration. In 1967, the VA purchased drugs and biologicals costing $39.5 million for use in its own hospitals and pharmacies, and also procured drugs for other Federal agencies, such as the Public Health Service and the Office of Economic Opportunity.

Of the drugs used in VA pharmacies, about 86 percent are purchased from some 250 manufacturers who have been approved by on-site inspections. Each VA hospital has its own drug formulary of about 700 to 2,000 items developed by its own pharmacy and therapeutics committee, and tailored to fit the needs of the institution. The

formularies are used as guidelines rather than prescribing limitations, since non-formulary drugs may also be prescribed.

Chemical equivalent drugs are widely used where available.

In addition, the VA Hometown Pharmacy Program provides out-of-hospital prescription drugs to eligible beneficiaries, generally those with service-connected disabilities. The hometown program, which involved an expenditure of $2.7 million in 1967, provides for reimbursement to pharmacies on the basis of acquisition cost plus a dispensing fee. No formulary is used in this program, and no deductible or co-payment is required.

Office of Economic Opportunity. Through its Neighborhood Health Centers, OEO provides pharmaceutical services for about 800,000 persons in 44 programs.

Eligibility requirements vary but generally are based on a "poverty line" schedule, on Medicaid standards, or on other guidelines established by the community. Each center makes its own determination about the use of a formulary. No deductible or co-payment is required.

Several of the centers provide direct drug services in their own pharmacies, while the others provide for

reimbursement to community pharmacies on the basis of acquisition cost plus a dispensing fee.

Public Health Service. In 1967, PHS expended more than $4 million for drugs for its own operations, and also purchased drugs for Civil Defense stockpiling.

Of the drugs procured for PHS activities, some were used by the National Institutes of Health and the National Institute of Mental Health, but most were dispensed through the Division of Direct Health Services--with 11 hospital and 14 clinic pharmacies--and the Division of Indian Health. The latter operates 51 hospitals with pharmacies, and contracts with about 200 community pharmacies that furnish prescription drugs to Indian beneficiaries.

Each PHS hospital has its own formulary, but exceptions are made for the provision of nonformulary drugs. Physicians who contract with PHS are not obliged to use the formularies.

Pharmacies participating under contract with the Division of Indian Health are required to dispense the least expensive drug products they have in stock which will meet the physician's requirements when a generic

prescription is written. The price may not exceed the price to the general public.

No deductibles or co-insurance requirements are involved in any of the PHS out-of-hospital programs.

Medicare. Data from the Medicare program relating to the cost of drugs provided to beneficiaries in hospitals and extended care facilities are not yet available. However, on the basis of recent studies of drug use in hospitals in general, it is estimated that in fiscal 1967 roughly $230 million was spent under Medicare for drugs, with about half of this amount representing product cost and the remainder the cost of dispensing and administration. (See Table 1)

Under Medicare, in-hospital drugs must be listed in one of several official compendia or in a formulary established by the hospital's pharmacy and therapeutics committee. Medicare requires that drug charges to the government must be "reasonable."

Public Assistance. Under Medicaid and other public assistance programs with joint Federal-State support, an estimated $182 million was spent for prescription drugs in fiscal year 1967, of which an estimated $96.5 million was paid by the Federal Government, (Table 1). Federal-

State vendor payments of $182 million represented 7.8 percent of all medical care services provided in that year, and were made to hospitals, pharmacists, and other licensed vendors.

The Federal share of payments to vendors for drugs and drug services ranged from 50 to 83 percent, depending on the nature and extent of the program in each State, with an average of about 53 percent.

In such programs, no deductibles or co-payments are generally involved, although one non-Medicaid State program included a co-payment requirement but provided funds to the recipients to cover such payments.

Further details on these public assistance programs are presented in the following section.

State Programs

Vendor drug programs for recipients of Medicaid and other public assistance funds are now operating in 38 States and Territories. The range in their utilization, costs, and benefits is very large.

Thus, among all eligible beneficiaries, the utilization rates in 1967 ranged from 26 percent in Missouri and Tennessee to 91 percent in New Hampshire and 99 percent in Rhode Island.

The average annual number of prescriptions per user ranged from about 10 in New Mexico to 46 in Indiana.

The average annual expenditure per user ranged from $39.35 in New Jersey to $148.95 in Florida, $155.67 in Nebraska, and $158.58 in Indiana.

The average cost per prescription ranged from $2.91 in Kentucky and $2.94 in Illinois to $4.74 in New Mexico.

Because of the diversity and complexity of the various State drug programs, the Task Force selected five for intensive study--California, because of its size; Louisiana and West Virginia, because of their approach in approving drugs used only for the treatment of specific diseases; Kentucky, because of its limited formulary; and Pennsylvania, because of its extensive formulary, which is used primarily as a guide to prescribing.

Other studies were conducted on the programs in Indiana, Nebraska, North Carolina, Oklahoma, and South Dakota.

In nearly all of these States, per capita drug costs and average prescription prices for program beneficiaries were higher than those for the total public. Whether this was the result of program abuse or of the

greater health needs of those receiving public assistance cannot be readily determined.

There was no consistent pattern of vendor payment, with some States reimbursing on the basis of customary and usual charges, some on acquisition cost plus a percentage markup, some on acquisition cost plus a dispensing fee, and some using a combination of percentage markup plus dispensing fee. Several set dollar limits. There was no clearcut relationship between any of these methods and program costs.

Where acquisition cost was a factor in the reimbursing formula, this was generally presumed to be the listed wholesale price, although it is understood that this list price has little if any relationship to the actual acquisition cost. Few States made any efforts through spot audits to determine actual acquisition cost.

Administrative expenses have been estimated to average about 50 cents per prescription, with the lowest cost--about 20 cents--reported in Louisiana. Differences in estimating administrative costs, however, make it impossible to make exact comparisons.

Among the States studied, none was applying data processing techniques to the extent necessary for effective utilization review.

Only one State--North Carolina--had tested the effect of a deterrent charge to the patient. In February 1967, North Carolina required the recipient to pay the first dollar of the cost of each prescription, and at the same time provided beneficiaries with monthly cash payments from which to pay medical expenses. Within about two months, although the number of prescriptions actually increased, the total cost of the prescription drug program was reduced.

While there seemed to be wide agreement among officials of many States that such a co-payment requirement would probably be a highly effective method of cost control, there was no such agreement on the effect of this technique in limiting the access of welfare beneficiaries to the health care they required.

The influence of limited formularies alone also appears to be questionable. Although the use of a highly restrictive formulary is associated in several States with effective cost control, such control also has been noted in Pennsylvania, with a virtually unlimited

formulary but with restrictions on quantity and number of refills.

Many States urged or required the dispensing of low-cost chemical equivalent products where available. Under such conditions, no significant instances of lack of clinical equivalency were reported.

We find, therefore, that in Medicaid and other State public assistance programs, no single method will by itself guarantee program efficiency, but without at least two features--reasonable formulary restrictions and effective data processing procedures--program controls will be ineffective. Although a co-payment requirement may not be widely acceptable in public assistance drug programs, its value in controlling costs in other programs seems evident.

Private Programs

Several nongovernmental programs to provide prescription drugs to members of unions and other groups have been in operation in this country for many decades, and others have been developed in more recent years.

For special examination, the Task Force selected six of these--Prepaid Prescription Plans, Inc.; Paid Prescriptions, Inc.; United Mine Workers; the Kaiser

Foundation Health Plan; Group Health Cooperative of Puget Sound; and the new Blue Cross plan.

As in the case of State programs, these private programs offered a variety of approaches. Some utilized their own pharmacies, and some used community pharmacies. Several used restrictive formularies, while others reimbursed for any prescribed product.

All were financed through monthly dues or premiums.

Major economies in these private plans were found associated with the use of formularies, frequent field audits to determine actual acquisition costs by vendors, and the use of a co-payment or similar requirement. The greatest economies were noted in those programs in which the institution served as the purchaser of the drug products, rather than as a reimburser, and thus could obtain competitive or negotiated bids.

Several of the programs included in this study either urged or required the use of available low-cost chemical equivalents. No significant problems with lack of clinical equivalency were reported.

Foreign Programs

The greatest experience with prescription drug programs has been achieved in a number of foreign countries.

Fifteen of them in eleven nations were selected by the Task Force for special study--Australia, Belgium, Denmark, France, Great Britain, The Netherlands, New Zealand, Norway, Sweden, West Germany, and the provincial programs of Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan in Canada. Less intensive studies were conducted on the programs in Italy and Switzerland.

All of these nations show wide variations in demographic characteristics, government operations, industrial development, social philosophy, local tradition, and even medical tradition, and certain portions of their health insurance programs may not be suitable for use in the United States. Nevertheless, most of the procedures considered for prescription drug insurance programs in this country have already been tried in one form or another in these foreign programs.

In all of the countries included in the Task Force study--which represent nearly all of the major prescription drug programs in the world--the program is financed by employee or employer contributions, or by voluntary or compulsory participation in various "sickness funds" and insurance plans.

Some, including several of the Canadian programs, are designed exclusively for public assistance beneficiaries. Others cover the entire population, regardless of economic status, while still others have programs providing one set of benefits to welfare beneficiaries or pensioners, and another set to those who are not public assistance recipients.

Most of the prescription drug programs, especially in Europe, are integral parts of national health insurance systems.

In most countries for which statistical data are available, it is evident that there has been a steady increase in the average number of prescriptions per year, in the average prescription cost, and in the cost of the entire program. Except in Canada, the prices of specific drug products and of average prescriptions are generally lower than those in the United States; these differences appear to reflect lower labor costs, lower purchasing power, and similar factors, and also more intense price competition among drug manufacturers.

In nearly all countries surveyed in this study, a formulary of one type or another is used to improve rational prescribing, ensure drug quality, and control

costs. In most, but not all cases, there are provisions for prescribing an unlisted drug when this is clinically indicated.

The drug lists of Norway, Sweden and Denmark are structured to provide only essential drugs for serious diseases. In France, Great Britain and West Germany, formularies are essentially unlimited, and in the last two countries are noncompulsory; all three of these countries, however, are currently considering the use of more restrictive formularies.

In Australia and New Zealand, and in several European countries, formularies have proved to be highly effective in controlling costs. The Australian government, for example, has no authority to set prices for drugs but uses inclusion in the formulary as an indirect means of price control--that is, if the price is considered too high in relation to its therapeutic advantages by a committee of medical advisors, a drug may not be included in the list. New Zealand negotiates prices, but will pay only at the level established for an acceptable chemical equivalent where one is available. Most of the countries have either established maximum retail prices or negotiated price agreements with manufacturers.

Compulsory licensing of patents is provided by law in most of the countries, but the law is seldom invoked. It may be used if the manufacturer of an "essential" or "necessary" drug refuses to reduce its price to what the health program considers to be a reasonable level.

With the exception of France, all countries in this group reimburse the drug vendor rather than the patient. The price paid to the vendor is usually determined on the basis of acquisition cost plus an established percentage markup, a dispensing fee, a container fee, or a combination of any of these. In The Netherlands, a capitation system is used in which the patient is required to have his prescription filled at a single pharmacy, and the pharmacist is paid a per capita fee for each patient registered with him.

In several countries, drug utilization review is provided through central or local boards or committees of physicians. In New Zealand, for example, medical representatives visit physicians to discuss drugs, local prescribing patterns and any individual prescribing habits which might seem to represent irrational prescribing. In Australia and Great Britain, these visits occur

when the individual physician's prescribing pattern appears to represent unusually high costs.

Nearly all of these countries recommend or require the use of low-cost chemical equivalents where available. No significant problems with lack of clinical equivalency have been reported. Controversy over generic name prescribing in Australia, New Zealand and most of the European countries studied by the Task Force has not reached the heights noted in the United States.

Quality control in many of the countries is achieved by registration of all drugs sold in the country, as well as by various types of drug testing. Often a drug evaluation committee or commission composed of physicians, pharmacists, and drug industry representatives has the responsibility for determining which drugs will be registered and which tests will be imposed. Testing varies from batch analysis to complete laboratory research of the formulation and its possible side effects.

Some programs call for patient participation through a fixed co-payment or percentage co-insurance. The effect of such a requirement was demonstrated in

Great Britain, when the co-payment requirement was abolished and program costs promptly rose substantially.

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From its consideration of ongoing prescription drug programs, the Task Force finds that a permanent mechanism is needed at the Federal level to collect, analyze and exchange information, and to provide effective coordination of drug-related activities among the agencies involved.

We therefore recommend that the Federal Interdepartmental Health Policy Council should concern itself with the coordination of all ongoing Federal prescription drug purchase and reimbursement programs.

We recommend that a special subcommittee of the Council should be appointed for this purpose.

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DRUG CLASSIFICATION AND CODING

Within a few years, it may be expected that prescription drug benefits under existing public and private programs will involve several hundred million prescriptions annually.

Without a universal coding, classification and identification system--a common language for communicating essential information--the administrative and accounting costs for processing such a volume will inflate program costs beyond acceptable limits.

To find methods of coping with this problem, the Task Force appointed ad hoc committees of experts on classification and coding which began a series of meetings in July 1967. In these conferences, criteria were established for a system under which all known pharmaceutical preparations could be identified and desired data stored and retrieved by use of existing and planned electronic data processing techniques and equipment.

Classification

By July 1968, the proposed classification system was in final draft. It is the result of the joint efforts of representatives of the American Medical Association, the

U.S. Pharmacopeia, the National Formulary, the American Society of Hospital Pharmacists, the Drug Information Association, the National Pharmaceutical Council, the Pharmaceutical Manufacturers Association, the Food and Drug Administration, the National Library of Medicine, and various universities and State agencies.

Based on the vital necessity to relate cost analysis and utilization studies to how and why drugs are being used, the classification scheme is designed to accomodate products by categories reflecting their intended therapeutic action. This version makes it possible to place drugs in multiple settings. Final data collection will survey these settings and provide cost breakdowns and other cost analyses according to actual drug usage.

Application of the classification will have obvious importance for economic administrative procedures. More significantly, it will play an important part in developing information needed for improving the quality of health care.

The Task Force recommends that the Department of Health, Education, and Welfare, the Department of Defense, and the Veterans Administration should test the proposed

drug classification system to determine the feasibility of its eventual use in all public and private drug programs.

We commend those whose efforts made possible the development of the system.

Drug Coding

In the different aspects of drug manufacturing, distribution, sales, use, utilization review, accounting, cost analysis, and other marketing or administrative procedures, many different kinds of information may be needed. Basic to all of them, however, is information which will identify (a) the manufacturer, (b) the product, dosage form and strength, and (c) the package size, and which also is in a form which can be transmitted, stored and retrieved through electronic data processing systems.

Logically, the identification number would be assigned for all drugs on the market, and for any new drug at the time the New Drug Application is approved.

The number should be part of the required labeling, and ideally could be used to identify each individual tablet or capsule by printing techniques which are already being used by some drug manufacturers.

In addition, the number should be utilized in the coding for a proposed international adverse drug reaction reporting system which is now under consideration.

As a result of Task Force studies, it appears that an appropriate code can be developed by the use of a nine-character identification system utilizing both letters and numbers. The first three numbers would identify the labeler of the product (in most cases the labeler would also be the manufacturer), the next four would identify the drug, dosage form and strength, and the last two would identify the package size.

It is believed that such an identifying system would be able to accomodate a virtually unlimited number of different drug products.

The Task Force recommends that--

(a) An appropriate identifying code number should be made part of all drug labels, package inserts, catalogs and advertising;

(b) An appropriate coding system should be developed and tested by government and industry for this purpose;

(c) After consideration of the results of this test, appropriate legislation should be introduced to require coding of all drug products in interstate commerce.

We commend those whose efforts are making the development of a new coding system possible.

As part of its activities in this field, the Task Force also supported development of an experimental National Drug Code Directory, prepared in preliminary form by the Food and Drug Administration to serve as a directory of essentially all prescription and over-the-counter drugs.

We recommend that the drug code adopted by government and industry be utilized in the National Drug Code Directory.

UTILIZATION REVIEW

In any drug program, utilization review is a dynamic process aimed first at rational prescribing and the consequent improvement of the quality of health care, and second at minimizing needless expenditures.

In many hospitals, staff committees of experts have long taken the responsibility of reviewing the records of their fellow physicians and offering such advice or taking such disciplinary action as they deemed necessary. During the past two years, utilization review programs have been instituted to improve the quality of medical care under the hospital program of Medicare. Similar reviews are used in several American and foreign drug programs to improve the quality of drug prescribing.

It should be the responsibility of a program administration to institute a drug utilization review, and provide the necessary data and whatever statistical analysis may be required.

But the implementation--the establishment and improvement of quidelines, the provision for acceptable deviations, the limitation of irrational prescribing, the prevention of fraudulent practices, and other professional judgments--

should be mainly the responsibility of clinicians, pharmacologists, and pharmacists who are widely respected as objective, well-informed, and appreciative of the needs of both physicians and patients, and who would work with their colleagues at the State or local level.

There is an evident need for further research to develop and test various approaches to effective utilization review--approaches which would be most acceptable to physicians, pharmacists, consumers and others, and which would obtain their effective support.

The Task Force therefore recommends that the National Center for Health Services Research and Development, in cooperation with State and local medical groups, community pharmacies, hospitals, and consumer groups, should support pilot research projects on prescription drug utilization review methods.

(Whereupon, at 12:05 p.m., the subcommittee adjourned subject to the call of the Chair.)

APPENDIXES

APPENDIX I

CORRESPONDENCE FROM DR. ROBERT E. HOWARD, PRESIDENT, OHIO STATE MEDICAL ASSOCIATION, TO SENATOR NELSON, DATED OCTOBER 18, 1967, RE DRUGS

OHIO STATE MEDICAL ASSOCIATION,
Cincinnati, Ohio, October 18, 1967.

Senator GAYLORD NELSON,
Chairman, Subcommittee on Monopoly,
Senate Select Committee on Small Business,
Washington, D.C.

DEAR SENATOR NELSON: The Ohio State Medical Association is taking this means of submitting its views on certain matters of pressing concern to the medical profession which have emerged during the current investigation of the drug industry by the Monopoly Subcommittee of the Senate Small Business Committee. The Association is composed of more than 10,000 practicing physicians representing all 88 counties throughout Ohio.

We respectfully ask that this statement be included in the published record of the hearings.

Much has been said during the investigation regarding "generic equivalency" in the drug field. Our deep and most sincere apprehensions have been aroused by reports of the testimony which have been widely published in the press and broadcast over the air.

We note that some witnesses have stated categorically, and others have implied, that there is little or no difference in the therapeutic effectiveness of drugs bearing the same generic name; that, if they meet the minimum standards of the U.S. Pharmacopoeia or the National Formulary, their manufacturing source does not matter. Further, it has become plain that the testimony has been weighted as to associate wrongfully the word "generic" with the word "cheaper" in its connotation to the public.

The result of this has been to promote the fallacious and dangerous belief that generic prescribing is not only safe from a medical viewpoint but is a desirable way for the physician to save the patient money in the purchase of his medicines. The particular rationale in this instance is that generic prescribing is a reasonable way for the government to hold down the cost of the health care it finances. Certainly, the saving of tax funds is a laudable aim and, in this frame of reference, the generic prescribing proposal can be expected to have broad popular appeal.

Nor can the patient be blamed if he is enticed by the promise of just as good drug products for less money. Like everybody else, he wants a bargain when he can get one. Lacking scientific knowledge and understanding of the many complexities involved in this matter, neither the taxpayer nor the patient can help but be swayed by arguments which carry the authority and prestige of a Congressional committee.

We have not seen produced any scientific data or substantive expert testimony which has been offered the Subcommittee to support the claim of generic equivalency of drugs. Indeed, we are certain that such evidence has not been placed before you because we know it does not exist. A comprehensive study of this question, so basic to your entire inquiry, is now being made by the Department of Health, Education and Welfare at the direction of the President. When it is completed, we feel confident it will illuminate the fallacy of so-called "generic equivalent." We urge you to withhold until then judgment on the testimony, the sweeping claims, the unsupported generalizations you have heard over the past several months; for, without incontrovertible scientific evidence, this controversy cannot be resolved by the public or members of Congress.

On the general question of drug costs, we would first point out that this is by far the smallest portion of the health care bill and it has declined in recent years, both as to the prices of the drugs themselves and the proportion they represent of the total costs of an illness. Prescription drugs now account for only 9.8¢ of the health care dollar, according to the Department of Commerce, compared with 11.7¢ a decade ago.

The Department of Labor reported in September that the price of prescription drugs on its Consumer Price Index has dropped 11.2% since the 1957–59 base period. We believe these trends, registered in a period when the prices of virtually all other commodities have been going up, raise serious questions as to the validity of the argument over drug costs as a pretext for requiring generic prescribing for any segment of the population, especially when such a program is advanced as a government economy measure.

We are in complete accord with the position taken by the American Medical Association on several occasions that physicians should supplement their medical judgment with cost considerations when prescribing for their patients. But this cannot mean that price is to be established as the paramount consideration in the selection of a medicine, over safety, and effectiveness. As physicians, we are professionally and ethically concerned that our patients receive only the highest quality products made by manufacturers who value highly their names and reputations and are known to, and trusted by, the prescribers.

The pressure for economy in prescriptions, as in many consumerist arguments, makes use only of the fact that fit a tendentious hypothesis. It is indeed a fact that some medications are available at a lower cost in identical form without a brand name. It is also a fact that, to some patients, it would make little, if any, difference what brand of a particular medication were prescribed. In these instances, the physician may wish to specify the least costly variety, provided quality is not sacrificed.

But the minor advantages of prescribing generic drugs stop at that point and the disadvantages begin. Health care personnel, knowledgeable in pharmaceutical manufacture and dispensing, are fully aware of the dangers of using non-brand-name drugs. And this danger does exist. We know of no hospital that requires generic prescribing of its staff members, including military hospitals about which so much has been said before the Subcommittee.

One of our professional colleagues, Doctor Durward Hall, Congressman from Missouri, has informed you of the rigid standards enforced by the military in the procurement of drugs, and the meticulous care exercised to assure the purchase of only quality products. We assume it has been established to the Subcommittee's satisfaction that the formularies of military hospitals are stocked with products of proven quality. Even beyond this, there is not a physician practicing in one of those institutions who does not possess complete discretion to prescribe precisely the medicine he deems best for a particular patient. His peers have not limited him to the formulary, stocked as it may be with products obtained under the most stringent requirements. If the medicine he prescribes is not on the shelves it will be specially purchased.

There must be a reason for this. There is. It lies at the heart of the generic prescribing issue.

From the physician's point of view, brand name drugs often have important and vital properties, in addition to the active chemical ingredients, that make them especially valuable in the treatment of certain patients. The carefully controlled and precisely stated characteristics of the drug are significant information that the prescribing physician relies on when he specifies the drug for his patient. The patient's response to a prescribed drug can be scientifically evaluated because the physician knows exactly what it was that he prescribed. If the doctor is forced to prescribe a generic drug, he may lose an important element of control over the treatment of his patient.

Where there are successive refills for long term treatment, the physician would again be deprived of control over his patient's treatment unless each new supply had the same variables—coating, solubility, disintegration time, base, etc. We submit that this is impossible when the medicine comes from several different manufacturers with different methods and standards of quality control. Under these conditions, there could be variations in therapeutic response which might mislead the physician in his diagnosis or alter the patient's progress. This hazard can be avoided if each refill comes from the same manufacturer who is known and trusted by the prescribing physician.

Interestingly, there is nothing at the present time that prevents physicians from prescribing generically. We believe most of our colleagues do in cases compatible with the patient's needs. But when we prescribe, for example, Dicumarol, an anti-coagulant, the dose and the therapeutic action msut be precise and reliable. Too much means internal bleeding; too little means clotting. In either instance, the result could be fatal. And once the proper dosage has been established for the individual, it must remain constant. It could be altered by a change from the product of one manufacturer to that of another, thereby causing a dangerous reaction in the patient.

There is no other way to express it. Professionally and ethically—for the good of the patient—we cannot but be seriously alarmed by the possibility that we may be confronted with the unscientific requirement that we prescribe generically for our patients without knowing anything about the medicine that will be dispensed, its pharmacological components, actions and reactions and what manufacturer stands behind it.

Chances cannot be taken with any medicine; they simply cannot be taken in the area of critical drugs. When we prescribe digitalis or nitroglycerin for our heart patients, we must know what we can expect the medicine to do, and our experience with the same product in the past tells us that. We cannot know if the medicine is from an indeterminate or questionable source which may change each time the prescription is refilled. The range between a toxic dose and a therapeutic dose is too narrow to allow room for the slightest doubt about these drug products to exist in the physician's mind.

We previously mentioned Dr. Hall's testimony before this Subcommittee. You will recall that he dealt with the high proportion of rejections of both drug manufacturing plants and drug products by military procurement officers as a result of their analysis and inspection procedures. The facts which he provided, we believe, constitute a devastating refutation of the arguments for generic prescribing, whether enforced by direct or indirect means.

Obviously, there were drugs offered to the government which were not manufactured under effective and exacting quality control methods. There were plants seeking to do business with the government which were found wanting for sanitary or other important reasons.

There are no assurances that the same drugs are not being sold to the public at the present time, or that the rejected plants are not on the market with products of dubious effectiveness. These could be the "inexpensive" generic drugs, the dangerous drugs, which would be dispensed under prescriptions failing to identify the manufacturer of the product desired by the physician or to specify it by brand name.

Proposals are now pending in Congress for the establishment of a national drug formulary from which prescribing physicians would be required to select medicines in order for their patients to be reimbursed for drugs under federally financed health programs. These are complicated measures and raise many questions for which the answers are notably lacking; questions over the selection of drugs for the proposed formulary; the propriety of forcing the use of generic terminology; the prospect of government price fixing of drugs; the adjudication of "acceptable quality" by the federal formulary committee, and the enormous administrative burden which the bills entail.

The effects of the legislation, in our opinion, would be a reduced quality of medical care and direct government intervention in the practice of medicine. For many Americans, it would no longer be a case of the patient's best interests being served according to his individual needs and the physician's judgment. Rather, the therapy available at government expense would be determined by committee. The physician would find himself facing the dilemma of whether to prescribe a drug from the formulary so his patient could be repaid, even though he did not regard it as the most desirable drug, or of prescribing a drug not listed in the formulary because he knew it best to fit the individual circumstances, thereby penalizing his patient financially.

In addition, the establishment of two classes of citizens would also be written into the laws of the United States under these measures. To require physicians to use "generic" drugs for their less fortunate patients would create an unethical double standard of therapy. One class would get those medications which the physician knew were best and in which he had confidence; the other would get those drugs listed in the formulary by the committee.

We mention the legislative proposals in this statement because of their close ties with the issue of generic equivalency about which this Subcommittee has

heard volumes of testimony. Introduction of the legislation has heightened the importance of your work and the conclusions you reach.

We urge you to be wary of over-simplified answers to very difficult questions, and of highly colored expressions of opinion, betraying extreme prejudice on occasion.

The miracle of modern medicine owes much to the pharmaceutical advances of the last 30 years. An amazing 75% of the 200 drugs most commonly prescribed today were unknown just a decade ago. The products of quality-conscious, research-oriented manufacturers have all but revolutionized the practice of medicine, relieving suffering, prolonging life and serving as a boon to patients everywhere in the treatment of their ills. Quite frankly, we are fearful of any developments that seem to threaten the future of this unrivaled pharmaceutical system by relegating quality and drug innovation for tomorrow to secondary consideration, by placing unwarranted and unscientific emphasis on cost, and by insisting all drugs must be the same, regardless of the manufacturer's standards or the conditions under which they are produced.

As physicians, we cannot stand idly by while the nation is urged to embark on what we are convinced would be an ill-conceived therapeutic misadventure. Our purpose here has been to offer our views on this subject, the administration of drugs, which has been a major factor in professional lives for a great many years.

Again, we urge you to support our serious judgment that the relative efficacy of drugs has no scientific basis, and that required generic or formulary prescribing would be detrimental to the public health and welfare.

Sincerely,

ROBERT E. HOWARD, M.D., *President.*

APPENDIX II

CORRESPONDENCE FROM JOHN L. LACH, PROFESSOR OF PHARMACY, UNIVERSITY OF IOWA, TO SENATOR NELSON, DATED JUNE 16, 1967, WITH ACCOMPANYING STATEMENT AND BIOGRAPHICAL MATERIAL

THE UNIVERSITY OF IOWA,
Iowa City, Iowa, July 16, 1967.

Hon. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: You are no doubt aware that, subsequent to my correspondence with you requesting an opportunity to appear before your Subcommittee on Monopoly on June 7 and 8, I phoned your office on June 5 to determine whether it would be possible to accommodate me on either of those dates.

In your absence on the date of my call, I talked with Mr. Cherkasky of your staff who informed me that the schedule of hearings as presently planned would not permit an appearance prior to my departure for Switzerland on June 21. It is my understanding from conversation with Mr. Cherkasky that additional hearings will be held in the month of June and that hearings may be continued throughout the next seven or eight months.

I am disappointed that it will not be possible for me to appear before your Subcommittee at this time. As indicated in my letter, I deem it to be of great importance to the conduct of these hearings that experts in the scientific and technical aspects of the issues under consideration have an opportunity to present their views. It is my strong conviction that the hearings, to date, have placed undue emphasis on economic factors. There are other important considerations in the comparison between drug products which must be considered by your Committee in order to establish complete objectivity and fair balance in the testimony or statements presented. The fact that it was not possible for me to appear on the dates requested does not alter my interest or concern and it is for this reason that I am writing to you at this time.

The enclosed statement was prepared for the express purpose of documenting some of the scientific evidence which exist concerning comparative quality of drug products. It is a statement which I believe deserves very careful consideration by you and the members of the Subcommittee. Because of its importance, I respectfully request that the statement be made a part of the official records of the hearings and that appropriate reference be made to it during those portions of the hearings which may deal with the subject of generic or therapeutic equivalency. A personal presentation would, of course, be more informative for the

Subcommittee but in the absence of such an opportunity, due consideration by you and members of the Subcommittee will help to assure the objectivity and fair balance I mentioned earlier.

I have also enclosed a biographical sketch and a list of publications in support of my qualifications.

I trust that submission of this statement for the record will in no way prejudice my chances for an opportunity to appear before the Subcommittee at some later date should hearings continue after my return from Switzerland. If in fact, the hearings do extend beyond December, I would respectfully request at this time that I have an opportunity to personally present a statement as soon after my return as possible.

Sincerely yours,

JOHN L. LACH,
Professor of Pharmacy.

JOHN L. LACH

Birthplace: Blairmore, Alberta, Canada, February 10, 1927; U.S. Citizen, Registered Pharmacist (Iowa).

Education: B.Sc. Pharmacy, University of Alberta, 1950; M.S. Pharmacy, University of Wisconsin, 1925; Ph.D. Pharmacy, University of Wisconsin, 1954.

Married: Wife: Carol, born in Milwaukee, Wisconsin; B.A. in Education, University of Wisconsin, 1950.

Children: 3 girls, ages 13, 10, and 6; 1 boy, age 3.

Professional Experience: After receiving the Ph.D. degree under Dr. T. Higuchi, I was appointed instructor in pharmacy at the University of Wisconsin, February to June 1954; appointed assistant professor, College of Pharmacy, University of Iowa, July, 1954; appointed professor of Pharmacy, July, 1962.

Experience is mainly in the area of undergraduate and graduate instruction. I was actively involved in the revision of both curriculums including our hospital pharmacy program.

Experience also includes the manufacturing area in that I served as co-ordinator (January, 1954 to July, 1965) of this division. Duties involved a complete reorganization of this area with respect to revision of product master formulas, production control, and quality control.

Membership: American Chemical Society, American Pharmaceutical Association, Iowa Pharmaceutical Association, U.S.P. Division Committee 1960 to 1965, Sigma Xi, and Rho Chi.

Other Activities: Member of the University of Iowa Faculty Council and other university committees; Member of several A.A.C.P. committees; Member of Official Church Board of the First Methodist Church, Iowa City; Served as chairman and speaker for a number of our seminars sponsored by the College of Pharmacy for the pharmacists of Iowa.

JOHN L. LACH PUBLICATIONS

1. Investigation of Some Complexes Formed in Solution By Caffeine.
IV. Interactions Between Caffeine and Sulfathiazole, Sulfadiazine, p-Aminobenzoic Acid, Benzocaine, Phenobarbital and Barbital (J. Am. Pharm. Assoc. (Sci. Ed.), June 1954).

2. Investigation of Some Complexes Formed in Solution By Caffeine.
V. Interaction Between Caffeine and p-Aminobenzoic Acid, m-Hydroxybenzoic Acid, Picric Acid o-Phtalic Acid, Suberic Acid and Valeric Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

3. Investigation of Complexes Formed in Solution By Caffeine.
VI. Comparison of Complexing Behaviors of Methlated Xanthines with p-Aminobenzoic Acid, Salicylic Acid, Acetylsalicylic Acid and p-Hydroxybenzoic Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

4. Study of Possible Complex Formation Between Macromoleules and Certain Pharmaceuticals.
III. Interaction of Polyethylene Glycols with Phenobarbital, Barbital, Pentobarbital, Resorcinol, Catechol, Phenol, p-Hydroybenzoic Acid, Salicylic Acid and o-Phthalic Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

5. Study of Possible Complex Formation in Aspirin-Polyethylene Glycol Suppositories (Drug Standards, Jan.-Feb. 1956).

6. The Chromatographic Separation of Morphine from its Degradation Products (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1956).
7. Study of Complex Formation of Dimethylurea with Some Pharmaceuticals (J. Am. Pharm. Assoc. (Sci. Ed.), Oct. 1957).
8. Study of Moisture Vapor Transmission Through Closures (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
9. Determination of Chlorobutanol in Pharmaceuticals by Amperometric Titration (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
10. The Chromatographic Separation and Determination of Diphenylhydantoin and Phenobarbitol (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
11. Study of Possible Complex Formation of Polyoxylstearate 40 with some Pharmaceuticals (Drugs Standards, Sept. 1957).
12. A study of Ascorbic Acid Tablet Formulations (Drug Standards, Nov. 1958).
13. Interaction Between High Molecular Weight Polyethylene Glycols and some Pharmaceuticals (Drug Standards, Jan. 1959).
14. The Kinetics of Degradation of Chlorobutanol (J. Am. Pharm. Assoc. (Sci. Ed.), July 1959).
15. The Influence of Various Complexing Agents on Benzocaine Degradation (Drug Standards, July 1959).
16. Stability of Morphine in Aqueous Solution.
I. Formulation of a Stable Morphine Solution (J. Am. Hosp. Soc., Fed. 1960).
17. Quantitative Separation of N-acetyl-p-Aminophenol and p-Aminophenol by Ion-Exchange Chromotography (Drug Standards, March 1960).
18. A Note on the Quantitative Ion Exchange Chromatographic Separation and Determination of Para-Aminosalicylic Acid (Drug Standards, May 1960).
19. Determination of N-Acetyl-p-Amenophenol in some Pharmaceuticals (Drug Standards, July 1960).
20. Separation of Morphine from Its Degradation Products (J. Am. Pharm. Assoc. (Sci. Ed.), Nov. 1960).
21. Kinetics of Morphine Degradation in Aqueous Solution (J. Am. Pharm. Assoc., (Sci. Ed.), Nov. 1960).
22. The Kinetics of the Degradation of N-Acetyl-p-Aminophenol in Aqueous Solution (J. Am. Pharm. Assoc., (Sci. Ed.), Feb. 1961).
23. "Buffers In Pharmacy" (Proc. Amer. Assoc. Coll. Pharm. Teachers' seminar 1961).
24. Interaction of Pharmaceuticals with Schardinger Dextrins.
I. Interaction with Hydroxybenzoic Acids and p-Hydroxybenzoates (J. Pharmaceutical Sciences, Feb. 1963).
25. Interaction of Pharmaceuticals with Schardinger Dextrins.
II. Interaction with Selected Compounds (J. Pharmaceutical Sciences, Feb. 1963).
26. Gas Chromatographic Separation of Amines by Special Selectivity (J. Pharmaceutical Sciences, Nov. 1963).
27. Interaction of Pharmaceuticals with Schardinger Dextrins.
III. Interaction with Mono-Halogenated Benzoic Acids and Aminobenzoic Acids (J. Pharmaceutical Sciences, Jan. 1964).
28. Schardinger Dextrin Interaction.
IV. Inhibition of Hydrolysis by Means of Molecular Complexation Formation (J. Pharmaceutical Sciences, Aug. 1964).
29. Rapid Method for the Determination of Mixtures of p-Hydroxybenzoate Esters by Gas Chromatography (J. Pharmaceutical Sciences, March 1965).
30. Spectrophotometric Determination of Some Quaternary Compounds (J. Pharmaceutical Sciences, Oct. 1965).
31. Kinetics of Hydrolysis of Monothionsuccinimides (J. Organic Chemistry, Nov. 1965).
32. Interaction of Pharmaceuticals with Schardinger Dextrins.
V. Interaction with a series of Phenyl-Substituted Carboxylic Acids (J Pharmaceutical Sciences. Dec. 1965).
33. Diffuse Reflectance Studies of Solid-Solid Interactions.
I. Interactions of Oxytetracycline, Phenothiazine, Anthracene, and Salicylic Acid with Various Adjuvants (J. Pharmaceutical Sciences, Dec. 1965).
34. Interaction of Pharmaceuticals with Schardinger Dextrins.
VI. Interactions of β-Cyclodextrin, Sodium Deoxycholate, and Deoxycholic Acid with Amines and Pharmaceutical Agents (J. Pharmaceutical Sciences, Jan. 1966).

35. Effect of a Panothenic Acid–Deficient Diet on Monamine Oxidase (MAO) and Deoxyribonucleic Acid (DNA) in Rat Liver (J. Pharmaceutical Sciences, Jan. 1967).
36. Diffuse Reflectance Studies of Solid-Solid Interactions.
II. Interaction of Metallic and Non-metallic Adjuvants With Anthracene. Prednisone and Hydrochlorothiazide (J. Pharmaceutical Sciences, Oct. 1966).
37. Diffuse Reflectance Studies of Solid-Solid Interactions.
III. Interaction Studies of Oxytetracycline with Metallic and Non-metallic Adjuvants (J. Pharmaceutical Sciences, Oct. 1966).
38. Comparative Hydrolytic Rates of N-Substituted 6-Amino-thiouracils (J. Pharmaceutical Sciences, May 1967).

PAPERS TO BE SUBMITTED

1. Kinetics of Meperidine Degration.
2. Synthesis and Antifungal Activity of Some Halogenated Diphenolic—In print.
3. Kinetics of Glutethimide Decomposition—In print.
4. The Effect of Schardinger Dextrin on the Hydrolytic Rate of O, M and P-ethylaminobenzoate.

STATEMENT OF DR. JOHN L. LACH

I am Dr. John L. Lach, Professor of Pharmacy in the College of Pharmacy, University of Iowa. I have previously served as an Assistant Professor and Associate of Pharmacy at that institution, and also served as an instructor in pharmacy at the University of Wisconsin after securing my Ph.D. degree there. Well known to the Chairman of this Subcommittee is the fact that the University of Wisconsin is considered one of the leading research centers in the world in the field of physical pharmacy.

For the past several years my special field of interest in pharmaceutical research has been the application of physical-chemical principles to pharmaceutical systems involving stability studies, complex formation, formulation and analytical techniques, and more recently drug excipient interactions in dosage forms.

I appreciate the privilege that has been extended to me to submit my views, for your consideration, on certain aspects of the important questions before this committee.

For some time physicians, pharmacists and the general public have been subjected to considerable discussion of a widely proposed answer to the rising costs of federally financed health care programs—namely, the prescribing of generic drugs as one means for holding down the expenditure of tax funds for the care of the elderly and welfare recipients. These discussions have not only appeared in professional and trade journals but also in the lay press. A good deal of it has taken place on the floor of Congress.

In the time I have today, it is not my purpose to try to examine the entire generic issue. Rather, I will limit my discussion to the subject of "generic equivalency," about which you have heard much and doubtless will hear more during the course of these hearings.

With all the sincerity I can muster, I would like to ask you to delve deeply into this matter for so much depends on it in reaching sound and objective conclusions in the overall controversy.

Before there can be a realization of the full implications of what is being proposed, for example, I believe there must be a much broader understanding than now exists as to what goes into the manufacture of a quality dosage form or pharmaceutical product.

There are the raw materials, of course, but there is more. Quality and therapeutic effectiveness must be built into the drug product by the manufacturer through each step in the formulation process. The public, members of the health team, and, yes, members of Congress, must be educated to the fact that manufacture of a quality drug product or dosage form involves many aspects other than a minimum knowledge of how to make a tablet, a suspension, an injectable or solution. An awareness and recognition and an understanding of these other factors is absolutely essential before one can objectively examine the term "generic equivalent." It is indeed unfortunate that this term has been so frequently used, not only by people in government but by physicians and pharmacists—unfortunate in the sense that these individuals have applied this generic term to dosage forms—one which was never intended.

The question of so-called "equivalency" arose the first time a drug product became available from more than one source.

To each new drug discovered (which already has a precise chemical name) a generic name or nonproprietary name is chosen as the common name for the drug. For example, "Prednisone" the generic name for the chemical compound 17,21-Dihydroxypregna-1,4-diene-3,11,20-trione. Upjohn's product of this chemical is Deltasone which is a trade name. Deltasone is a trade name for a finished dosage form containing this chemical or steroid.

This generic or common name is required by federal law. Now, while a generic name has nothing to do with the finished product or with the quality, somehow the expression "generic equivalent" has come to be used erroneously to imply equivalent quality, not only of the drug itself but of the dosage form.

A pharmaceutical company does not simply sell a drug in its basic chemical form. It sells one or more dosage forms of the drug. A compressed tablet of a given drug sold by company X is not necessarily equivalent to a compressed tablet sold by company Y in spite of the fact that each tablet contains the same active ingredient.

For purposes of this discussion, suppose you and I were asked to make an aspirin tablet—and to make ourselves as "equivalent" as possible we are told that we can use the same manufacturing equipment and the same lot of the pure aspirin or acetylsalicyclic acid chemical. Let us here also suppose that the two batches of tablets prepared are labelled A and B. The question we, as drug specialist should ask ourselves is—just how equivalent are the two lots of tablets? The only thing equivalent is that we both used the same aspirin chemical and the same manufacturing equipment—and it stops here. Not only will there be a significant difference in the excipients and fillers used by both of us since this choice is not part of any regulation but also to (a) the method used in preparing the granules prior to compression of the tablet, (b) the amount of pressure used in the tabletting operation, (c) the amount of aspirin in each tablet since decomposition of this chemical does occur during the manufacturing operation, and (d) the availability of the aspirin to the patient once taken.

I would, for the next few minutes, like to examine this "generic equivalent" term more closely by citing actual examples taken from clinical and pharmaceutical journals. But before I do let me quote from Dr. Nelson's and Levy's paper which appeared in the Journal of the American Medical Association (1) dealing with Pharmaceutical Formulations and Therapeutic Efficacy. They state that, and I quote, "Formulations of drugs into various dosage forms may modify profoundly the onset, intensity, and duration of physiologic response. It may also modify the correct dosage required by the patient, the incidence and intenstiy of side effects and the stability of the drug. Because of these modifications it is clear that in some cases choice of dosage form and manufacturer's brand may be as important as the choice of the actual therapeutic agent."

There are many factors which go into the manufacture of a quality and therapeutically active drug product. Dr. Max Sadove (2), a clinical researcher of the Veterans Hospital in Chicago, with some twenty years experience in drug evaluation lists some twenty-four factors. Time does not permit a discussion of all these, however, I would like to mention the more important ones—potency; compatability; purity; drug availability; drug solubility; effect of vehicle, base or other ingredients; quality of active ingredient; particle size; dissolution rate; stability; pH; and viscosity.

Differences in therapeutic efficacy among different generically equivalent dosage forms are often due to differences in the date at which the active ingredient or ingredients become available for absorption. This difference in the rate of absorption may greatly modify the onset, intensity and duration of the desired physiological response. Not only is this response modified but depending on the degree of absorption of the therapeutic agent from the dosage form, the incidence and intensity of side effects from the drug may also be altered. This difference in therapeutic efficacy may also be due to lack of stability, contamination and to sub-potent preparations. What I'm saying is simply this—the drug must be in solution and absorbed to be therapeutically effective. Factors then such as particle or crystal size, disintegration time, dissolution rate, etc., all have a tremendous bearing with respect to this absorption rate. Let me illustrate with some examples.

A European pharmaceutical firm (3) was asked to increase the physical size of their Dicumarol (bishydroxycoumarin) tablets to facilitate breaking the tablets for administration of half doses. This they did easily by just making the tablet larger. Patients who switched from the smaller tablets to the larger ones

(containing the same amount of dicumarol) required larger doses in order to maintain prothrombin levels in the therapeutic range. Why? Laboratory tests showed that the rate of dissolution of the drug from the larger tablets was much slower than from the smaller tablets. Yet there was no change in the amount of drug but only in the amount of excipients used to produce this larger tablet. So the tablets were reformulated to increase this rate of dissolution of the drug. Yet it was discovered that some patients, who had their prescription filled with these new tablets still showed prothrombin levels below the therapeutic range. The only solution here was to have the physician retitrate the patients with respect to their dicumarol requirement for that tablet or dosage form.

It is quite likely that no two manufacturer's brands of dicumarol tablets will act alike in therapeutic activity and it is conceivable that a change from a slow release brand to a fast release may be extremely detrimental to the patient.

Every tablet obviously must disintegrate and release the medicament in a manner which makes the drug available for absorption. For the treatment of certain emergency conditions, such as an asthmatic attack, it is important that the tablet disintegrate rapidly and release the drug. On the other hand, where tablets contain drugs which may produce gastric irritation on rapid release of concentrated drug quantities, it is important that this disintegration and release of drug not be too rapid.

A study conducted by Chapman and co-workers (4) which appeared in the Canadian Medical Journal dealt with the disintegration time of twenty-nine tablets of two different drugs and found that sixteen of these took longer than sixty minutes to disintegrate. The tablets were still intact and the drug present in a form not available for therapeutic activity. The authors state that, "While it is relatively simple to assay a preparation and ensure that it meets labelled claim, it is more difficult to determine whether the drug is available to the patient once administered."

In a later study the same author (5) examined the absorption characteristics of riboflavin tablets. Generally speaking, the data showed that the riboflavin tablets showing the longest disintegration time were least absorbed—one to the extent of less than 14%. A drug must be absorbed in order that a therapeutic response be obtained.

An interesting study and one I want to mention here is one recently completed by the Food and Drug Directorate of Canada (6). This agency examined some ten different hydrochlorothiazide tablets produced by ten different manufacturers. They report that t ½, that is the time necessary for the tablet to dissolve and release 50% of its drug into solution varied from some two minutes to over five hours from these various tablets. The important point here was the fact that all of the tablets contained the same amount of drug and that all of the tablets disintegrated within the sixty minute time limit set down by the USP. Release of the drug from the disintegrated particle was another matter. The tablets here were equivalent—equivalent in the sense that they all contained the same amount of drug—but certainly not equivalent in their ability to release the drug to the patient for the required therapeutic response.

An increase in the pressure used in the compression of tablets, which is reflected by an increase in the disintegration time and medicament release, may markedly influence the intensity of the therapeutic effects and the availability of the drug. Again studies (7) have shown that substantially different blood levels vs. time curves were obtained when various penicillin V tablets compressed at different pressures and having different disintegration times were assayed in vivo. It should be noted here that at sixty minutes, which is the upper disintegration limit set by the U.S.P., only about 60% of the drug was available for absorption. Beyond sixty minutes the patient was in effect getting a placebo since the amount of drug released from these particles was below a therapeutic level.

Another rather dramatic example of marked potency difference involved Prednisone tables (8, 9). This is of particular interest to me in that we had a similar experience at the University of Iowa. Prednisone, as you are aware, has been one of the drugs which was the subject of much public discussion in Washington with respect to equivalency of product irrespective of the manufacturer.

Certain published reports involved prednisone tablets prepared by two manufacturers. Both showed the same prednisone content by laboratory analysis and both disintegrated into small particles in the time set forth by the U.S.P. Yet only one tablet gave the expected physiological response when administered to patients—the other was inactive. Why? The difference here was in a formula-

tion know-how—a konw-how by one manufacturer to formulate in such a manner that the tablet not only disinitegrated but released its drug for absorption and a physiological response. What detrimental effect this lack of therapeutic response had on the patients in this report I do not know. I do know, however, this detrimental effect with respect to the case I was personally involved in and I might say that it was a serious one. A change from a trade name brand to a generic one did save this patient several dollars at a cost of permnent physical body damage.

One way of administering the large doses of p-aminosalicylic acid needed in the treatment of tuberculosis with minimum discomfort to the patient is to prepare granules with shellac or other coatings. Now the availability of the drug from shellac coated granules decreases with age of the granules and after some time the blood levels attained are usually below the minimum therapeutic concentration. Since there are no standards for such coatings it again should be obvious that various brands of coated PAS granules cannot be considered equivalent—equivalent only in the sense that these products may contain the same amount of the drug. But certainly not equivalent with respect to clinical efficacy.

The effect of dicalcium phosphate and other metallic salts in depressing tetracycline absorption is well known to members of the profession of pharmacy. Prior to the time that this effect was known, interchanging brands of tetracycline made large differences in blood levels and therapeutic effects obtained and was discouraged. Why? Here obviously the filler maateirals used had some marked effect on the product. Again we can ask ourselves this generic equivalent question. The products all contain tetracycline—why then should some inert excipient mateiral prevent us from making the statement that these products aren't generically equivalent.

I would like to digress here for a few moments and point out some research that my students and I have been engaged in at the College for the past several years. We, as pharmacists, have been extremely interested in this question of generic equivalency. The increasing number of reports dealing with the therapeutic discrepancies of a drug in tablet form prepared by various firms certainly suggested that all tablets containing a certain drug do not behave alike. It was our belief that these discrepancies must be due to more than just effects of disintegration times, method of manufacture, size of drug particle and so on. We felt that, since many of our drugs are complex sophisticated molecules containing many functional groups capable of undergoing interaction or reactions with the various fillers that these interactions or complexes would occur when a tablet was manufactured and compressed. Our research started out with dogs which have been reported to show these therapeutic discrepancies. I've already mentioned some of these, for example, diuril, tetracycline and prednisone.

We have, for the first time by chemical and spectrophotometric methods (10), been able to show that drugs, such as those I've mentioned, do undergo surface chemical reactions with the fillers or so-called inert materials used to prepare these tablets. For example, tetracycline reacts chemically with the surface of the insoluble dicalcium phosphate filler used in the manufacture of such tablets. Such a complex keeps the drug tightly bound so that it dissolves at such a slow rate that no therapeutic level is obtained for the necessary physiological response. Prednisone undergoes similar surface interactions with many of the common filler materials used in the manufacture of solid dosage forms. This prednisone-excipient or filler interaction would certainly account for the lack of therapeutic response I mentioned earlier. Diuril also undergoes this type of interaction.

Our research with these and many other drugs point out that this type of interaction is common and that it depends on what type of filler is used.

One then, in formulating a tablet, does so as to minimize this effect by a scientific approach to this selection of excipient material.

The drug manufacturer, striving for the highest quality in his products, not only recognizes that these undesirable drug-excipient complexes may exist and formulates in such a way as to avoid these but also sends the product to the clinic to be absolutely sure the drug does give the desired therapeutic response. This type of approach is not only expensive but one that is absolutely necessary from the patient's point of view.

Can the generic house formulate in this manner and still produce cheap therapeutically active drugs? Some in Washington unfortunately think so.

This problem of clinical or therapeutic efficacy of drug products is a question which all members of the health team must be concerned with now and not the

cheapness or the price. At least not until the F.D.A. demands this "clinical efficacy" requirement for all drug products manufactured and sold.

Let us continue with several more examples of pharmaceutical dosage forms where this equivalency term should be questioned. The area of sustained release medication and enteric coated materials should be mentioned. Many studies have shown that the rate of release of drugs and subsequent absorption and therapeutic response varies tremendously for such dosage forms prepared by various firms. For example, a study (11, 12) on the rate of release of dextroamphetamine sulfate in sustained release dosage forms of a number of companies showed that no two products behave alike. Some products released the entire twelve hour supply in less than three hours—others released only 30% of the drug in this time. Dextroamphetamine sulfate is a potent drug. A drug response designed for a twelve hour period produced in less than three hours is one, I'm sure, the patient or for that matter the physician didn't expect. The important point here is that all of the products contained the same amount of drug and all supposedly were generically equivalent.

Since there is, as I've already mentioned, no uniformity or for that matter no standards with respect to the coating used for the preparation of enteric tablets, it is not surprising then to find, in the literature, a wide variation in the activity of such porducts. Reports show that some of these so called enteric coated tablets dissolve rapidly in the stomach with extreme discomfort to the patient—a product not meant to dissolve here. Other products go right through and are recovered intact. Such a coating, I'm sure, should be investigated and would have tremendous potential in fields other than therapy.

So far, I've dealt with tablet formulations primarily. What about other dosage forms such as ointments, suspensions, etc.

Let me say here that these same considerations apply. Again the medical and pharmaceutical literature lists many reports of such therapeutic discrepancies.

I should like to point out that such factors as suspending agents, surface active agents, particle size, fillers and so on, all have a tremendous effect with respect to the therapeutic efficacy of a drug product. In addition, such surface interactions as those that I pointed out for tablets, also manifest themselves in suspensions and ointments. Studies have shown that not only the type of vehicle—oil or water—is important but also the type of drug salt used with respect to therapeutic activity and proper blood levels of the drug.

The antibiotic novobiocin exists in two forms, an amorphous and a crystalline form. Only the amorphous form is biologically active (13). In aqueous suspensions the amorphous form changes to the inactive crystalline form. Only an awareness of this and the use of special manufacturing techniques ensures a quality product, a biologically active product. Some products of this antibiotic may have been sold in the crystalline inactive form. Chemical analysis cannot distinguish between these two crystalline forms. So consequently a chemical analysis of a product stating that the drug is present in the labelled amount means nothing. In this case only a biological assay will show whether the product is active or not. Yet comparable products would be considered to be generically equivalent.

The type of bases used in ointment preparations, as you know, is very important with respect to the rate of release of a medicament. For example, it has been shown (14) that the rate of release of aspirin in a carbowax or polyethylene glycol base was approximately 95% of that obtained from oral absorption—from a cocoa butter base 66% and from a glycerinated gelatin base only 53%.

This high degree of absorption from a PEG base looked interesting—interesting enough for one of our drug firms that they marketed a phenobarbital suppository in this same base. After the product was on the market for some time, and much to their embarrassment, they were told that the therapeutic effect was missing. Chemical analysis showed the phenobarbital to be present and, oh yes, the suppository did dissolve. Why then the lack of therapeutic activity? Research conducted in our laboratory provided the answer.

In the case of the PEG-aspirin suppository the aspirin interacted with the PEG to form a soluble complex, a complex which was rapidly absorbed.

On the other hand, in the case of the phenobarbital-PEG suppository, the phenobarbital also interacted with this base only to form a very insoluble complex, a compound which was not absorbed.

It was pointed out to me here that all was not lost, at least from the patient's point of view. He did get an effect even though it was a psychological one.

The point here is simply this—one cannot use these bases indiscriminately, one

has to know whether the drug exists as such in a base or whether it has undergone sime reaction with it. And, is the resulting product therapeutically active?

With respect to ointment bases Lafferty and Gross (15) reported that it had been established that the particle size of medicinals dispersed in ointment bases has a direct influence on tissue irritation, drug absorption and the therapeutic efficacy of the medicament, but that, "The examination of competitive products indicated a wide range of control or lack of control of particle size between various manufacturers of the same product." They studied many ointments, to name but a few, boric acid, zinc oxide and mercuric oxide, all U.S.P. They conclude by saying that here is another example where dosage forms can meet official requirements in active ingredient content yet vary widely in certain important characteristics, depending on the skill of the manufacturer.

To me, this is not surprising since we have no regulations governing such things as the type of fillers one can use, the size of the drug particle permissible, and so on. Yet such things are of extreme importance with respect to the performance of the finished drug product.

These are but a few examples of how drug products can be generically equivalent and yet be so generically unalike with resepct to their biological activity or performance.

Now that we have established the fact that there is a definite difference in similar drug products and that this difference may exist with respect to trade name products and generics let us examine the point even more closely. Let us take a common drug product—a generic one, Prednisone.

An examination of the Red Book reveals that some eighty-seven drug firms produce, not the drug chemical itself but the finished dosage form. Pharmacists have eighty-seven different sources for this product and the price for this product is going to vary.

How then could I be sure of any of these eighty-seven products? This I'll try to answer later.

Getting back to these eighty-seven companies producing the tablet form of this drug, how many of these same companies market an ophthalmic ointment or an injectable?

The answer is very simple—only a few.

Why? Again the answer is simple.

It costs money to produce sterile ophthalmics and sterile injectables, the profit margin would be too small when compared to a trade name product. And, of course, the market for this type dosage form isn't as great as that for tablets. There is more money to be made in the tablet area and also one doesn't have to bother with sterility control or special equipment and manufacturing procedures.

Thus, when pharmacists handle generic products or trade name drugs unfamiliar to them, they must consider the following:

(*a*) Is this product "equivalent" in all aspects to an established and therapeutically effective product they are familiar with.

(*b*) They must not be misled by some company advertisements which state that all its products are chemically assayed or that analytical data will be sent on request. This, in itself is meaningless with respect to the therapeutic activity of the drug product.

(*c*) They should ask for absorption and excretion data, blood level data or any clinical data available. This is usually available for quality products. Only with this type data can the pharmacist be reasonably assured that the product is therapeutically active.

Pharmacists have a responsibility, not only to the physician and patient, but also to the drug industry which is in business to develop new drugs and to produce quality drugs and therapeutically effective drug products.

Let me, at this point, touch briefly on some of the comments which have appeared over the past seven months in the Green Sheet of the publication "Weekly Pharmacy Reports" concerning this generic equivalent controversy. Since time does not permit any discussion, I'll just capsulize these.

Enforced generic system for welfare prescriptions under federal-state medicare program by-passed by HEW Department after fifteen months of vigorous internal discussion.

The cheapest or lowest-cost-drug concept has been all but eliminated for generic drug legislation in the 90th Congress. Senator Montoya's bill introduced January 11 would pay for the lowest cost drugs * * * which is of a quality acceptable to a Formulary Committee to be established under a separate bill.

Compulsory generic prescribing on government programs not feasible until *clinical equivalency* is proven. Both F.D.A. Commissioner Goddard and Surgeon

General Stewart are interested in getting funds to start clinical equivalency studies of drug products. * * * (I'm sure this was not their thinking of a year ago.)

Pro-generic Senators Long and Montoya want to develop a compendium that would stress the "lowest cost" drugs of the best quality for federally sponsored medical programs.

Unfortunately true F.D.A.'s Goddard tells house committee when asked whether comparing drugs by generic name is like comparing a Model-T to a Cadillac.—Goddard was appearing before "get acquainted" hearings held by the Interstate Committee, when Representative Nelsen asked him: "It has come to my attention that, for example, to compare a drug by a generic name would be like comparing a Model-T to a Cadillac, and the effectiveness of a drug of a similar generic name may not be exactly the same." Nelsen continued his questions: "Then when you get into the prescribing of a drug, is it true or is it not true that there may be a variation as to the effectiveness of a drug of a similar generic name, ignoring trade or brand name?" "Yes," Goddard replied. "This is unfortunately true. I say unfortunately, because it means we are not performing our functions as well as we have to. We view our goal as being one where the physician can prescribe any drug that is in the market place on any basis he wishes in terms of whether he uses brand names or generic names, and be assured that those drugs are all effective and they are safe. This is not the case today and there is variation. The Defense Supply Agency in its procurement program for drugs has clearly demonstrated differences between brands and we have seen some of this."

Need I say more * * *?

Most physicians know very little about the formulation of drugs for clinical use. They assume that the Food and Drug Administration, the United States Pharmacopeia and the National Formulary exert the necessary controls and that therefore, when the product is ready for clinical use, it represents an accurate amount of drug which is clinically or therapeutically effective. This is, as we have seen, not always true.

It is obvious then, that there is a definite need for these agencies to enlarge their interest in the formulation of stable, safe and therapeutically active drug products.

Until this comes about, the public, the medical profession, pharmacy and the drug industry must seriously concern themselves with this problem of "cheap drugs".

I would like to conclude by saying that a *therapeutically inactive* drug product no matter how cheap, whether it be a generic or a brand name is an *expensive* drug for the patient be he on a privately or government sponsored health program.

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APPENDIX III

CORRESPONDENCE FROM DR. CLARENCE L. GANTT, ASSOCIATE PROFESSOR OF MEDICINE AND ASSISTANT DIRECTOR OF CLINICAL RESEARCH CENTER, UNIVERSITY OF ILLINOIS, TO SENATOR NELSON, DATED OCTOBER 19, 1967, RE DRUGS

UNIVERSITY OF ILLINOIS,
COLLEGE OF MEDICINE,
Chicago, Ill., October 19, 1967.

Senator GAYLORD NELSON,
Chairman, Subcommittee on Monopoly,
Senate Select Committee on Small Business,
Washington, D.C.

DEAR SENATOR NELSON: The problems of the cost of drugs in the U.S. presently under consideration by your distinguished subcommittee are of such magnitude and importance, both now and for at least a generation to come, that I wish to offer some comments on these matters. Please be assured that my remarks are intended only to assist your distingiushed group in this very complex mixture of science, sociology and economics. Since I am neither a sociologist or an economist, I will limit my remarks to the area that I can make responsible judgments—the scientific.

I am a physician, Board Certified in Internal Medicine, an endocrinologist, an Associate Professor of Medicine, and a clinical investigator, working with both humans and animals. A great deal of my work is in the field of animal and human pharmacology. The remarks are entirely my own and are not to be related to the College of Medicine, University of Illinois.

Backing far enough away from the problem to be able to at least find the forest, one is first struck by a fact of medical history. Except for a very few isolated individuals, the academic community many years ago turned over to an industry the search for new therapeutic agents. The academicians have until very recently looked down on their colleagues who were interested in new agents. This atmosphere still persists to a lesser degree today. Therefore, for good or bad, the only real source of therapeutic agents today is the pharmaceutical industry. As the complexities of chemical synthesis and biological screening have greatly increased in the past few years, it is likely that this will be even more true for the next few decades. The academic community can not take over this function for society.

The pharmaceutical industry is a motley group composed of companies that have made very far reaching advances in the field of therapeutics; others that have acted principally as developers of others ideas; other companies that have performed chiefly as a production operation, selling items such as intravenous fluids without patent protection; still others that have acted as huge sales organizations, and lastly, other companies that have made no effort at research or development but only compounded what is easily available to be sold on a competitive price basis, keeping all production and sales costs at a minimum. It is apparent that certain aspects of this large group need to be strengthened while others need to be radically changed or eliminated. The only real advancements will come through research and an absolute premium should be placed on this.

The next point that one sees in relation to drug costs is the "development" of the profession of pharmacy, from the apothecaries, who knew and practiced a little chemistry and a lot of pharmacology, to the present corner "drug store" pharmacist who sells everything from ice cream sodas to cigarettes, cosmetics and basketballs, while increasing by approximately 100% the price of every prescription drug that he pours from one bottle to another. To double the cost of drugs just as they pass to the patient is a dear price indeed to pay for having a drug store on every corner. Still on an average there are not a lot of wealthy pharmacists, suggesting a problem of proper distribution of manpower somewhere in that profession. It is quite possible with existing technology to perform the functions of the pharmacist with a computer.

A third obvious point that is easily discerned by moving slightly closer to the problem is that relating to the United States Pharmacopeia. Many of the concepts of purity put together by the U.S.P. committees on this subject were developed before the era of effective drugs and before the techniques of chemical synthesis became so complicated. As a result of this it is generally not possible for me to use chemical reagents in the laboratory that meet only U.S.P. requirements as they are usually so impure that they invalidate our chemical tests. These facts are well known to any analytical chemist or laboratory technician. The attached price

lists[1] of chemicals pulled at random from suppliers (who do not make drugs and therefore are not involved in the drug price controversy) demonstrate very readily that if they have to go through further steps of purification beyond U.S.P. purification standards, the price is higher per unit weight. Our inability to use them in the laboratory and the price differential suggest that the requirements of chemical purity of U.S.P. chemicals are so low as to be of very questionable use in the area of human therapeutics.

The United States Pharmacopeia in cooperation with United States Adopted Names Council controls the generic or public name of drugs. For some reason they have tried to use a chemical basis for naming new drugs. The result has been names so long that most physicians can not even pronounce some of their tongue twisters, let alone remember or spell them for writing prescriptions. The contractions of chemical nomenclature that result are also of no value in deciphering the structural formulae of the compounds. For good or bad, most physicians have to use trade names short enough for them to remember in their practice.

Moving still closer to the problem of generic versus trade name drugs, we found very little scientific evidence on either side of the fence. The companies with the brand name products maintain that their products are better, while the generic equivalent companies maintain that theirs are equal but cheaper per unit. It is unfortunate, but true, that at present one is forced to rely not on scientific data, but on the gross reputation of past performance of the manufacturers in the selection of drugs for the patient.

The U.S.P. criteria are for a tablet to *contain* a drug while the experience of a company as it develops new agents indicates that the tablet *delivers* a certain pharmacologic effect. Several of the bad experiences with generic drugs have already been pointed out by others to your distinguished committee, and do not need to be repeated here. There must be good experiences with these agents also, but in the area of health it is not wise to experiment broadly.

Having no other basis other than the gross past performance of an older established company to rely on and being fully aware that the other possibility is a vast experiment too broad to foster on an aged and/or poor population group, who could not even give their informed consent to participate in such an experiment. I sympathize with you and your distinguished colleagues in this dilemma.

My suggestions would be that before you reach any conclusions in this matter: (1) wait until the special study committees on Efficacy Review of the National Academy of Science, National Research Council report to Commissioner Goddard of the Food and Drug Administration on those drugs that were on the market prior to the new F. and D.A. regulation on efficacy; (2) request that the pharmaceutical industry provide over the next few years proof that their particular brand name or generic name drug will pass certain rigidly controlled tests of blood levels of the drug, efficacy, stability, etc. so that at some point in the reasonable future there can be some scientific basis for a rational judgment; (3) study means by which to reward scientific investigations and the development of new therapeutic concepts to such an extent that this is significantly more profitable than simply marketing someone else's drug or a slight modification thereof, (my statement here is meant to be positive and not negative since being restrictive will do no good in the long run to advance medical care and this must be an overriding interest); (4) contemplate new methods of distribution such as automation to cut the very major costs created by a group that contributes nothing to the therapeutic agent; (5) determine what can be done to update the U.S.P.; (6) avoid highly inflammatory issues directed at the public, such as Dr. Burack's book since this approach generates a lot of glib opinion and little or no scientific data on which to base a rational decision, and (7) lastly develop bold new concepts that will succor the truly productive aspect of the only industry that can make new therapeutic agents available to the public, while weeding out those aspects that contribute little to the long-term advancement of the human race.

Thank you for your kind consideration of these remarks. I do hope that they can be made a part of your hearing record. I have taken the liberty of sending copies of this letter to all the members of your subcommittee.

Sincerely,

CLARENCE L. GANTT, M.D.,
Associate Professor of Medicine and
Assistant Director of Clinical Research Center.

[1] Retained in committee files.

APPENDIX IV

DOCUMENTS ON VIBRAMYCIN (DOXYCYCLINE) FROM FDA FILES

Labeling for "Vibramycin" (doxycycline HC1, Chas. Pfizer & Co. NDA 50-007)

JUNE 29, 1967.

ROBERT M. HODGES, M.D.,
Director, Office of New Drugs.
Dr. ALAN E. SMITH,
Acting Deputy Director, Division of Anti-infective Drugs.
JOHN M. DAVITT,
Pharmacologist, Division of Anti-infective Drugs.

As requested, here are the statements proposed by DAD pharmacologists for inclusion in appropriate sections of Pfizer's labeling for Vibramycin:

1. At relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

2. As with some of the other tetracycline antibiotics, gross discoloration of the thyroids, ranging in intensity from brown to black, can be produced by high oral doses of Vibramycin in several species of experimental animals. The significance of these changes is uncertain. I^{131} uptake studies in rats and dogs failed to demonstrate any interference with thyroid function.

The Pfizer people maintain the first statement is superfluous since both GI disturbances and evidence of hepatic effects in humans are already mentioned in the labeling.

Although they agree that the second statement is factual and belongs in the labeling, they object to its use at this time on the grounds that it would result in an unfair competitive disadvantage for their product. They have indicated willingness to include this statement in their labeling only when competitive products are similarly labelled.

JULY 31, 1967.

NDA 50-006, 50-007

MEMORANDUMS OF CONFERENCE AND TELEPHONE CONVERSATION

CONFERENCE

Present: Dr. Monroe Trout, Chas. Pfizer & Co., Inc.; Mr. Joseph P. Aterno, New York, N.Y.; and Dr. Herbert L. Ley; Dr. Edwin I. Goldenthal; Dr. Alan E. Smith; Dr. Kent Potts, FDA; Mr. Julius Hauser; Mr. Ola Bain.

Subject: Vibramycin (doxycycline) NDA 50-006 and 50-007.

Proposed changes in the label and labeling for Vibramycin as outlined in the Memo of Conference of July 28, 1967 were reviewed in detail. The Pfizer representatives objected to any changes because the requests were being made too late, they thought final agreement had previously been reached, they have already printed many package inserts and containers. Dr. Ley pointed out that antibiotics are unique in that the Commissioner, not the Bureau of Medicine, has the final judgment regarding their approval. Hence a company takes a risk if printing is started before approval of the Commissioner is granted.

Discussion proceeded to the specific changes which had been recommended. In the labeling under "Action" we had suggested that the sentence about in vitro antibacterial activity be omitted or followed by the statement: "This is of no known clinical significance". Pfizer objected as they believe this degrades the importance of in vitro sensitivity testing. Dr. Ley said he would prefer that they omit the whole thing as the differences noted were so small that we believe they are of no consequence. Other suggested changes in the package insert were considered minor by Pfizer and they voiced no specific objections.

With regard to the immediate label and carton changes the visitors strongly objected as they are using the same format for Vibramycin that they have previously used for other tetracycline products, they don't see how all the requested information can be included on the front panel, they have already printed a number of these pieces and it would be expensive and time-consuming to have them redone.

After considering all facts presented Dr. Ley offered the following suggestions:

1. The company could use their present supply of immediate labels and cartons

until the next printing or 120 days from the date of publication of the monograph for doxycycline in the Federal Register.

2. With regard to the package insert he would discuss three possibilities with Commissioner Goddard: Immediate modification, modification within 120 days of publication of the monograph with assurance that the contested areas would not be used in promotion, immediate modification now with the new insert to go in all unstuffed supplies (old insert to be left in supplies which have been stuffed). The Pfizer representatives were invited to consult their Management personnel and comment on these possibilities today.

KENT H. POTTS, M.D.
ALAN E. SMITH, M.D.

TELEPHONE CONVERSATION

Between: Mr. J. Aterno, Chas. Pfizer & Co., Inc., and Dr. Alan E. Smith, Acting Deputy Director, Division of Anti-infective Drugs.

Mr. Aterno called to say that he had met with other members of his firm, after his return to New York today (following this morning's meeting in Dr. Ley's office).

The firm has agreed to change the package insert as discussed this morning:

Under "Actions" the second sentence will be deleted in its entirety. The proposed third sentence, therefore, will not be used.

The other changes will be made.

The revised insert will be used, even in the samples already processed with a "July 1967 insert".

The immediate labels and cartons will be revised within the time limit agreed to this morning (90 days after effective date).

Typewritten copies of the revised insert will be brought on August 1, 1967.

Dr. H. L. Ley, Jr. was advised of this at about 4:15 p.m. and he requested that I notify Mr. Julius Hauser of ACC by telephone. Dr. Ley said that he thought this would obviate the need of further notification.

Mr. Hauser agreed to this.

ALAN E. SMITH, M.D.

Forms 5, NDA 50-006, 50-007

AUGUST 24, 1967.

MEMORANDUM OF CONFERENCE

Present: Mr. Jerry Avergun, Chas. Pfizer & Co., New York, N.Y.; and Dr. Max B. McQueen, Division of Anti-infective Drugs; Dr. Kent H. Potts; Dr. Alan E. Smith (part time).

Concerning: Promotional material for Vibramycin (doxycycline)

A compendium and file card were officially submitted for our review after Mr. Avergun pointed out how these differed from rough draft or mock up copies which we had previously seen, but which were not formally submitted to FDA. Mr. Avergun was told that these appeared to be satisfactory, but that his firm should await an official letter of approval before printing these or any other promotional pieces. Mr. Avergun asked when such a letter could be anticipated and was told that no definite time could be set as the approval would have to be made through administrative channels and that the time required for this would depend upon whether questions or problems arose. He seemed unhappy with this answer and said Pfizer was "heavily committed in this project." He, nonetheless, was again encouraged to await official approval before proceeding with printing.

KENT H. POTTS, M.D.

U.S. GOVERNMENT MEMORANDUM

AUGUST 31, 1967.

To: William R. Jester, Director, Division of Antibiotics & Insulin Certification
From: Deputy Director, Bureau of Medicine
Subject: Vibramycin labeling

Chas. Pfizer & Co., Inc., New York, N.Y. (AF 12-118).

"Vibramycin Capsules," NDA 50-007.

"Vibramycin for Oral Suspension," NDA 50-006.

Bureau of Medicine has checked and approves the package labeling (insert), carton and bottle labeling for these products.

All promotional labeling for these products is still under review by the Bureau of Medicine and none of this should be used by the firm until it receives our approval in writing at a later date.

Because preliminary review of the submitted promotional labeling has raised significant questions, Pfizer should be cautioned that no journal advertising should be placed regarding these products unless it is fully in accord with the approved package labeling and otherwise meets the requirements of the regulations under section 502(n).

B. HARVEY MINCHEW, M.D.

DECEMBER 22, 1967.

Mr. JACK POWERS,
Charles Pfizer & Co., Inc.,
235 East 42d Street,
New York, N.Y.

DEAR MR. POWERS: This is to confirm our telephone conversation today concerning the details of Vibramycin at a recent American Academy of Pediatrics meeting. Statements have been received from members of my staff as well as practicing physicians indicating that your firm's representatives stated that the drug was less apt to cause tooth staining because of the lower calcium binding capacity. It also stated that the drug was more effective over a larger spectrum of gram positive and gram negative organisms including certain staphylococcus and pseudomenas species, than were the other tetracyclines. Both of these statements are, of course, inconsistent with your final printed labeling and therefore false and misleading.

You indicated your willingness to clarify any existing misunderstandings by a personal letter from you to your representatives clearly stating that drug detailing will be limited to that which is approved in the final printed labeling. I would appreciate your providing me with a copy of the letter you send to your employees concerning this matter.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

APRIL 9, 1968.

Chas. Pfizer & Co., New York, N.Y. (AF 12–118)
NDA 50–006 Vibramycin, 50–007

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Mr. Charles Hagan, Chas. Pfizer & Co. and Dr. R. S. McCleery, Mr. H. W. Chadduck, Division of Medical Advertising/OMS

Subject: Vibramycin Journal Advertisement, example: MD Medical Newsmagazine, April 1968

The subject ad, consisting of a two-page spread of promotional copy plus one column on a third page presenting a "Brief Summary," was brought to the attention of Pfizer representatives at a meeting in the Commissioner's office on April 8, during a discussion of Urobiotic-250 promotion and package labeling.

Defects in the Vibramycin ad were of the same type as those in the Urobiotic-250 advertisement discussed at the 4–8–68 meeting.

This telephone conversation with Mr. Charles Hagan (Pfizer) was by way of follow-up to obtain a record of the firm's agreement to correct the Vibramycin ad defects. The gist of the information and commitments given by Mr. Hagan is as follows:

1. The above-described Vibramycin ad is not scheduled to run after April 1968.

2. Future ads will include corrections of (a) side effect statements that emphasize minimal specific side effects without calling attention to other and more serious side effects listed in the "Brief Summary" of the ad and/or package insert, and (b) broad promotional claims such as ". . . oral broad-spectrum tetracycline antibiotic*" without adding information qualifying the claim so as to bring out limitations of effectiveness and to make the claim more meaningful and informative. The purpose here is to provide some specificity of knowledge of drug without necessarily going into great detail at that point in the ad.

On point 2(b) above Mr. Hagan said that he would discuss with Mr. George Strong (Pfizer) the language to be used in qualifying such a claim and would telephone us on Friday, April 12, and propose language for an opinion.

3. Mr. Hagan indicated that he would send the FDA a letter in regard to Vibramycin ad and it was left that such a decision was to be that of the firm. Unless such a letter of commitment is received, however, additional attention to the ad should be considered by FDA.

H. W. CHADDUCK.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
April 18, 1968.

To: Max B. McQueen, M.D., Office of Marketed Drugs (MD–330)
From: William E. Dye, Ph. D., Office of New Drugs (MD–140)
Subject: Proposed labeling change for package insert for Vibramycin Capsules, Charles Pfizer dated March 1, 1968

1. This is a request to add the following sentences to the insert: "The spectrum of Vibramycin is essentially that of the other tetracycline analogues. Certain strains of organisms, including Staph. aureus, may exhibit greater susceptibility *in vitro* to Vibramycin than to the other analogues. *In vitro* susceptibility testing should be conducted.

2. There is no objection to the first sentence.

3. Although the references quoted do show some increase in *in vitro* susceptibility to Vibramycin when compared to other tetracycline analogues, I recommend that the second sentence be deleted. The effect seen could easily be a laboratory artifact based upon a difference in the stability of the analogues or to a difference in the pH at which they display maximal antibacterial effectiveness. This sentence implies that Vibramycin might be effective in clinical infections caused by tetracycline-analogue resistant Staphylococcus aureus. There is no evidence for this. If the sentence is permitted to remain, it can be expected to be the basis for advertising claims for this drug with the above implication.

4. There is no objection to the third sentence.

WILLIAM E. DYE, Ph. D.,
Clinical Microbiologist, DAD.

MEMORANDUM OF CONFERENCE

April 23, 1968.

NDA No. 50–006, 50–007

Between: Mr. Avergun, Dr. McDermott, Dr. Sikowski, Pfizer; and Dr. Ortiz, Dr. McQueen, Dr. Hurwitz, Dr. Dye, Dr. Borowsky, FDA

Dr. Hurwitz discussed the proposed labeling for Sterane. He stated that the changes were satisfactory, but a pregnancy warning was necessary. The company disagreed about the wording of the warning but agreed to consider it.

Discussion of the labeling of the proposed 20 million unit vial of Penicillin G centered on the labeling.

A supplement to revise labeling on Vibramycin was considered next. The supplement, dated March 1, 1968, inserted in the labeling words to the effect that the drug was particularly indicated for use in infections caused by staph. aureus. Dr. Dye contended that the results in the article on which this claim was based were invalid because they could well be due to laboratory artifact. He also cited an article in the American Journal of Medicine stating tetracyclines should not be used in staphylococcal infections at any time. These facts coupled with the fact that this new wording might well be used for misleading advertising claims led to FDA position that the supplement should be denied. The company disagreed, but stated they would withhold action until they received our letter.

STEPHEN A. BOROWSKY, M.D.,
Division, Meta/Endo Drug Surveillance.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
June 5, 1968.

To: John J. Jennings, M.D.
From: Edwin M. Ortiz, M.D.
Subject: Memo dated May 28, 1968 from Dr. Minchew regarding Vibramycin

I would like to know the names of the Pfizer representatives who met with Dr. McCleery, Mr. Chadduck and Dr. Minchew.

Pfizer submitted a supplement to their Vibramycin form 5 (NDA 50-006, 50-007) to state under "Actions" the results of a study which showed Vibramycin to be more active *in vitro* against certain strains of staphylococci than other tetracyclines. This submission had been reviewed by Dr. Dye and Dr. Borowsky. In our meeting of April 23, 1968 (with memo) we told Mr. Avergun, Dr. McDermott, and Dr. Sikowski that the supplement was not acceptable for the following reasons:

1. It was based on only one *in vitro* study.
2. Incorporation of these data into the labeling would give a false implication of clinical efficacy.
3. Tetracyclines are not drugs of choice in the treatment of staphylococcal infections.
4. As voluntarily stated by Dr. Sikowski, this represents a transient phenomenon. Staphylococci develop resistance to new tetracyclines in a short period of time.

Multiple attempts by the representatives to modify the statement were immediately rejected by us. It was decided that Pfizer will submit a rephrased statement for our review and evaluation. Several weeks later we received a communication from Pfizer withdrawing the original supplement.

FDA never encouraged the use of these data in promotional material. In fact, our main objection to the incorporation into the labeling was its potential use in promotional literature if it became part of the approved labeling.

APPENDIX V

DOCUMENTS ON DYNAPEN (DICLOXACILLIN) FROM FDA FILES

CHRONOLOGY OF DYNAPEN (DICLOXACILLIN) CASE

BRISTOL LABORATORIES, SODIUM DICLOXACILLIN MONOHYDRATE (DYNAPEN)

November 10, 1965.—Antibiotic Form 5 for sodium dicloxacillin monohydrate submitted by Bristol. This contains suggested regulation for certification of 125 and 250 mg. capsules and 62.5 and 125 mg/5 ml. oral suspension. Clinical data on 198 clinical cases treated with dicloxacillin are also included.

January 6, 1966.—Letter to Bristol from FDA recommending 1) performance of a reproduction study if the product is to be used in premenopausal women and 2) submission of methods, controls and acceptance limits for potency, moisture, pH, identity, crystallinity and microbial assay.

January 28, 1966.—Memorandum from A. Kirshbaum to Mr. Ogles concerning tests performed by FDA on samples of dicloxacillin. The following tests were performed: 1) Assay of 1 mcg. sensitivity discs, 2) Acute toxicity in mice, 3) Microbiological assay for dicloxacillin using the cylinder plate assay method and *Staphylococcus aureus* as the test organism. Using this method 7 of 9 batches showed no loss of potency in two weeks, 4) Bristol's recommended chemical analysis using the infrared spectrum of the beta-lactam moiety. Since this group is shared by all other penicillins, it is suggested that an oxygen flask combustion method for chlorine content be used in addition to assure the identity and purity of dicloxacillin. It is further recommended that Bristol be asked to supply stability data and a reference standard of the drug.

February 10, 1968.—Telephone conversation between J. Davitt and J. Lamar (FDA) and Dr. G. Woodard (Woodard Research Corporation). Concerning teratology studies to be performed by Dr. Woodward for Bristol, FDA recommended that rabbit pups to be delivered by cesarean section should be examined first

grossly, then autopsied for visceral examination and finally examined for skeletal abnormalities. Furthermore it was recommended that all pups be examined.

February 28, 1966.—Memorandum from A. Kirshbaum to R. Norton containing review of proposed regulations for dicloxacillin. The following recommendations are made: 1) A method for percent dicloxacillin in terms of chlorine content should be submitted. 2) Tests for optical rotation and free acid content are possibly desirable but not absolutely necessary. A method for chlorine content is described in detail.

January 27, 1968.—Amendment by Bristol to the Form 5. This contains a revision of the Finished Product Specification with methods for moisture content and pH. The tolerance limits given are moisture—maximum 1% and pH—range 5.0–7.5.

March 25, 1966.—Submision by Bristol of a status report of clinical investigators of dicloxacillin. A total of 469 case reports had been received from 21 investigators at this point.

June 20, 1966.—Conference between FDA and representatives of the sponsor. The following areas were covered: 1) Reproduction studies. Rabbit, mouse and rat studies had been performed. In rabbits, diarrhea had resulted from the initial dose of dicloxacillin causing difficulty in impregnation. In the mouse study stunting and light weight pups had been obtained. The company agreed to repeat this study. In rats there was a question of whether dicloxacillin had decreased fertility. Sections of testes were to be examined but it was unclear whether the ovaries were still available. 2) Toxicity studies. Previous requests by FDA had been satisfied; it was now requested that, since in the 12 week chronic toxicity study autopsy data had been submitted for only a single animal, the information be supplied for the remaining animals. 3) Labeling. It was recommended that the observation that dicloxacillin interfered with the enteric flora of rabbits and inhibited subsequent impregnation be included in the labeling. This would be discussed at a later conference. Dr. Peltier (Bristol) agreed to add to the labeling, statements to the effect that "where sensitivity tests indicated a given staphylococcus was sensitive to Penicillin G, a change to this drug may be considered", that eosinophilia and "occasional but transient SGOT elevations" are adverse reactions to dicloxacillin and that it is advised that "the drug be administered on an empty stomach."

July 1, 1966.—Submission by Bristol of revised package circular incorporating the changes discussed in the conference of 6/20/66 and advising that the trade name "Hypen" has been chosen for dicloxacillin.

July 12, 1966.—Letter from FDA to Bristol advising that, in order to bring the labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face as the beginning of the "Indications" section: "Hypen is particularly suitable against infections due to staphylococci resistant to Penicillin-G (or phenethicillin)," and that, in addition, the following should appear in the same section; "If it is determined that the infection is not due to a Penicillin G-resistant staphylococcus, a change to Penicillin G or Phenethicillin may be considered."

July 12, 1966.—Drug Control Review Notes (FDA). It is concluded that controls are inadequate and that the sponsor should be notified as follows: 1) The 3(2,6 dichlorophenyl)-5-methyl--isoxazole carbonyl chloride should have a specific identity test. 2) The Form 5 should be amended to specify that the bulk drug and the finished dosage formulations should conform to the applicable Federal Regulations 3) Extended stability data should be submitted for the bulk drug and for all dosage forms.

July 13, 1966.—Submission by Bristol of new labeling incorporating recommendations made in FDA's letter of 7/12/66 and by telephone. Dr. Peltier (Bristol) adds that "We still feel that . . . such a statement (recommending a switch to another penicillin if the patient's infection is not due to a penicillinase-producing staphylococcus) is not justified by the facts. We will continue to accumulate data and will bring this to your attention as more experience becomes available so that we may review it again."

July 15, 1966.—Letter from Dr. William M. M. Kirby (Professor of Medicine, University of Washington) to Dr. Barzilai (FDA). Dr. Kirby states that he has discussed with Dr. Peltier the labeling for dicloxacillin. He says that "it occurs to me that the time has arrived when it is appropriate to say that these drugs (the semisynthetic, penicillinase resistant penicillins) are effective in staphylococcal, streptococcal, and pneumococcal infections . . . In vitro, these drugs are appreciably more active against streptococci and pneumococci than they

are against staphylococci, and by now large numbers of cases have been accumulated to demonstrate clinical efficacy . . . Actually, the wording (of the labeling recommended by FDA) has been based principally on concern about development of resistance of stapyhlococci to these penicillins, and there is no evidence that this has occurred . . . I am of course advocating penicillin G or V for clearcut streptococcal and pneumococcal infections, but there are certainly many cases where the diagnosis is not clearcut and one wants to start cloxacillin or dicloxacillin . . ."

July 14, 1966.—Initial Medical Officer's Review. 662 of the 780 cases submitted were found acceptable for review by Dr. O'Neill, the reviewer. In all groups of cases, the failure rate was under 6% except in some 51 cases of pneumococcal infection in which a failure rate of 18% was obtained. The following comments are taken from the conclusions reached by this review. 1) "It was expected from early information that this dichlorinated compound would be irritating to the gastric mucosa. This fear was not born out as seen by the 1.5% figure for gastric complaints." 2) "Superinfection occurred 15 times, an incidence of 1.3%. This contrasts with Louria's statement (reference given) that superinfection may be expected up to 30% of the time with semi-synthetics." 3) "Since the blood levels produced by comparable amounts of cloxacillin are half those of dicloxacillin, the dosage of dicloxacillin may be halved . . . The sponsor recommends 12.5 mg./kg./day for children and this is usually adequate, although one investigator frequently felt he had to go up to 25 and 30 mg./kg./day to obtain results. Doses of 4 to 8 grams a day have and can be used in adults," 4) "Dr. J. Lamar of DTE in private communication June 17, 1966 stated that while he is not entirely satisfied with reproduction studies, in essence they were adequate. Studies have been done in rats which are normal; studies done in mice reveal some stunting effect on offspring; and studies on rabbits have shown such peculiar species toxicity of an ecological nature as to make this species of at least very doubtful value. A decision as to whether this information should go into the labeling will have to be made at a higher level." 5) "In summary, then, I certify that this drug is safe and efficacious when used as directed in the proposed labeling."

A note appended by Dr. H. C. Anderson states "I agree except that I do not believe the recommended dose of 125 mg. for 'minor infections' is a safe one and that the minimum dose should be 250 mg. to allow an adequate therapeutic ratio of dose to MIC" (mean inhibitory concentration).

July 20, 1966.—Telephone conversation between Dr. J. C. O'Neill (FDA) and Dr. H. C. Peltier (Bristol). Dr. Peltier registered his continued objection to the concept that the semi-synthetic penicillins, with activity against penicillinase-producing staphylococci, should be reserved for these organisms primarily." He quoted from Dr. Kirby's letter (see 7/15/66 above). Dr. O'Neill told him that the matter would have to be reserved for Dr. Barzilai's consideration.

July 20, 1966.—Submission by Bristol of a literature survey and analysis entitled "Emergence of Methicillin-Resistant Staphylococci". From this review, the sponsor states the belief that "resistance will not become a problem." This review contains 31 references. The following conclusions are offered by the sponsor:

1. There is no evidence that excessive use of methicillin, oxacillin, or cloxacillin has resulted in the emergence of *Staph. aureus* strains resistant to these antibiotics. A higher incidence of restraint strains has been reported in English hospitals where the use of these antibiotics was restricted than in the United States or Canadian hospitals where they were more widely used.

2. Naturally occurring resistant strains have been isolated from individuals who were not treated with these antibiotics and in hospitals where they had not been used. These strains produce penicillinase and are resistant to several antibiotics in addition to penicillin.

3. The emergence of strains resistant to methicillin and the isoxazole penicillins does not appear likely to occur to the same extent as seen with penicillin G. Large scale studies over a five-year period indicate an incidence of less than 1% resistant strains in England and a lower rate in the United States and Canada.

4. Naturally occurring methicillin-resistant strains consist of a mixed population, with a majority of sensitive organisms and a small minority (1 per 1000 or less) of highly resistant cells. The latter are selected by growth in high concentrations of the antibiotic, but tend to revert back to the original mixed population when grown in antibiotic-free media.

5. Methicillin-resistant strains show variable resistance to the isoxazole penicillins, depending on inoculum size and length of incubation. Dicloxacillin is more effective than oxacillin against a large inoculum and may be useful in treating methicillin-resistant strains.

6. Resistance to dicloxacillin develops in vitro in the same step-wise fashion found for methicillin, oxacillin, and cloxacillin. There is no evidence that the use of dicloxacillin in vivo would be more likely to result in the emergence of resistant strains.

July 25, 1966.—Submission by FDA to Bristol of draft monographs to provide for certification of sodium dicloxacillin monohydrate and pharmaceutical dosage forms thereof. In the same letter it is recommended that a more specific quality control procedure for establishing the identity of the 3-(2,6 dichloro-phenyl)-5-methyl-4-isoxazole carbonyl chloride be established.

July 29, 1966.—Telephone conversation between Dr. A. E. Smith (FDA) and Dr. H. Peltier (Bristol). Dr. Smith requested that the sponsor make 3 minor changes in the package insert for dicloxacillin.

July 29, 1966.—Submission by Bristol of the revised draft labeling incorporating the changed requested by FDA (telephone conversation of 7/29/66). The trade name for the drug is to be changed to "Dynapen".

August 9, 1966.—Telephone conversation between Dr. P. J. Weiss (FDA) and Dr. H. Frediani (Bristol). Dr. Frediani stated that 100 gm. of a proposed standard for dicloxacillin and the 5A molecular sieve to be used in proposed tests would be shipped to FDA. Analytical data for the standard would also be sent.

Augwst 12, 1966.—Submission by Bristol of a manuscript copy of the layout for a five page announcement advertisement for dicloxacillin. The sponsor points out that this advertisement contains the text of the package circular.

August 12, 1966.—Submission by Bristol of proof copy of labels and cartons for dicloxacillin. The sponsor requests that FDA review this material before he proceeds with final printing.

August 15, 1966.—Response by Bristol to the proposed dicloxacillin monograph. The following suggestions are offered: 1) That the concentration used in the toxicity test be changed from 20 to 16 mg. to put it in accord with the dosage used on oxacillin and cloxacillin. 2) That the solution used for the pH test be prepared to contain 10 mg. instead of 30 mg. per ml. 3) That a more specific assay for organic chlorine content be used. 4) That the oral preparation of dicloxacillin be referred to in the labeling as a suspension and not a solution.

Bristol states in this submission that it is their intention to market a 62.5 mg. capsule of dicloxacillin in addition to the 125 and 250 mg. preparations. The formula, manufacturing instructions, finished product specifications, label, carton, and insert are included.

August 17, 1966.—Letter from FDA to Bristol acknowledging receipt of the proposed dicloxacillin standard, lot #66132. Assay data for the stated potency, the reference used, and the assay data for the infra-red and organic chloride results are requested.

August 15, 1966.—Conference between FDA and Bristol. The major subject discussed was the sponsor's claim that Dynapen is effective at a dosage level of 125 mg. given four times daily. It was pointed out that the Form 5 contains data for only 9 adults with penicillin-resistant staphylococcal infections treated at this dose. The sponsor agreed to review their material from this point of view. In addition, the fact that 13 clinical investigators of dicloxacillin have submitted no cases was brought up and an explanation was promised. It was recommended that the statement in the labeling that larger or more frequent doses may be used for more severe infections be changed to read that they should be used.

August 30, 1966.—FDA review of Bristol's letter of 8/15/66. The following remarks are made. 1) There are no objections to the proposed change in the pH test. 2) Potency should not be corrected. "If bulk material is sold for manufacture in finished products, the potency 'as is' should be considered." 3) The percent chlorine test should be retained with the additional statement the "the free chloride content must not exceed 0.5%". 4) The toxicity dose should be kept at 20 mg. since this was proposed by Ayerst and, in any case, different doses are used for 2 forms of oxacillin.

September 6, 1966.—Submission by Bristol of new package circulars for dicloxacillin incorporating several editorial changes. Also included is Bristol's review of resistant staphylococcal infections treated with the low dose form of dicloxacillin.

September 12, 1966.—Telephone conversation between Dr. H. Peltier (Bristol) and Dr. A. E. Smith (FDA). Dr. Smith recommended that in the dosage section of the proposed package insert the words "of the upper respiratory tract" be placed after "mild to moderate infections" and the phrase "higher and more frequent dosage in more severe infections and in infections due to penicillinase producing staphylococci" be inserted.

September 12, 1966.—Submission by Bristol of package circulars incorporating the changes suggested by Dr. Smith (9/12/66).

September 18, 1966.—Submission by Bristol of 111 case reports of patients treated at a dose of 12.5 mg./kg. or less per day and 14 cases treated at doses of 12.5 mg./kg. to 17 mg./kg./per day The sponsor claims that all but one patient were bacteriologically cured and offers the following points with reference to use of these doses: 1) The average MIC's for dicloxacillin *in vitro* range from 0.016 to 0.3 mcg./ml. 2) After administration of an oral dose of 125 mg. to an adult, peak serum levels are considerably higher than the highest MIC's of sensitive organisms. 3) Although the drug is considered to be highly bound *in virto* (by serum proteins) the clinical significance of this binding is not known, particularly in view of the rapid excretion and short half-life of the drug. 4) The cases presented offer clinical and bacteriological evidence that the drug is effective in mild to moderate respiratory infections at the recommended dose. 5) Additionally, the 117 staphylococcal infections treated of which 80 were treated at 12.5 mg./kg. or less per 24 hours (including 46 of the 80 due to penicillinase-producing staphylococci) indicate that the agent is highly effective in these infections as well. However, we will accede to your request to gather more data on the treatment of patients infected with penicillinase-producing staphylococci at the low dose.

October 10, 1966.—Letter from FDA to Bristol concerning experience with the assay procedure for dicloxacillin. The recommended infrared method was found to use up too much of the standard and a modification is proposed.

October 12, 1966.—Conference between FDA and Bristol called to discuss Bristol's revised clinical protocol for evaluation of dicloxacillin 125 mg. tablets in streptococcal infections. Under this protocol, cultures are to be taken before therapy, and 48–72 hours following its termination. FDA advised that the least number of laboratory studies which would be acceptable is a white count, hematocrit and urinalysis in each case and that complete specification of the bacteriological methods used should be provided.

November 25, 1966.—Submission by Bristol of revised labeling for Tegopen (sodium cloxacillin monohydrate). In this, the statement advising that therapy be switched to penicillin G in the event that bacteriological studies show the infecting organism not to be a penicillinase producing staphylococcus is deleted. The reasons given for this change are intended by the sponsor to apply also to dicloxacillin, and are as follows: "1) Clinical data obtained to date demonstrates that cloxacillin is safe and effective when used in the treatment of infections due to Group A streptococci, pneumococci and nonpenicillinase-producing strains of staphylococci. 2) It may be ill-advised to change therapy if a staphylococcus initially moderately sensitive to penicillin has been treated with cloxacillin since such an organism might have become more resistant in the interval before the bacteriology results were obtained. 3) There is no evidence from available data to support the development of resistance by staphylococci to the penicillinase-resistant penicillins. In the period during which methicillin has been commercially available, there has been no increase in the incidence of staphylococcal strains resistant to the drug. When resistance does occur, there is no evidence that it is related to exposure to methicillin. If resistance were to develop through a process of mutation, it would be reasonable to have expected a slow but inexorable increase in the percentage of resistant strains during the last six years, probably with outbreaks of resistant staphylococcal infections in individual hospitals or wards. Since neither of these events has occurred, we submit that this constitutes further evidence to support our position."

December 21, 1966.—Submission by Bristol of pathologist's report on the testes of male rats used in teratology studies on dicloxacillin. This report states that all sections were within normal limits and that the treated and control groups were not distinguishable.

January 6, 1967.—Submission by Bristol explaining that in view of difficulties encountered in previous teratological studies with mice, another study had been performed. This study demonstrates that there was no difference between dicloxacillin and penicillin V with regard to parental or fetal findings. No adverse changes with respect to viability, number of pups born, resorption sites or ab-

normalities at birth were found, and examination of the detailed gross findings of skeletal tissues with respect to number of ribs and sternal bone structure and humerus length failed to reveal any difference between the controls and animals receiving graded doses of these antibiotics administered either orally or subcutaneously. A maximum dose of 600 mg./kg./day was employed.

January 13, 1967.—Submission by Bristol of a marketing report for a number of penicillins. This is submitted as support for Bristol's contentions that the incidence of methicillin-resistant staphylococci has not risen despite widespread use of the semi-synthetics. The general utilization of cloxacillin is shown to be comparable to 1) the total penicillin market and 2) that of Bristol's preparations of penicillin G and V.

February 15, 1967.—Comments by Dr. W. E. Dye (FDA) on Bristol's letter of 11/25/66 concerning labeling changes for Tegopen. Dr. Dye offers these remarks: (1 "Expert academic medical opinion continues to support the present labeling for these drugs and to maintain that penicillin G is the drug of choice for the treatment of infections caused by susceptible strains of Gram positive cocci, and that the penicillinase-resistant penicillins should be largely reserved for the treatment of disease caused by penicillinase producing staphylococci. This advise has been obtained from experienced infectious disease experts with well staffed and equipped laboratories . . . Expert medical opinion does, however, concede that '. . . . for initial therapy while awaiting the results of laboratory tests when the presence of resistant staphylococci are suspected . . . a penicillinase resistant penicillin is indicated." Opinion is divided on whether or not to switch to penicillin G or V if subsequent cultures revealed the presence of penicillin G susceptible streptococci, pneumococci or staphylococci. It is known that short periods of therapy with penicillinase-resistant penicillins can induce the formation of penicillinase in certain strains of staphylococci. This means that the staphylococcus isolated prior to penicillinase-resistant penicillin therapy might be penicillin G resistant 24 to 48 hours later when the results of the drug susceptibility testing on the initial isolate become available . . . I know of no instance where this phenomenon has been of clinical importance. 2) There is no doubt that the safety and efficacy of Tegopen . . . has been or can be demonstrated in the dosages recommended for the treatment of infections caused by susceptible strains . . . 3) The emergence of strains of staphylococci resistant to penicillinase-resistant penicillins does not, on the basis of several years of experience, appear to be a significant problem in this country or in England . . . The (existence) of these organisms, however, and their cross resistance wish other penicillins should be incorporated into the new labeling for these antibiotics. 4) If significant changes are made in the labeling of Tegopen, all other manufacturers of penicillinase-resistant penicillins should be notified simultaneously."

February 16, 1967.—Telephone conversation between Dr. H. C. Anderson (FDA) and Dr. H. C. Peltier (Bristol). Dr. Anderson asked whether Bristol would be willing to combine their clinical data with that obtained by the other two producers of dicloxacillin in order to obtain early approval of the Form 5. Dr. Peltier responded that his lawyers were concerned about the possible antitrust aspects of this proposal and that, furthermore, Bristol was anxious to have the application approved at the 125 mg. dose, which had not been investigated by the other companies.

March 17, 1967.—Conference between FDA and representatives of Bristol. Dr. Anderson (FDA) informed the sponsor that our review of clinical data for dicloxacillin 125 mg. capsules and oral suspension indicated that the low dose is effective against upper respiratory infections due to Group A streptococci and against mild soft-tissue infections caused by *Staphylococci Aureus.* The sponsor is to submit a draft package insert covering these indications.

March 21, 1967.—Submission by Bristol of revised package circulars for dicloxacillin. Minor changes are incorporated in this revision. Also included are case reports for 18 patients with staphylococcal infections treated with the low dose of dicloxacillin (125 mg. 4 times daily in adults and 12.5 mg./kg/day or less in children). The sponsor states that bacteriological cure was established in 17 or 18 cases.

March 27, 1967.—Submission by Bristol correcting a minor error in the submission of 3/21/67.

March 28, 1967.—Medical Officer's Review of addendum to Form 5 on use of low doses of dicloxacillin in clinical infections. This report is summarized by Dr. Shurin (FDA) as follows:

Cases of staphylococcal infections treated with oral dicloxacillin have been reviewed. Doses of 1 gram daily in divided doses seem to provide adequate therapy for these infections when combined with other appropriate treatment (i.e. surgery). A very low rate of side effects and no serious complications occurred in 148 patients. The evidence available supports the use of low doses (125 mg. q.i.d. of 12.5 mg/kg/day) in mild and localized infections.

The majority of pneumococcal infections reported in the Form 5 were pneumonias. 250 mg. q.i.d. seems to be the lowest adequate dose for this infection. It may be expected that minor and localized pneumococcal infections will respond to lower doses, but few of these were reported and considered acceptable.

The data strongly supports the efficacy of dicloxacillin, 125 mg. q.i.d. or 12.5 mg/kg/day orally, in treating mild to moderate upper respiratory infections due to betahemolytic *Streptococcus pyogenes*. Cures were obtained in over 95% of cases and no instance of post-streptococcal complication or adverse reaction occurred.

March 29, 1967.—Initial pharmacology review of Form 5. A summary of this review by Dr. Orthoefer (FDA) follows:

Structurally, dicloxacillin differs from cloxacillin and oxacillin only in the number of chlorine atoms present in the side chain of the 6–APA molecule. It shares many biological properties with these acid stable penicillin, including their relative low toxicity and adequacy of blood levels obtainable by oral administration.

As with other penicillin compounds, rabbits and guinea pigs suffer a high mortality following treatment with relatively small oral doses of the drug. . . . This is usually attributed to an upset of the normal gastrointestinal flora of these animals leading to toxic manifestations and death. The data presented indicated that dicloxacillin and nafcillin produce somewhat more gastrointestinal damage in these species than other penicillins. . . .

The disastrous effects of dicloxacillin on the dams makes interpretation of the rabbit teratology study, in terms of effects on the fetus, extremely difficult. However, no consistent trends were noted in mouse teratology studies and a 2-litter reproduction study in rats yielded no remarkable evidence of adverse effects.

The rat and dog studies revealed no unusual findings. Dosage levels of over 20 times the proposed human dose were administered to these animals for 12 weeks without adverse effects. Other studies in our files (Ayerst) have shown that dogs can tolerate 500 mg. kg for 6 months and 1000 mg/kg for 2 weeks without adverse effects.

The urinary excretion rate of dicloxacillin for man and dog differ significantly. In human studies 40–75% of a given dose was excreted in the urine within 6 hours . . . in the dog less than 2% is excreted . . . within 4 hours. . . . This difference may be explained by percent protein binding or by a greater metabolism of the drug in the dog.

The data submitted thus far indicate that dicloxacillin capsules are acceptable from a safety standpoint providing all precautions pertaining to penicillin are clearly stated in the labeling.

March 30, 1967.—Conference between Bristol and FDA on labeling. Minor revisions were requested by FDA and agreed to by Dr. Peltier. In their summary, Drs. Smith and Anderson (FDA) state that with these changes, labeling is acceptable.

March 31, 1967.—Telephone conversation between FDA and Bristol concerning controls. With Bristol's agreement to use a minimum potency limit of 850 mcg./mg. for the bulk drug and a dose of 20 mg. for the toxicity, Mr. Norton (FDA) states that "all points of controversy have been resolved."

March 31, 1967.—Drug control review notes state that controls are adequate.

March 31, 1967.—Briefing memorandum by Dr. H. C. Anderson (FDA) concerning dicloxacillin. Dr. Anderson cites the medical officer's reviews of 7/14/66 and 3/28/67 as support for the safety and efficacy of dicloxacillin. The results of a poll of specialists conducted by FDA on the question of labeling for dicloxacillin is discussed as follows:

"We polled a number of specialists in the field of infectious disease and they would agree in large part to the old form of labeling. However, it is my feeling that we sampled a very biased group of individuals, almost none of whom would in their academic work see or treat many of the diseases (streptococcal pharyngitis, bronchitis, superficial skin infections) for which these drugs are advocated. I am in complete agreement with (Dr. Peltier's) letter (of 11/25/66) . . . I am therefore recommending that NDA 50–028 be approved for certification and the labeling as submitted be approved also."

March 31, 1967.—Submission by Bristol of revised labeling incorporating several minor revisions.

April 26, 1967.—Addendum to medical officer's review stating that cases submitted by Dr. William Abruzzi were not considered for evaluation.

April 26, 1967.—Telephone conversation between Dr. Anderson (FDA) and Dr. Peltier (Bristol). Dr. Anderson advised that FDA would like the statement "This drug should not be prescribed for neonates because safe conditions for use have not been established", added to the labeling and that indications for the drug should be revised to mention that the drug is specifically effective against penicillin G resistant staphylococci, and that the latest stability data on the capsules should be submitted.

April 26, 1967.—Submission by Bristol of stability data on 12 lots of dicloxacillin.

April 27, 1967.—Conference between FDA and Bristol. It was recommended that certain questionable side-effects such as listlessness and tiredness be removed from the labeling.

April 28, 1967.—Telephone conversation between Dr. David Holvey (Bristol) and Dr. P. Shurin (FDA). Dr. Holvey inquired about certain cases which were cited in FDA's medical review. Dr. Shurin supplied him with the case numbers of these cases.

May 1, 1967.—Submission by Bristol confirming the results of conference of 4/27/67.

May 31, 1967.—Conference on current problems in labeling of dicloxacillin. Bristol reiterated the desire to recommend dicloxacillin for infections due to all sensitive Gram-positive cocci. Their position is as follows: (1) In well controlled studies, Bristol has not been able to demonstrate any disadvantage of dicloxacillin, as compared to penicillin G or V in the treatment of streptococcal pharyngitis. (2) The early fear that staphylococci would develop widespread resistance to semi-synthetic penicillins has not been borne out by many years' usage. (3) The contested claims are now permitted for such drugs as novobiocin, tetracycline and triacetyloleandomycin. Therefore, more stringent requirements for dicloxacillin are discriminatory. (4) It is possible though not borne out by any clinical evidence, that an infecting strain of *Staphylococcus* may increase its level of penicillinase production during the course of an infection. In such a case, switching treatment from dicloxacillin to penicillin G following the results of original cultures, would be contraindicated. (5) It is unwarranted to change treatment when the patient is responding well, if there are no real or theoretical disadvantages associated with the original medication. Dr. Hodges (FDA) agreed to take the matter under further consideration.

June 10, 1967.—Drug control review notes state that "a 12 month expiration period could be approved for all potencies of the capsules and for both potencies of the powder for oral suspensions. The stability data for the reconstituted suspension indicate that it would be stable for 7 days at room temperature and for 14 days on ice."

June 13, 1967.—Submission by Bristol informing FDA that the original oral suspension of dicloxacillin has been found to be so bitter as to be unpalatable. The company has, therefore, developed a method of wax coating the drug and claim to have "determined that the drug in this coated form is as readily available as the original formulation." This amendment contains manufacturing instructions, specifications, test methods, stability data, labeling, blood level studies and samples of this formulation.

June 14, 1967.—Letter from FDA to Bristol recommending that the package insert be revised as follows: 1) The listing of the organisms should include "penicillin G resistant and penicillin-G sensitive staphylococci. 2) There should be a statement to the effect that "if it is determined that the infection is not due to the penicillin G resistant staphylococcus, a change to penicillin G or phenethicillin may be considered . . .

June 19, 1967.—Conference called to discuss inclusion of the above statement (item 2, 6/14/67) in the labeling for dicloxacillin. Bristol's position on this has been exhaustively cited above (see notes for 5/31/67, 11/25/66 and 7/20/66). The FDA position remained that widespread use of dicloxacillin and related drugs for various infections due to Gram-positive cocci may lead to their declining usefulness as antistaphyloccal agents and thereby produce a serious public health problem.

June 28, 1967.—Medical Officer's review of data pertaining to the coated form of dicloxacillin for oral suspension. Blood levels and urinary excretion obtained with this preparation were comparable to those obtained with the old formula.

July 25, 1967.—Interoffice memorandum (FDA) concerning test results with the new formulation of dicloxacillin for oral suspension. No difficulties are cited.

July 6, 1967.—Submission by Bristol. In the conference of 6/19/67, it had been agreed by Bristol and FDA to cooperate in preparing a poll of experts on the labeling of dicloxacillin. This submission states that since FDA had subsequently, through Dr. Minchew, declined to cooperate in a personal presentation of this poll, Bristol had gone ahead with it. The written responses of 16 physicians tend to support Bristol's position as outlined above.

July 17, 1967.—Interoffice memorandum (FDA) points out that Bristol's poll did not raise question of whether therapy should be switched from dicloxacillin to penicillin G., if warranted by bacteriological results.

July 18, 1967.—Submission by Bristol giving tabulated summary of results of their poll on dicloxacillin. The important questions and responses are as follows:

(1) Is there data to indicate a trend to an increasing number of strains of staphylococci becoming resistant to the semi-synthetic penicillinase-resistant penicillins?

Yes—4, No—10.

(2) In your opinion should a penicillinase-resistant penicillin be reserved for the treatment of infections due to penicillinase-producing staphylococci when the penicillin has been shown to be highly effective both bacteriologically and clinically in infections due to streptococci and pneumococci?

Yes—2, No—12.

(3) In your opinion would reserving a penicillinase-resistant penicillin for infections due to penicillinase-producing staphylococci prevent or materally delay the appearance of resistant strains of the organism?

Yes—0, No—13.

September 1, 1967.—Telephone conversation between Dr. Peltier (Bristol) and Dr. McQueen (FDA) concerning labeling for dicloxacillin. Dr. McQueen stated that the recommendation of the Medical Advisory Board on this question would be ready within a week.

September 7, 1967.—Telephone conversation between Dr. Peltier (Bristol) and Dr. McQueen (FDA). Dr. Peltier was informed of the wording for the indications section of the package insert recommended by the Medical Advisory Board.

September 12, 1967.—Conference convened to discuss Britsol's latest proposed labeling for dicloxacillin in the light of the Medical Advisory Board recommendation. The only point remaining at issue was the statement advising use of penicillin G or phenethicillin in the event that the infecting organism prove not to be a pencillinase producing staphylococcus. Bristol wanted to substitute the phrase "other appropriate antibiotic therapy" for mention of specific drugs. Dr. Hodges (FDA) stated that this substitution seemed to obscure the intent of the advisory board and would not be acceptable. After discussion this statement was agreed to by both parties: "When the infecting organism is susceptible to penicillin G the physician is advised to use penicillin G, phenoxymethyl penicillin, phenethicillin or other appropriate antibiotic therapy, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semi-synthetic penicillins."

* * * * * * *

September 21, 1967.—Telephone conversation to Bristol by Dr. Smith (FDA) to request minor revisions in the labeling.

September 25, 1967.—Conference between FDA and Bristol on moisture limits, pH and chlorine content of dry powder for oral suspension. Resolution of these matters was agreed upon.

September 26, 1967.—Submission by Bristol of additional stability data to substantiate their claim of a 12 month expiration date.

September 26, 1967.—Submission by Bristol of confirmation of matters discussed in telephone conversation of 9/21/67.

October 5, 1967.—Pharmacology review of coated form of dicloxacillin oral suspension. There is no expectation of increased toxicity associated with this formulation but it is suggested that data on toxicity of the flavoring agents be requested "as a final precautionary check."

October 9, 1967.—Telephone conversation to clarify questions about flavoring agents in dicloxacillin oral suspension. Bristol is to submit toxicity studies of this formulation in the near future.

October 16, 1967.—Submission from Polak's Frutal Works, Inc. Middletown, New York, supplying information on the composition of Imitation Antibiotic Flav-O Lok 3X 610049.

October 17, 1967.—Submission from Fritzsche Brothers, Inc. New York, N.Y. containing the formula for Aromalok Pineapple Imitation # 31194.

October 19, 1967.—Letter from FDA to Bristol stating that approval of package circulars for dicloxacillin has not been made.

October 23, 1967.—Submission by Bristol containing formulas of flavoring agents used in spray-coated dicloxacillin for oral suspension and acute toxicity data in rats and dogs on this product.

October 30, 1967.—Pharmacology review stating that the material contained in the submission of 10/23/67 satisfies the requests raised in the previous review of 10/5/67.

November 16, 1967.—Interoffice telephone conversation in which it is stated that Dr. Wright (FDA) approves of minor change in the wording of the dicloxacillin monograph.

November 16, 1967.—Telephone conversation between Bristol and FDA in which FDA states a preference for retention of the analytical tests originally proposed in the monograph. This was accepted by Bristol.

November 17, 1967.—Drug control review notes stating that stability data are now adequate to support the sponsor's requests, that the flavoring agents are acceptable and that an inspection has indicated that good manufacturing practices are being followed.

December 1, 1967.—Medical Officer's review of additional clinical studies designed to compare the efficacy of two dosage schedules—250 mg qid and 125 mg. qid in the treatment of minor infections due to coagulase positive staphylococci. The following conclusion is offered: "Bristol's contention that dicloxacillin at a dose level of 125 mg qid provides adequate therapy for staphylococcal infections of the skin and soft tissues of moderate severity, is probably justified. I feel that higher doses should be recommended in those cases where there is significant expectation of complications arising from the infection.

January 5, 1967.—Telephone conversation between Dr. Smith (FDA) and Dr. Holvey (Bristol) in which the sponsor was informed of certain further suggested revisions in the labeling.

February 23, 1968.—Conference between Bristol and FDA in which Bristol again presented its position on methicillin resistant staphylococci (see notes of 5/31/67.) 11/25/66 and 7/20/66). Additional data was presented in which it was demonstrated that among Bristol's employees, exposure to semi-synthetic penicillins was not associated with any nasal carriage of methicillin resistant staphylococci, but that a high level of exposure caused carriage of *S. aureus* to be changed to carriage of *S. Epidermidis.* Dr. Minchew (FDA) stated that the other two producers of dicloxacillin had now submitted labeling conforming to all our requests and that these would be acted upon. Similar labeling has been prepared by Bristol but not yet submitted.

February 23, 1968.—Telephone conversation between Dr. Smith (FDA) and Dr. Peltier (Bristol). Dr. Peltier stated that revised labeling would be submitted but said also that Bristol might consider withdrawing its application.

February 26, 1968.—Submission by Bristol of revised labeling for dicloxacillin. The sponsor wishes "to state for the record that we are not in agreement with" the changes requested by FDA and now accepted. The statement noted in the above note of 9/19/67 is deleted.

February 19, 1968.—Submission by Bristol of preliminary results of an in-plant survey of nasal flora. These results are noted in the above note of 2/23/68.

March 5, 1968.—Telephone conversation between Dr. Smith (FDA) and Dr. Peltier (Bristol) confirming wording changes suggested by Dr. Smith for the labeling submitted on 2/26/68. Dr. Peltier agreed that previously submitted promotional material is no longer to be considered.

March 5, 1968.—Submission by Bristol of corrected package inserts for dicloxacillin.

March 5, 1968.—Submission by Bristol confirming the telephone conversation of the same date, and clarifying points raised by a letter of 1/13/67 (these points are clear in the above note for that date).

March 8, 1698.—Interoffice memorandum from Dr. Smith (FDA) to Dr. Ley (FDA) confirming the opinion of the Division of Anti-infective Drugs that the applications of all three companies for sodium dicloxacillin should be approved, and that the labeling submitted by all of them is acceptable.

PAUL A. SHURIN, M.D.

FOOD AND DRUG ADMINISTRATION, BUREAU OF MEDICINE

12TH MEETING MEDICAL ADVISORY BOARD

August 31 and September 1, 1967, Crystal Plaza Office Center, Arlington, Va.

Members of the Board present: Dr. Mark W. Allam, Dr. Harry F. Dowling, Dr. William M. M. Kirby, Dr. John G. Morrison, Dr. Arthur P. Richardson, Dr. Wesley W. Spink, Dr. Norman Kretchmer (September 1 only).
Member of the Board absent: Dr. William R. Mann.
Executive Secretary: Dr. Jean D. Lockhart.

PROCEEDINGS

Dr. Minchew welcomed the Board and announced that Dr. Ley was at the American Society of Pharmacology and Experimental Therapeutics meeting being held at Howard University on the same day.

Dr. Paul Shurin presented the first agenda item: dicloxacillin. After discussing the general pharmacology of this semi-synthetic penicillin he pointed out that in the past, labeling for such agents included a statement advising the physician to switch to penicillin G if culture showed the infecting organisms to be sensitive to it. However, the three companies producing dicloxacillin are resisting the inclusion of such a switch statement in the labeling of these drugs, all of which are ready for new drug approval in other respects. Questionnaries sent both by FDA and by the pharmaceutical firms to antibiotic experts have not resolved the issue.

Dr. Hodges pointed out that if Bureau policy is changed on dicloxacillin it should also be changed for methicillin, nagcillin and oxacillin. As things stand now manufacturers of the latter three drugs may not promote their drugs as the drugs of choice for routine use against susceptible gram-positive cocci.

Dr. Minchew indicated the concern of the Bureau of Medicine, that the semi-synthetic penicillins will be used for routine practice and that in the next few years resistance to these organisms will develop. Already seven strains of staphylococcus at Boston City Hospital have been shown to develop complete cross-resistance.

Dr. McCleery explained the implications of the labeling as they apply in advertising.

Dr. Kirby doubted that there was a sound rational basis for placing these restrictions on the labeling of semi-synthetic penicillins. During the past seven years, there is little or no evidence of any resistance developing. Dr. Dowling agreed with Dr. Kirby that the evidence is slight, but was impressed with the strains found at Boston City. Dr. McCleery expressed the wish that the switch statement be strengthened rather than deleted.

Dr. Dowling expressed reluctance to label a drug advising the physician to use one or another drug, since this comes close to deciding relative efficacy, something the Congress did not wish the FDA to do at the time of the 1962 amendments.

Dr. Morrison pointed out that the care of many patients especially the aged is conducted not in hospitals but in nursing homes or in other sites where no culture facilities are available. Several Board members expressed concern at the physician's choice being restricted.

Dr. Morrison moved that the labeling for dicloxacillin contain 3 general statements; 1) "When the infecting organism is susceptible to penicillin G the physician is advised to use penicillin G, V, or phenethicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semi-synthetic penicillins." 2) "The principle indication is in treating infections due to penicillinase producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcic infection." 3) "This product is also effective in treating streptococci, pneumococci, and penicillin-sensitive staphylocci."

Dr. Dowling seconded the motion. Those in favor were Drs. Allam, Dowling, Morrison and Spink. Those opposed were Drs. Kirby and Richardson.

Following lunch the Board reconvened and Dr. Charles N. Rice, Chief, Toxicology Information Program, National Library of Medicine, described his program and its relationship to the recommendations of the President's Science Advisory Committee on the handling of toxicological information as well as to the FDA handling of toxicologic data. The program headed by Dr. Rice aims to develop a user-oriented system which will supply information services and

product. It is also planned to develop a directory. Dr. Rice noted that the FDA is a source of valuable data on toxicology and has made strides in making this information available, FDA will logically be a prime contributor and client of the bank at the TIP.

Dr. Rice's plan includes; (1) The establishment of a registry of sources of information. (2) The establishment of a center for the dissemination of literature including technical reports, working papers, etc., and (3) The establishment of a program for critical evaluation of literature.

Dr. Allan B. Lisook spoke next on prison facilities for clinical investigation. He raised questions about what constitutes adequate records, how closely an investigator should be associated with the study and with other investigators, and how carefully should the progress of the investigation be monitored. In tracing the history of investigations which have been questionable he pointed out that in 1962 the work of one investigator was found to be fraudulent and he was eventually convicted for submitting false data to the Government. At present, an investigator's exemption can be revoked by the FDA if his work is determined to be questionable. The Bureau of Medicine is especially interested in the Phase I investigations being performed in prisons. Dr. Lisook noted that the investigational set-up at the McAlester Penitentiary under the University of Oklahoma may be considered a model for good drug investigational procedures.

Dr. Minchew pointed out that FDA guidelines have been developed for the handling of possibly falsified data so that an investigator is brought in for discussion and has several oportunities to explain his manner of conducting drug studies before the Commissioner might take action to withdraw his exemption.

Dr. Kirby noted that the FDA's high standards have upgraded research and Dr. Richardson wondered if ultimately some sort of certification of investigators will develop.

Dr. Wentz stated that industry has trouble getting good studies done. Reference was made by Dr. Minchew to the recent publication of a synopsis of the New Drug Regulations, copies of which had been distributed to the Board members.

Dr. David B. Leof next reviewed the 1967 first phase training program for the new Scientific Associates. In his estimation the course provided a good introduction to the work at FDA. He urged an ongoing professional education program in the Bureau of Medicine. Dr. Ethridge of George Washington University, who was present during this presentation, concurred. Dr. Minchew felt that the Bureau will have to have some type of course annually. Dr. Richardson commented that such a course would be a good opportunity for Fellows in clinical pharmacology as well.

Mr. Julius Hauser, of the Office of the Associate Commissioner for Compliance, next reported on the comments received from the public on the proposed new advertising regulations. Twenty-three such comments had been received to date, prominently lengthy comments from the PMA and the Pharmaceutical Advertising Club of New York. The PMA comments consist of a 27 page letter discussing the regulations in detail and a 46 page legal brief. Mr. Hauser quoted from some of the comments and noted that of them all those of the PMA were the most intelligent and constructive. He indicated, however, that a hearing would likely be necessary on the subject. Dr. Dowling suggested that the opinion of the Board members as to the answers received be solicited again either by mail or at the next meeting of the Advisory Board. There seemed to be general concurrence.

In answer to a question, Mr. Hauser stated that he did not think the advertising regulations would result in a decrease in advertising since the pharmaceutical firms need to promote their own brand name product.

On the second day of the Advisory Board meeting, Dr. Ley presided as Chairman.

Dr. Ley opened the discussion by soliciting comments on a proposed "Dear Doctor" letter on sulfonamides which had been distributed to the Board members on the close of the previous day's meeting. The FDA purposes to send this letter to all physicians. Essentially, the letter points out that sulfonamides, while recognized as effective in the *prophylaxis* of streptococcal infections, have not been shown to be effective in the *treatment* of streptococcal infections so as to prevent subsequent occurrence of Rheumatic Fever. The Board members requested some discussion of the papers on which the conclusions presented in the letter had been based. Dr. Ley pointed out that these papers had been reviewed both by FDA staff and by the American Heart Association. Several of

the studies were cited and quoted. The general problem of comunicating with the physician was discussed, as there seemed to be disagreement concerning the effectiveness of "Dear Doctor" letters.

Dr. Ley noted that a periodical to physicians has been suggested and is under consideration. Dr. Dowling urged more signed articles in Journals such as the *JAMA* or the *New England Journal of Medicine.*

Dr. Richardson also supported some form of regular communication.

The "Dear Doctor" letter itself was not discussed further except for Dr. Spink's comment that penicillin itself does not prevent the development of rheumatic fever, as implied in the letter.

The next three speakers discussed the desirability of uniform labeling.

Dr. Edwin Ortiz first described the steps leading up to the uniform labeling of oral contraceptives. The most recent revision of oral contraceptive labeling was in June 1967. Several meetings have been held with the oral contraceptives manufacturers concerning labeling and also one concerning the manner in which effectiveness may be expressed.

Dr. Alan Smith described problems with uniform labeling for tetracyclines. The FDA proposes two package inserts; one for pediatric dosage (liquid), and the other for adults (tablet/capsule dosage forms). The manufacturers of tetracyclines, however, vigorously resist generic labeling and oppose the concept of uniform labeling. They raise various objections, including differences of opinion about the age for the tooth staining warning. Dr. Kirby, who is on the NAS efficacy review committee which is considering tetracyclines, pointed out that physicians are *disease* oriented, not bacteria oriented and recommended the phrase "Diseased, due to ——— organisms" rather than a list of organisms, in the labeling of tetracyclines. Dr. Alan Smith noted that Lederle's Acromycin lists 50 different diseases. Drs. Spink and Morrison concurred that diseases should be listed. Dr. Dowling pointed out that the tooth warning would not be needed in parenteral products and Dr. Kirby agreed.

It appeared to be the consensus of the Board that pediatric and adult labeling inserts should be different, and that one should accompany the liquid and the other the tablet/capsule preparations.

(Dr. Morrison left the meeting)

Dr. Ley noted that on about August 1, the need for developing a recommended format for the package insert was discussed. The Bureau felt that it would be better to develop a set of *guidelines* for package inserts. This would later be useful for a compendium. A Bureau of Medicine committee has deliberated and has set down a tentative suggested outline of labeling guidelines.

Dr. Jennings continued the discussion of the labeling guidelines, reminding the Board that at their previous meeting some of these questions had been described: the wording of pediatric dosages, pregnancy warnings, and the need for detailed pharmacology discussion and bibliographic references. He supported the concept of uniform labeling in that it would convey information and provide education as well as avoid promotional aspects. Dr. Jennings also distributed an example of a package insert (Indocin) as well as revision suggestions for the same drug insert. "The package insert is our principle product," said Dr. Jennings.

Dr. Dowling suggested that under the Adverse Reactions heading a distinction be made between reactions *definitely* established and those *not definitely* established, as was done with the oral contraceptives. He also noted that a long list of reactions to drugs loses its effect, if it is so lengthy.

Dr. Jennings favored a package insert in two parts, the first part having simple directions for use and the second part containing a fuller explanation.

Dr. Ralph Smith noted that there are two different types of uniform labeling: (1) for related drugs (like oral contraceptives, phenothiazides and phenothiazines) and (2) for the same drug put out by a number of firms. The latter is a simpler problem, some of the panels at the National Academy of Science are talking about developing model package inserts for drugs of the latter type. Dr. Smith noted that the format for a package insert is already pretty much standard and has been fairly well accepted by the firms without need for any regulation. Both Dr. Smith and Dr. Ley pointed out that the guidelines for labeling were still in a draft form and did not represent established policy. Dr. Ley solicited the comments of the Board members in the next several weeks, both on the guidelines and on the "Abbreviated" package insert which Dr. Jennings had written for Indocin.

Following lunch Dr. Arthur Wentz discussed the Conference on Experimental Design which was held on August 24 and 25, at the FDA. The drug category considered was anti-convulsive drugs. Five workshops were held on the first day and each included representatives from industry, FDA and from the academic world. The purpose of the conference was to exchange ideas on the problems of good experimental designs.

Each workshop had been given a series of questions for their consideration and on the second day there was open discussion of the workshop findings. Dr. Wentz read some of the conclusions of the workshops and agreed to send the summary of the conference proceedings to the Board members.

Dr. Ley discussed the labeling of fatty foods. A few months ago the AMA Committee on Nutrition recommended; 1) In foods containing over 10% fat the manufacturer will be allowed to label the fat content by quantity. (example: 50% polyunsaturated fat) 2) This labeling would be voluntary. The FDA is having to review these recommendations carefully and revise its agency position. The Bureau of Medicine has recommended to the Commissioner that no medical claims be permitted on the labeling or in the advertising. The new proposal would however, enable the physician to identify foods with certain fat contents, for the guidance of his patients.

(Dr. Morrison returned to the meeting)

Dr. Ley described the recruiting program planned by FDA to replace the Public Health Service officers who will be leaving in July of '68 and of '69. He noted that Dr. Goddard is interested in developing an active training program here.

After a coffee break Dr. Ley commented on several problems facing the Bureau including the backlog of supplements, the labeling guidelines, the Modell criticisms, the creation of many new Bureau of Medicine Advisory Committees, and the continuous problem of how to communicate with the practicing physicians.

Dr. Kretchmer invited the Board to meet at Stanford in December and the dates of December 14 and 15 were chosen before the meeting adjourned.

I certify that I attended the twelfth meeting of the Food and Drug Administration Medical Advisory Board on August 31 and September 1, 1967 and that these minutes accurately reflect what transpired.

JEAN D. LOCKHART, M.D.,
Executive Secretary.

MARCH 26, 1968.

Director, Bureau of Medicine
Acting Director, Division of Medical Advertising/OMS
Labeling for Dicloxacillin products
Bristol Labs, Syracuse, N.Y. (AF 15–068) "Dynapen," NDA 50–028
Wyeth Labs, Philadelphia, Pa. (AF 13–548), "Pathocil," NDA 50–011 NDA 50–092
Ayerst Labs, New York, N.Y. (AF 19–003), "Veracillin," NDA 50–046

The proposed package inserts, as revised, for the subject products have been reviewed as requested. The major differences between the 3 labels appear to have been resolved. However, several differences still exist which may deserve consideration before final approval.

I. Dr. Minchew, in his addendum at the end of our memo of December 5, 1967, expressed concern over the open-ended dosage recommendations in the "Veracillin" labeling. In reviewing this, it became apparent that now *all three* package inserts have open ended dosage instructions. Also, the "Veracillin" dosage instructions, in addition to being open ended, recommend a dosage for both adults and children with severe infections twice that of the other two products, i.e. 500 mg v.s. 250 mg and 50 mg/Kg/day v.s. 25 mg/Kg/day respectively.

II. *Wyeth's labeling for "Pathocil"*

A. The disclaimer statement leading into the "Adverse Reactions" section has not been omitted. Not only is this type of language absent from the other two package inserts, but it is the type of statement which lends itself to misuse and abuse in promotional material, and in our opinion, has no rightful place in official labeling.

B. "Indications section—In reference to page 1:

1. Present paragraph 4 should be moved to follow present paragraph 1.
2. Present paragraph 3 should be moved to follow present paragraph 5 so that it will immediately precede the paragraph beginning "Indicated surgical procedures . . ."

C. "Adverse Reactions" section—The statement dealing with changes in liver function studies is still vague and non-specific. The other two package inserts specify that these consisted of elevations in SGOT and alterations in cephalin floculation.

D. "Dosage and Administration" section—The statement that dicloxacillin is best absorbed when taken on an empty stomch (1 to 2 hours before meals) is still absent, although it is present in the other two package inserts. In his memo of January 15, 1968 Dr. Hodges stated that this point had not yet been resolved, but would be the same in all three inserts. If this point does have some merit, we would suggest it be included in all three package inserts.

III. *Bristol's labeling for "Dynapen":*

A. In reference to page 2: The second and third sentences of paragraph 1 should be inserted as a separate paragraph following present paragraph 2.

B. The "Actions" section of the package insert for Dynapen capsules omits the word "most" in the sentence "Dynapen is active against [most] Gram-positive cocci . . ." while the package insert for Dynapen suspension includes the word "most." It is recommended these inserts for the same product be consistent.

IV. *Ayerst's labeling for "Veracillin":*

A. The first page marked January, 1968, job number 66–517, is in the form of an ill-concealed promotion and must be rejected. We suggest that the properties of the drug which follow the "dots" be rewritten in an appropriate discussion form comparable to the "Description" section of the Bristol package insert for Dynapen.

B. In reference to page 2: The present second paragraph of the "Indications" section should be moved below the present fourth paragraph.

C. It was suggested by Dr. Minchew and others during revision of the dicloxacillin labeling that the precautionary statement regarding intestinal overgrowth should read ". . . discontinuation of dicloxacillin therapy should be considered" since in some instances it might not be advisable to discontinue the drug. However, the "Veracillin" labeling states ". . . medication should be discontinued . . ." It is recommended that the "Veracillin" labeling be made consistent with the other two.

V. It was noted that the labeling for Bristol's and Wyeth's products contain within the "Indications" section the instruction regarding 10-day treatment of Group A Beta-hemolytic streptococcal infections, while Ayerst includes this information in the "Dosage" section. Since dicloxacillin is not ordinarily recommended for treatment of Group A Beta-hemolytic streptococcal infections, it might be considered contradictory to include instructions for treating such infections in the "Indications" section. Because of this consideration it would be appropriate to limit this statement to the "Dosage" section of all the dicloxacillin labels.

Also the words "Group A" should precede "beta-hemolytic" in the Wyeth "Pathocil" labeling.

R. S. McCLEERY, M.D.

MEMORANDUM OF TELEPHONE CONVERSATION

MARCH 27, 1968.

Between: Hubert C. Peltier, M.D., vice president and medical director, Bristol Meyers (AF 15–068); and Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine.

Dr. Ley read to Dr. Peltier the three changes in the approvable letter for the Bristol dicloxacillin product. Dr. Peltier objected mildly but indicated that the changes were consistent with the general philosophical approach the agency was taking to this drug.

Dr. Peltier objected that in his opinion the FDA action on dicloxacillin was discriminatory against this particular product in view of the existing labeling for other products. Dr. Ley pointed out that it would be wise for Dr. Peltier to observe changes in product labeling over the next year. The two individuals engaged in a long discussion regarding the philosophical concept of restriction in usage of the semi-synthetic penicillins. At the conclusion of the discussion neither individual had changed his position and it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semi-synthetic penicillins.

HERBERT L. LEY, Jr., M.D.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
April 10, 1968.

To: Director, Bureau of Medicine.
From: W. B. Rankin, Deputy Commissioner.

Mr. Thomas Corcoran, an attorney representing Bristol Laboratories, presented the attached paper to Dr. William H. Stewart, acting for Dr. Philip Lee, on April 9.

Please let us have by close of business April 16, proposed comment from Dr. Goddard to Dr. Lee on this paper.

W. B. RANKIN.

Enclosure: Copy of paper.

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, naficillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or by penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.

Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling. It is understood, however, that it is based on the possibility that some time in the future, there might appear in the environment organisms resistant to semi-synthetic penicillins if they are widely used now. Thus, semi-synthetic penicillins should be reserved for future use by implementing the reserve drug theory through labeling.

However, other antibiotics which have been marketed in the last few years have labeling which omits the elements of the reserve drug theory even though they are indicated also for use in the treatment of infections caused by pneumococci, streptococci and both resistant and non-resistant staphylococci. Such drugs include gentamycin, cephalothin, cephaloridine, methacycline, doxycyline and lincomycin. FDA approval of the omission is peculiar in view of the fact that resistant staphylococci strains have previously appeared shortly after market introduction of similar classes of antibiotics including many of the tetracyclines. Most recently, resistant staphylococci strains have appeared after lincomycin was marketed.

By comparison, although there are rare staphylococci in nature resistant to these penicillins, no significant increase in pathogenic strains which are resistant to the semi-synthetic penicillins have appeared even though methicillin has been in use over eight (8) years and oxacillin for over six (6) years. In contrast, strains resistant to penicillin and penicillin G appeared and increased shortly after those drugs were introduced. This omission, particularly with respect to the labeling for cephalothin and cephaloridine, is indefensible since these drugs are primarily used in hospitals where the problem of resistant infections developing is the most serious.

There are a number of explanations based on experience as to the reasons for the development of strains resistant to some antibiotics and not others. One turns on the distinction between bacteriostatic antibiotics (where resistant strains have usually developed) and bactericidal antibiotics (where resistant strains have not usually developed). It should be noted that such semi-synthetic penicillins as dicloxacillin are bactericidal rather than bacteriostatic, while many of the antibiotics not subject to the reserve drug theory are bacteriostatic.

These random applications of the FDA's policy become even less defensible when it is understood that the failure to apply the theory to the labeling of non-semi-synthetic-penicillin antibiotics would have a patient allergic to penicillin defenseless against some future epidemic of resistant staphylococci infection.

The scientific underpinnings of the reserve drug theory are extremely questionable. But unquestionably, its application has been discriminatory, arbitrary and scientifically unsound. Most recently, by applying the reserve drug theory to dicloxacillin, the FDA is in effect applying the test of relative efficacy in

reverse despite the abundant legislative history that this factor cannot be considered by the FDA in approving new drugs. The FDA has refused to approve labeling allowing the marketing of dicloxacillin for streptococci, pneumococci and sensitive staphylococci because it has been shown to be better than penicillin G and penicillin V in the treatment of bacterial infections in that it is effective against penicillin G-resistant staphylococci.

It is urged, therefore, that the FDA either immediately discard the theory by deleting its elements from the labeling for semi-synthetic penicillinase-resistant penicillins or apply it even-handedly by requiring it in the labeling for all antibiotics which are indicated for use in the treatment of infections caused by pneumococci, streptococci and staphylococci. After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformally imposed or discarded.

MARCH 28, 1968.

To: William H. Stewart, M.D., Surgeon General, PHS
From: James L. Goddard, M.D., Commissioner of Food and Drugs
Subject: Dicloxacillin as a subject of hearings by the Nelson committee

Reference is made to inquiries directed to you by Mr. Thomas Corcoran, attorney representing Bristol Laboratories, regarding the origin of suggestions that the drug, Dicloxacillin, be considered by the Nelson committee.

In early March the Nelson committee staff contacted the Administration with the request that information be furnished the committee on the investigational drug, MER–29, and on a number of marketed drugs approved post-1962. These requests were handled by the Office of Legislative and Governmental Services of the Food and Drug Administration.

The allegation of Mr. Corcoran that the drug, Dicloxacillin, was suggested for consideration by Dr. Robert McCleery is false; a fact we have verified by interview with Dr. McCleary. The request for information on this drug came from the committee staff.

We recently prepared an information memo for Dr. Lee, dated April 18, 1968, which summarizes the history of Administration position on Dicloxacillin. A copy is attached. This memorandum provides insight into the pressures imposed by drug firms on the Administration in its clearance of new drugs for marketing.

Answering your request for our views about whether you and Dr. Lee should meet with Mr. Corcoran:

There is nothing in FDA's handling of this matter that requires such a meeting. We see no objection to a meeting at which the facts are laid before the attorney. If there is a meeting, the Department should not be apologetic for its position of Dicloxacillin. We have a sound position and should adhere to it.

To: Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs
From: James L. Goddard, M.D., Commissioner of Food and Drugs
Subject: Labeling of semisynthetic penicillins

Recently, Mr. Thomas Corcoran, an attorney representing Bristol Laboratories, questioned the action FDA has taken with regard to a semisynthetic penicillin produced by Bristol.

The attached staff paper gives in considerable detail the FDA position and the manner in which we reached it. I believe we have a sound position and think that we should adhere to it.

Mr. Corcoran is in error when he implies that we are discriminating against his client. You will note from the staff paper that we are taking steps to achieve uniform administration of the statute to the semisynthetic penicillin manufacturers.

MAY 23, 1968.

COMMENTS ON BRISTOL'S "DYNAPEN" LETTER

1. The headline characterization of the drug as a "—High Potency Pencillin— for Skin and Soft Tissue Infections" on envelope and letter is inconsistent with the limited approved indications for the drug. It is indicated, in Skin and Soft Tissue Infections, but only those due to Pen-G resistant staph.

2. The representation that dicloxacillin is "—useful in a *broad range* of skin and soft tissue infections". may be interpreted to mean "broad range" in terms of types of lesions, or "broad range" in terms of etiologic organisms. The latter would be inconsistent with the package labeling.

3. The featuring in the letter of statements such as "low incidence of side effects," "side effects—are exceptionally rare," "lower dosage does mean a lower incidence of side effects," "no direct toxicity," and "a notable lack of side effects" are misleading, especially in the absence of balancing information regarding the facts that, (a) the incidence and severity of adverse reactions are not shown or expected to be less than with other penicillins, (b) super-infection with resistant organisms may occur, (c) safety for pregnancy has not been established, (d) nausea, vomiting, flatulence, loose stools, pruritis, urticaria, skin rashes, allergic symptoms, changes in liver function tests, and eosinophilia have been associated with Dynapen therapy.

4. At no point in the letter, is the need for cultures and sensitivity, and the need to switch therapy if a Pen-G sensitive organism is isolated, expressed.

5. In the 1st paragraph, the indication is given "—in infections of the skin and underlying tissue where resistant staph are *so often* known or suspected." The words "so often" distort the meaning in such a way as to subvert the need to know by cultures or reasonably suspect resistant staph in any specific case.

6. Throughout the letter, in several places where "resistant staph" are mentioned, they are not specified as *Pen G*-resistant staph.

7. In the 2nd paragraph the question of resistance is brought up in a very clever way—"Resistance has not developed *during therapy.*" This is misleading in the absence of the information that, however, strains of pathogenic staph resistant to Penase resistant penicillins, including Dynapen do exist and are increasing in numbers and may cause clinical disease and even death.

8. The comparison of blood levels with Pen G and Pen V are objectionable, since Dynapen should not ordinarily be used exchangeably with Pen G or V. It might be appropriate to compare blood levels with oxacillin or cloxacillin.

9. The letter cites clinical data on "a variety of pathogenic staphylococcal infections" including Pen G sensitive staph. Also, overall percent improvement figures are given, I suspect based on clinical impressions and not on follow-up culture data, at least in some cases.

SUMMARY

The ad:

(1) Invites use of the drug in broader indications than those approved.

(2) Does not properly carry out the responsibility to emphasize the need to restrict the use of this drug to infections due to Pen G resistant staph infections.

(3) Does not present a fair and balanced view of the adverse reactions associated with use of this drug.

R. KAUFFMAN.

CORCORAN, FOLEY, YOUNGMAN & ROWE,
Washington, D.C., May 24, 1968.

DR. JAMES L. GODDARD,
Commissioner, Food and Drug Administration,
Arlington, Va.

DEAR DR. GODDARD: On behalf of our client Bristol Laboratories, this is to express our appreciation to the Commissioner's office for the expeditious handling of the procedures required for the release of Dynapen, the Company's brand of dicloxacillin. While the ambiguities and confusion resulting from the initial handling of the labeling, release, regulation publication and certification of the three brands of dicloxacillin have placed the Company at a competitive disadvantage, the Administration's remedial efforts should permit the Company to make up some of the lost ground.

Unfortunately, new confusion has arisen in connection with certain language contained in the regulation for dicloxacillin which appeared in the Federal Register of May 17, 1968. As you know, antibiotic regulations with respect to labeling normally provide simply that the labeling for a specific antibiotic shall be in accordance with Section 148.3 of the regulations. Section 148.3 in turn is in large measure based on the requirements of Section 1.106 issued under Section 502(f)

of the Federal Food, Drug and Cosmetic Act which requires the language of the label commonly referred to as the Official Package Circular (OPC). The OPC or label for two of the three brands of dicloxacillin are attached hereto. You will note that the 3rd and 4th paragraphs under "Indications" for Bristol Laboratories' brand of dicloxacillin state as follows:

"Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and non-penicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

"Indicated surgical procedures should be performed."

Section 149(a)(1) of the dicloxacillin regulation contains the usual language which requires the label and labeling to be in accordance with requirements of Section 148.3. However, Section 149(a)(2) and Section 149(a)(3) provide in effect that in addition to the labeling requirements of Section 148.3 that each package should bear on its label or labeling the following statements:

INDICATIONS

"The principal indications for sodium dicloxacillin monohydrate are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of these infections where a penicillinase-producing staphylococcus is suspected.

"Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

"Substantial changes in these indications will not be permitted. Elaboration to indicate results obtained in clinical trials will require approval."

You will note that this Indications Section differs substantially from that of the approved OPC in that it excludes the 3rd and 4th paragraphs of the OPC but includes a new 3rd paragraph.

As we understand it, the FDA interprets Dr. Ley's letter of May 7, 1968 (copy attached) to mean that after the labeling is approved and sample testing completed for release under Section 507(a), dicloxacillin may be prescribed, dispensed, labeled and advertised before an appropriate regulation appears in the *Federal Register*. Therefore, Bristol Laboratories had the same rights and opportunities with respect to dicloxacillin as its competitors but misunderstood the purport of Dr. Ley's letter.

It follows as a logical extension of the FDA's interpretation that batches of dicloxacillin released prior to publication in the *Federal Register* and batches of dicloxacillin certified after publication in the *Federal Register* are subject to identical label, labeling and advertising requirements, since a contrary conclusion would lead to chaos in view of the lead time involved in the preparation of labels, labeling and advertising and would amount to a negation of fundamental considerations of fairness and consistency which are implicit in the administrative process. Further, the first two paragraphs of the Indications Section for Veracillin (a competitive brand of dicloxacillin) differ in some measure from that required in the dicloxacillin regulation. The additional paragraphs in this OPC Indications Section differ from the OPC for Dynapen and are, of course, entirely omitted from the dicloxacillin regulation.

In attempting to reconcile the seeming difference between the language of the OPC and the dicloxacillin regulation, we have reached the following conclusions:

(1) A type-setting inadvertence accounts for the 3rd paragraph contained in the regulation and the language thereof is not required to be stated in the label or labeling for dicloxacillin.

(2) The Company has both the obligation and right to include the 3rd and 4th paragraphs of the Indications Section of the OPC in the labels and labeling for its brand of dicloxacillin.

(3) The language "substantial changes in these indications will not be permitted. Elaboration to indicate the results obtained in clinical trials will require approval" should be interpreted as follows:

(*a*) The label and labeling for dicloxacillin must substantially reflect the first two paragraphs under "Indications" contained in the dicloxacillin regulation.

(*b*) The Company may not elaborate on results obtained in clinical trials without FDA approval unless such trials accurately relate to the language contained in the Indications Section of the OPC.

(*c*) As a corollary, the Company may elaborate on results obtained in clinical trials if such results accurately relate to the language contained in the Indications Section of the OPC.

We have also considered the possibility that the 3rd and 4th paragraphs of the Indications Section of the OPC were inadvertently omitted from the regulations.

Bristol Laboratories is currently in the process of preparing a request for the convening of an advisory scientific panel to determine the validity and scope of the reserve drug theory. This request will contain the reasons for convening the panel, suggested issues to be decided, the make-up of the panel, suggested ground rules to be followed and reasons why the previous panel did not decide the issue in dispute and other pertinent factors.

In view of the controversies and misunderstandings which have surrounded dicloxacillin and other semi-synthetic penicillins, an early and detailed respose in connection with all these matters would be appreciated greatly if we are to be in a position properly to advise our clients with respect to the labeling and advertising for its semi-synthetic penicillins.

Very truly yours,

CORCORAN, FOLEY, YOUNGMAN & ROWE.

MEMORANDUM OF CONFERENCE

Bristol Laboratories, Syracuse, N.Y., AF 15-068.
Dynapen, NDA 50-028.

MAY 27, 1968.

Present (Bristol Laboratories): Mr. Morris S. Weeden, president; Mr. Robert B. Simonton, attorney; Hubert C. Peltier, M.D.; Messrs. Corcoran, Foley, Meers and Lane.

Present (Food and Drug Administration): Commissioner Goddard; H. L. Ley, Jr., M.D.; B. H. Minchew, M.D.; R. S. McCleery, M.D.; J. J. Jennings, M.D.; R. E. Kauffman, M.D.; K. H. Potts, M.D.; Mr. W. W. Goodrich; Mr. H. W. Chadduck.

Subject: Initial Dynapen promotion.

This meeting at 9:00 a.m. this date was requested by the Commissioner in his telephone conversation with Mr. Weeden late Friday, May 24, 1968. Parallel with this action, the Commissioner approved cancellation of certification of Dynapen, including all lots initially certified. Also, action was taken to embargo, at the wholesale level, all shipments of Dynapen. Meanwhile, the Secretary had been notified of the action taken and had been given a copy of the promotional letter in question as well as a copy of the complaint sheet.

Dr. Goddard opened the meeting and, using the DMA comments drafted on May 23, 1968, recounted the principal complaints against the "Dear Doctor" promotional letter headed "new high potency penicillin specific for skin and soft tissue infections." He said that the letter violated every principle discussed regarding the indications for use in the labeling of Dynapen and that was the reason why telegraphic action had been taken to cancel certification.

Mr. Weeden said Bristol had discussed the restricted use of Dynapen, and realizing the competition with penicillin-G decided to tell physicians about the site of infections rather than the cause (organism). Bristol selected skin and soft tissue, which, according to Weeden, were associated with "staph" infections. He went on to say that Bristol had not thought of expanding claims beyond the package insert allowances. On questioning, he and his associates said that the promotional letter had gone to the printer on May 15, was mailed out May 17 and that when the letter was written, Bristol did not have Dynapen available for marketing.

Commenting on the foregoing statement, Dr. Ley pointed out that the Dynapen labeling details had been known to Bristol on March 28. Dr. Goddard emphasized that even if Bristol hadn't been aware of the *Federal Register* monograph details, the promotional labeling was basically wrong due to its lack of fair balance, minimization of side effects, etc. He called attention to the Loridine current ad as a good example of advertising. He said it was hard to understand why Bristol's letter had been the way it was after he and his associates had met with

some 24 firms to discuss bad advertising practices. These had been followed by "remedial" letters, the published details of which are well known to the industry.

Expanding on this, Dr. Goddard read excerpts from the Dynapen promotional letter, one being the claim "notable lack of side effects." He said when the firm exercises the option of calling attention to side effects, it incurs the obligation of presenting a balanced view of side effects. In this case, a few of the more serious side effects should have been named.

Mr. Weeden suggested that the package insert with the letter listing side effects should overcome the fair balance problem. But Dr. Goddard said this was not a replacement for balancing "promotional" side effect information in the subject letter. Dr. McCleery said that the limited experience with the drug at lower dosage levels provides no valid basis for the general claim of lower side effects for the drug.

Messrs. Weeden and Simonton and Dr. Peltier joined in commenting on the concept used in the promotion. They said physicians had been consulted and the result was that they promoted for sites rather than organisms—sites associated with "staph" infections. They said they thought the approved indications had not been exceeded.

Dr. McCleery pointed out that some examples of infections recited in the letter are not typically staphylococus-associated but streptococcus-associated—"impetigo," "cellulitis," "lymphangitis" and "lymphadenitis"—and that some other listed things like "infected skin ulcer," "postoperative infections," "infected wounds, burns and lacerations" could be due to many organisms other than staphylococcus. He referred to the May 1968 issue of the *American Journal of Diseases of Children* in which there was reported a group of 214 patients with impetigo of which 74% was due to Group A streptococcus.

Dr. McCleery emphasized that there is no legal basis within the approved indications for the slogan "specific for skin and soft tissue infections." He indicated that the letter was replete with non sequitur statements, that there were ample opportunities to be clear, but that this was avoided in a well-tailored misleading message. He said the firm even chose to include a dangerous dose recommendation, in that it emphasized a 125 mg dose without stating it was limited for use only for mild-to-moderate (and localized) infections.

An exchange followed between Messrs Simonton and Goodrich in which the latter advised that the letter should have stood on its own, and while the package insert was included, it did not offset the side effect imbalance and, in any event, the letter was inconsistent with the package insert.

Mr. Goodrich then said that when it was learned how much of the drug had been certified (apparently enough for 44,000,000 units), it was apparent that there was a desire to get into the general penicillin market. Mr. Simonton took the opposite position and said an attempt had been made to limit marketing for approved indications.

Dr. Goddard said that the alternate indication seemed to be presenting problems. He said if it became necessary, that the package insert may be revised to delete the second indication, which permits the physician to start the drug without first knowing the identity of the causative organism. He added that the letter did not provide proper guidance and then asked what was the thrust of the journal advertising.

Mr. Weeden said all Dynapen advertising had been stopped but admitted that at least one ad will appear in the Medical World News issue of May 31.

Dr. McCleery reminded the visitors of the continuing disagreement over many months regarding the package insert reference to "strep" and "pneumo," and to the latest FDA move of that paragraph to the end of the indications section. He said that the information was intended not to expand indications but to assist the physician in knowing when it might be safe to prescribe it for the second indication.

The discussion turned to the development of resistance in relation to the letter sentence, "Resistance has not developed during therapy." Dr. McCleery said that the problem of resistance had been handled in a misleading way and called attention to various reports of resistance. When Dr. Peltier stated that "no patient has developed resistance during therapy," Dr. McCleery said this was not true. Dr. Peltier stated that he was not saying there are no resistant strains [which was a reversal of what he had said previously].

Dr. Goddard then said the problem under discussion primarily concerned violation of agreement regarding indications for Dynapen. He requested reports from the visitors as to what the firm is saying to its detail men. He requested

a list of where the ad(s) appeared. He requested copies of telegrams to detail men concerning the present incident.

The discussion turned to remedial considerations. Dr. Goddard said that the first obligation is to correct the bad impressions caused by the promotion.

Mr. Weeden commented about the lack of certified material to market and urged rapid action.

Drs. Goddard and Ley and Mr. Goodrich joined in requesting the following actions. The "remedial" letter should be sent air-mail. A draft will be prepared and sent to Dr. Ley for review. A corrective advertisement will be prepared and run in journals where the defective ad(s) have appeared. Accurate copy of the ads [there are two] will be sent in for detailed review. Corrective information for detailing will be prepared for review.

As to timing, Mr. Weeden said that some material had cleared to the retail level. Mr. Goodrich noted that such material could be subject to seizure. Dr. Goddard requested that Mr. Weeden sponsor the collection of information as to material shipped from wholesalers to retailers. After some discussion, Mr. Weeden said that efforts could be made to have the Bristol field force contact wholesalers. Also, a copy of the telegram will be sent to FDA regarding the embargo of stocks in the hands of wholesalers.

Before leaving the meeting at this point, Dr. Goddard indicated that there was no intention to prolong the embargo unduly but that full corrective action must be taken and that will take time, perhaps 30–60 days.

Dr. Ley continued the meeting and said, in view of the urgency, that a copy of the current ad and of the detail men's brochures should be sent to him for Dr. McCleery's review, which will require time. It was left to the visitors to propose copy for the "remedial" letter, and corrective ad copy if they wished. Dr. Ley said alternatives would be considered if proposed. One possibility suggested by Mr. Goodrich was to convert the remedial ad into a mailing piece.

At this point, Dr. McCleery said that Bristol's competitors had proceeded in an orderly manner and that his group is engaged in assisting them in their promotion; therefore, it would not be fair to postpone existing commitments to handle Bristol's problem exclusively. He said, however, that his review would proceed as rapidly as possible after receipt of the Bristol input.

There was a brief exchange regarding preclearance of promotional labeling of antibiotic drugs. Mr. Simonton seemed unclear as to this but it was emphasized that the regulation revised in February 1968 makes it certain that preclearance is not normally required.

At conclusion of the meeting after Dr. Peltier had summarized the required information to be submitted (copy of current ad, remedial letter draft, and detailing instructions), Dr. McCleery said that if Bristol could get the material to us by Wednesday May 29, we could probably meet Friday to discuss it. He said that, among other things, the material should include a straightforward scientific statement of the place of Dynapen in therapy.

After the meeting, it was arranged that Bristol would meet in Dr. Ley's office at 3:00 p.m., Friday, May 31 to discuss the remedial pieces.

[Note: In lieu of a critique, which because of lack of time could not be prepared in advance of this meeting, there are attached a xerox copy of a marked up copy of the Bristol promotional letter showing areas of error and a copy of a rough draft of comments on the letter dated May 23, 1968].

H. W. CHADDUCK.

BRISTOL LABORATORIES,
DIVISION OF BRISTOL-MYERS CO.,
Syracuse, N.Y., May 27, 1968.

Dr. HERBERT L. LEY, Jr.,
Director, Bureau of Medicine,
Food and Drug Administration,
Arlington, Va.

DEAR DR. LEY: Enclosed is the Dynapen promotional literature as well as the other material you requested from Mr. Weeden:

(1) *Exhibit A.*—Three copies of the enclosed manila index folder and its contents were given to our salesmen to be used as a "keeper." That means the folder was not left with the doctor but rather used as a visual aid by the salesman to help him acquaint the doctor with the new drug. The salesman's instructions were to use the quotation sheet (headed: Antibiotic Resistance

of Staphylococci) to point out the high incidence of resistant staph as a pathogenic organism both in and out of the hospital. The blood level chart was to be used to illustrate the excellent absorption of Dynapen. The balance of the sheets stapled in the folder were to be used to acquaint the doctor with *all* of the other information concerning Dynapen.

(2) *Exhibit B.*—Consists of a copy of a memo from our advertising department indicating those journals in which Dynapen advertising will appear. Tear sheets of each of the ads are also included. You will note, in that memo, the immediate action we took with regard to our advertising following notification from the Commissioner's office on Friday afternoon.

(3) *Exhibit C.*—Is a memorandum from our General Sales Manager outlining the action we took on the distribution front. A copy of the cablegram to our wholesale accounts is attached thereto.

(4) *Exhibit D.*—Finally, enclosed is another memo from our General Sales Manager estimating the amount of Dynapen which has been shipped into retail and hospital channels.

Very truly yours,

WILLIAM D. GULICK,
Vice President, Director of Marketing.

Enclosure: Exhibit A [exhibits B, C, D, omitted].

EXHIBIT A

DYNAPEN SALES APPROACH

Doctor ———, I'd like to talk to you about a new and unique antibiotic that Bristol has just introduced. We're very excited about this product because it's the kind that will fill a real need in your practice and the kind you will find a lot of use for.

It's a new high potency penicillin called Dynapen which is specific for skin and soft tissue infections—the kind you see everyday like abscesses, boils, and infected lacerations, and wounds. You will find even more use for Dynapen now during the summer when the incidence of skin infections increases.

Dynapen is an ideal specific for skin infections especially when you consider that over half of the staph strains isolated from office patients are resistant staph. Because Dynapen is a penicillinase-resistant penicillin, it kills these resistant organisms. Whereas, of course, neither penicillin G or V or erythromycin or tetracycline, for example, work.

Dynapen has undergone more than four years of clinical trials and it's been evaluated in thousands of patients. For example, in 587 staph infections where it was used, 202 were sensitive staph and the cured or improved record was 98%. In 385 cases of pencillin G resistant staph, the cured or improved record was 97%. These are pretty good results, wouldn't you agree?

Now why is Dynapen so effective?

First of all, Dynapen is bactericidal—it kills pathogens outright rather than merely inhibiting their growth. Consequently, resistance has not developed during therapy. On the other hand, therapy with bacteriostatic agents is frequently complicated by the development of resistance. The reason why we call Dynapen a high potency penicillin is its superior absorption. Dynapen is so well absorbed that 125 mg.—the usual dose—produces average blood levels far in excess of the concentration necessary to kill the organism (show blood level chart). This will give you an idea of just how well Dynapen is absorbed at only 125 mg. Peak blood levels are 5 times higher than 250 mg. of penicillin G and 2 to 4 times higher than 250 mg. of penicillin V. The fact is, Dynapen is superior in absorption to all other penicillins.

The 125 mg. dosage has still another advantage. The evidence to date clearly supports the contention that lower dosage means a lower incidence of side effects. In over 1500 patients evaluated for side effects, less than 1% experienced adverse reactions at the usual dose.

Dynapen is a safe drug, Doctor ———. There has been no direct toxicity reported to date—no tooth staining—no blood dyscrasias—no hepatotoxocity—and no photosensitivity. However, as with other penicillins, the possibility of an allergic reaction should be considered.

With all these advantages, you might think Dynapen would be an expensive drug. The fact is the patient cost will be no more than most brands of peni-

cillin—lower than most of the cyclines and mycins—and less expensive than many antibiotics you may now be using to treat skin infections.

What do you think of Dynapen, Doctor ———?

The dosage for Dynapen in skin and soft tissue infections is only 125 mg. q.i.d.—and you can be sure Dynapen will work at this low dosage. For more severe infections such as those you see in the hospital—like post-op infections, infected bed sores, and other traumatic wounds with infections—the dosage is 250 mg. q.i.d. For children, Dynapen is available in an 80 ml. bottle of oral suspension containing 62.5 mg. per teaspoon. The usual children's dose is 12.5 mg./Kg./day in divided doses q.i.d. For example, in a child weighing 44 lbs. the dosage is one teaspoon q.i.d. And, unlike some of the synthetic penicillins, Dynapen really tastes good.

Doctor, I have just given you the facts about Dynapen:

It's the best oral antibacterial you can prescribe for common everyday skin and soft tissue infections.

It's bactericidal.

It produces better blood levels than any other oral penicillin.

It is exceptionally well tolerated.

And, for a change, Doctor, here is a brand new penicillin that's really low in cost.

Doctor ———, I would like you to put Dynapen to the test. For wounds, boils, abscesses, and other common everyday skin and soft tissue infections, will you prescribe Dynapen?

(Make sure you call the Doctor's attention to the fact that details are available in the Basic Prescribing Information Brochure. This is most important with a new product.)

MEMORANDUM OF CONFERENCE

MAY 31, 1968.

Bristol Laboratories, Syracuse, N.Y., AF 15–068
Dynapen FDA 50–028.

Present (Bristol Laboratories): Hubert C. Peltier, M.D.; Mr. Robert Simonton; Mr. James Meers.

Present (Food and Drug Administration): H. L. Ley, Jr., M.D.; B. H. Minchew, M.D.; R. S. McCleery, M.D.; R. E. Kauffman, M.D.; Dr. Prince Harrill; Mr. W. W. Goodrich; Mr. L. M. Baukin; Mr. H. W. Chadduck.

Subject: Dynapen.

As planned, and reflected in the record of the meeting of 5/27/68, this conference began at 3:00 p.m., this date.

Prior to this meeting, establishment inspections had been carried out to determine distributions of promotional labeling and merchandise. Approximately 90,000 folders of promotional material for Bristol detail men had been produced; and about 30,000 had been mailed to some 300 such company representatives located west of the Mississippi and in Florida. Except for relatively small quantities of the oral suspension distributed outside the firm's control, about 64000 (x 24's capsules) had been distributed, about 42000 to retail pharmacies and about 3500 units to hospitals. [Figures to be coordinated with Inspector's reports]

Dr. Ley called Mr. Rankin and advised him of the results of inspections and, due to the large amounts of goods released, retail-level recall was recommended for consideration. Mr. Baukin was asked to prepare notification paper for Mr. Rankin's signature.

Three things were settled at this point:

1. Materials was to be recalled to company control.
2. Remedial letter was to be prepared using guideline prepared by Bureau of Medicine.
3. Remedial ad was to be prepared and run in the same journals as the original ad (*Medical Tribune* and *Medical World News*). The ad will consist of correct ad copy, which will also include an appropriate statement showing that this corrective action is required by the FDA.

The visitors joined the FDA group at this point.

Dr. Ley opened the discussion by informing the visitors that the material submitted with Bristol's letters of May 27 and 28, 1968 had been carefully studied on a priority basis. For record purposes, the May 28 letter enclosed a remedial letter draft, a corrected ad mockup, and an example of an envelope with the legend appropriate for transmitting the remedial letter. The May 27 letter enclosed Exhibit A (two manila folders containing promotional material to be

given to salesmen and said to be used as a "keeper") ; Exhibit B (copy of memo from Bristol ad department indicating journals in which Dynapen will appear, and ad tear sheets) ; Exhibit C (a memo from Bristol's General Sales Manager outlining action taken regarding distribution stoppage and copy of telegram to wholesale accounts) ; and Exhibit D (a memo estimating amount of Dynapen shipped into hospital and retail accounts).

Dr. Ley handed out copies of an FDA-prepared guideline to proper indications for Dynapen, which he proposed as the "core" of the remedial letter. He said the main thrust of the letter should be on these indications, and that other complaints about the initial promotional letter were of lesser importance and therefore not necessary to include.

Mr. Simenton then said he understood that the guideline plus opening and closing paragraphs would comprise the letter. Drs. Ley and McCleery commented that it would be appropriate to use the guideline and to return Monday June 3 with a second draft.

The discussion turned to details in the FDA guideline. Dr. Peltier claimed that the wording relating to "250 mg q. 6h" in the draft was not in accord with the package insert. Dr. Ley indicated that this and other points were open to discussion.

Next, the portion of the guideline dealing with the problem of staphylococcal resistance to the methicillin-family, including Dynapen, was discussed at length. This was led off when Mr. Simonton and Dr. Peltier asked about the scientific basis for the letter's emphasis on the appearance around the world, and recently in the U.S., of resistance to this class of antibiotics.

Dr. Peltier said (as he had said previously) that development of resistance during the therapy of a single patient was a minor problem. But Dr. McCleery interrupted and said it was contrary to reason to mix the two subjects. He agreed that the development of resistance during therapy is a minor problem, but said that the major problem is the increasing frequency of appearance in hospitals resistant strains of organisms of the microbial population in point.

Drs. Ley and Minchew supported this. Dr. Ley said there is good evidence to demonstrate that the widespread use of methicillin has been accompanied by the development of resistant strains. He said this has been the experience with all antibiotics in wide use (hospitals, etc.), but that proof of association beyond reasonable doubt has not been obtained, not even with penicillin G. It was also emphasized that the development of resistance to penicillin G by staphylococci does not occur by a particular strain during treatment of a single patient. However, presumably "genetic-environmental-selection" of penicillin-G resistant staphylococci has led to the prevalence of this problem. It was therefore re-emphasized to Dr. Peltier that the problem of a particular strain of staphylococcus developing resistance during therapy of a given patient is separate from the development and propagation of resistant strains among the microbial population as a whole and should not be equated.

Mr. Simonton said that he wanted Bristol to have the information that FDA had collected.

Dr. McCleery said he would give the references and said the record would show the information was supplied. He gave these references:

1. "The Resistance of Staphylococci to Penicillins and Cephalosphorins," a paper by F. H. Kayser, Institute of Medical Microbiology, University of Zurich, Switzerland, given June 26, 1967 at the 5th International Congress of Chemotherapy, Vienna, Austria (6/26–7/1, 1967)
2. "Methicillin-resistant Straphylococci in a General Hospital," E. W. Calley, et. al., *The Lancet*, 13 March 1965.
3. "A screening test for the detection of methicillin-resistant organisms," G. M. Churcher, Department of Pathology, Plymouth General Hospital, Plymouth, England, *J. Clin. Path.* (1968) 21, 213–217.
4. "Resistance to cloxacillin among hospital staphylococci," G. C. Turner and P. E. Cox, Department of Pathology, Sefton General Hospital, Liverpool, England, *J. Clin. Path.* (1967) 870–874.
5. "Antibiotic Susceptibility of Staphylococcus aureus isolated from cases of Bacteraemia in Denmark 1957–66," O. Jessen *et. al.*, an abstract (page 799 of proceedings, B 1–17) of presentation at 5th International Congress on Chemotherapy (see item 1 above).
6. "Combination Therapy of Infections Cause by Methicillin-Resistant Staphylococci with Rifampicin plus Pucidic Acid or Novobiocin," Klaus Jensen, an abstract (pages 783–784 of proceedings, A 1–6/19) of presentation at 5th International Congress of Chemotherapy (see item 1 above).

7. "The History and Development of Oral Penicillins in Japan," Ryochi Fujii, Tokyo University Hospital, a paper given at the 5th International Congress of Chemotherapy (pages 275–278 of proceedings, C 3/2).

8. "Sensitivity of staphylococcus aureus to lysostaphin, cephalotin, benzyl penicillin and semi-synthetic penicillins," Hawiger, J. and Jeljaazewicz, J., Poland, a presentation (p 35 *et seq.* of proceedings, B 1/8) at 5th International Congress of Chemotherapy.

9. "Studies on enterotoxin-B production in methicillin-resistant aureus-staphylococci, "Dornbusch K., Hallander, H. O., Laurell, O., and Lindbom, G., Sweden, an article reporting on cases during 1964–1966 in the University of Uppsala (27 deaths), presented at the 5th International Congress of Chemotherapy (proceedings p 39 *et seq.*, G 1/11).

10. "Changing Patterns of Bacterial Resistance to Antimicrobial Drugs," Gill, F. A. and Hook, E. W., Cornell University Medical College, a paper published in *American Journal of Medicine*, p. 780–795, 39: November 1965.

Other references were mentioned as being available. Later in the meeting Dr. Minchew gave the reference to an article in *Arch. Int. Med.* 111, No. 6, June 1963, titled, "Persistance of Staphylococcus to Methicillin and Oxacillin." He mentioned also that at the annual meeting of 1968 the Epidemic Intelligence Service, National Communicable Disease Center, 22 resistant organisms from 18 patients in one hospital were reported.

In sum, there is ample and continuing evidence that there is cause for concern by the Government and antibiotic producers in relation to the problem.

Dr. McCleery called attention to the Bristol submission in February regarding the resistance problem. He said the information had been discussed within FDA and with outside authorities and found to be invalid for the claims Bristol is making. Dr. Ley concurred and agreed that the Bristol submission was unresponsive to the question of resistance. He reiterated that he felt the FDA-prepared guideline to proper indications should be incorporated into the remedial letter.

The visitors again indicated that the guideline was not in accord with the package insert. The expansion of the contraindications was cited as an example. However, Dr. McCleery pointed out that the same information was in another part of the insert and that it should be emphasized. He said he had hoped that Bristol would be on the "side of the angels" and indicated that on further reflection the firm might come to agree with setting the place of Dynapen in proper perspective, notwithstanding the "legalistic" reliance on the package insert which it was entitled to take advantage of.

On the preceding point, Mr. Meers said in effect that his client is for public health protection assuming that it is reflected in the OPC (package insert).

The discussion turned to the proposed ad. Dr. Ley said the ad copy had been reviewed and found to require a small number of corrections. These were identified by Dr. Kauffman.

There was some discussion regarding the language to be used in identifying the ad as "corrective" (as distinguished from "correct"). This was left for Bristol to consider and to propose language at the next meeting.

Drs. Ley and Minchew emphasized that the Commissioner wanted a "corrective" ad and that it could take more than one form. It was left that Bristol would propose modifications in the submitted ad at the next meeting.

Dr. Ley turned the discussion to considerations of the status of shipment of goods beyond the firm's control. He said the FDA was concerned about the large amount of material so shipped.

Dr. McCleery commented that on May 24 a Bristol detail man had visited an Arlington physician and had left behind the so-called "keeper" promotional material. Dr. Ley indicated that preliminary reports from our inspectors reflected that 90,000 "keepers" had been procured, of which 25,000 were intended for hospitals and 65,000 for physicians.

Mr. Simonton admitted it was intended that the "keepers" be left behind and attempted to reconcile Bristol's (Gulick's) May 27 letter, which said that "3 copies were given to salesmen to use as 'keepers'."

Dr. Minchew said that about 30,000 were shipped on May 23 to some 300 salesmen—(see area covered in first of this memo).

Dr. Minchew asked if the firm had record of what the detailmen are saying now to physicians about Dynapen. (See comment by Bristol later on this question).

The discussion continued to the question of shipments of Dynapen. Dr. Ley said that the figures given in Bristol's letter were not in accord with the inspec-

tor's oral report. (The precise figures are subject to confirmation in the District's RIR).

Dr. Ley said that the Commissioner's office had approved recall of the goods from retail and hospital outlets and that Bristol could expect a communication to that effect.

Dr. Peltier said that recall would be very costly and that if the ad and remedial letter are satisfactory, perhaps recall could be avoided. He indicated that the FDA guideline would not be remarkably difficult to adopt.

Dr. Ley asked how Bristol could freeze the goods in retail stocks. Dr. Peltier admitted that this would be difficult. Continuing on this point, Dr. Peltier said that Bristol would rush out a revised remedial letter draft but that it would take time to implement a freeze order.

Mr. Goodrich said that we hadn't agreed yet as to the ad and that there is no basis for recertification. He added that the freeze order should get out promptly to drug stores.

In answer to Mr. Meers question as to means of expediting appearance of the corrective ad, Dr. McCleery recommended that contacts be made immediately with *Medical World News* and *The Medical Tribune* to reserve space.

The discussion resumed on the content of the remedial letter. Dr. McCleery presented a draft of the FDA version of the opening and closing paragraph. Mr. Meers said that he did not see much difference between the Bristol draft and ours. But Dr. Minchew said the difference between the two versions was that the Bristol letter would mislead physicians as to proper use of the drug, and that it was promotional.

Dr. Minchew asked about the disposition of the promotional pieces in the "keeper" folders. After some discussion of each piece, it was agreed by Dr. Peltier that salesmen would use only the "OPC" for detailing. He agreed to notify District Managers of this limitation.

The discussion resumed on the question of "freeze" and "recall." It was agreed that Bristol would submit for approval a draft of a letter to wholesalers covering letters to all retail accounts. The letters should state the reason for the "freeze." Meanwhile Mr. Rankin was to draft a "freeze" letter to Bristol for Mr. Rankin's signature.

The meeting concluded with minor comments concerning the substance of the remedial letter. [Bristol's revised draft reflects changes which they proposed for consideration.]

The next meeting to discuss continued matters was set for 10:30 a.m. Monday, June 3, 1968, and this meeting ended.

H. W. CHADDUCK.

ROUGH DRAFT OF PROPOSED RESPONSE TO DR. LEE BY DR. GODDARD

SUBJECT: CURRENT POSITION ON LABELING OF DICLOXACILLIN AND OTHER RELATED SEMISYNTHETIC PENICILLINS

I. Background

The Bureau of Medicine believes that the labeling of the semisynthetic penicillins should restrict their primary indications to the treatment of infections due to penicillinase-producing staphylococci or initiating treatment when there is the possibility of a resistant staphylococcal infection. The basis for this position is the view that it is a general public health matter relating to the possibility that penicillinase-producing staphylococci may develop resistance to these antibiotics.

At the present time available data indicate that there is complete cross-resistance of staphylococci among all currently available penicillinase-resistant semisynthetic penicillins. Therefore, the appearance of strains of penicillinase-producing staphylococci resistant to these antibiotics would mean a major setback in the antibiotic armamentarium for drugs effective against these particular bacteria. To date there is but little data to suggest that this problem of resistance is occurring. However, there are reports from Europe, and from at least one hospital in this country that resistant organisms have been isolated. We believe these findings warrant the caution and conservatism we are requesting in the labeling of these drugs at this time.

II. *Expert opinions in resistance*

A. In the process of attempting to resolve the controversy regarding the labeling of dicloxacillin, the FDA, approximately one year ago, drafted and sent a questionnaire to eleven recognized experts in the field of microbiology and antimicrobial therapy. Among those questions asked, two deal directly with the immediate problem:

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by gram-positive cocci susceptible to their actions?" All eleven experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patient is showing excellent clinical response but the cultures now show the causative organism to be a Beta-hemolytic streptococcus or pneumococcus, would you change chemotherapy to penicillin G or V?" Eight answered, "Yes." Two answered, "No." One said, "Probably would not change."

B. Following the FDA poll, Bristol Laboratories drafted a set of questions dealing with the same problem and submitted them to a group of 15 physicians, some of whom are also regarded as experts in the field:

1. Included in Bristol's questionnaire was, "In your opinion should a penicillinase-resistant penicillin be reserved for the treatment of infections due to penicillinase-producing staphylocci when the penicillin has been shown to be highly effective both bacteriologically and clinically in infections due to streptococci and pneumococci?" Eleven answered "No." Two answered "Yes." One felt the question inappropriate, and one did not give a "Yes" or "No" answer.

2. Bristol did not include a question regarding the desirability of changing therapy to Penicillin G or V if culture subsequently showed the organism to be sensitive to Penicillin G or V.

C. On August 31, 1967 the FDA Medical Advisory Board was asked to consider this problem and give their recommendations. The Board was presented with the Bureau of Medicine position and the expert opinions as expressed in answers to all the questions in the FDA and Bristol questionnaires. After considerable discussion, the concern was expressed that the package labeling for these semisynthetic penicillins should limit their indications to thus permit observation whether staphylococcal resistance to these agents does become a significant problem. With this concern in mind the Board voted 4 to 2 to adopt the recommendation: "That the labeling for dicloxacillin contain 3 general statements:

"1. 'When the infecting organism is susceptible to Penicillin G the physician is advised to use penicillin G, V, or phenothicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.'

"2. 'The principle indication is in treating infections due to penicillinase producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcic infection.'

"3. 'This product is also effective in treating infections due to streptococci, pneumococci, and penicillin sensitive staphylococci.' "

These recommendations were implemented by the Bureau of Medicine and equally applied in negotiating final labeling for all three dicloxacillin products (Wyeth, Ayerst, Bristol). The approach to labeling for dicloxacillin is well illustrated by the excerpt below:

The principal indication for sodium dicloxacillin monohydrate is in the treatment of infections due to penicillinase-producing staphylococci or in initiating treatment when there is the possibility of a resistant staphylococcic infection. Bacterilogoic studies should be performed. When the infecting organism is suspectible to penicillin G, the physician is advised to use penicillin G, V, phenothicillin or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

This product is also effective in treating infections caused by streptococci, pneumococci and penicillin-sensitive staphylococci.

III. *Comments on Bristol statement of March 28, 1968*

It is true, as Mr. Corcoran affirms, that the labeling advises the physician to use, or to change to, penicillin G when sensitivity studies indicate the pathogen is susceptible to it. It is not true (see the paragraph #1 above), as

Mr. Corcoran states, that "Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling."

The FDA did disagree with the desire of Bristol Labs, unique to it amongst the three companies involved, to insert into their package labeling a very extensive and discursive addition to the Medical Advisory Board's opinion. It was believed their additional paragraphs would weaken the labeling's public-spirited appeal to physicians to reserve the use of these drugs to the serious need for which they are so uniquely valuable, and for that reason, the Bureau of Medicine did not accept the Bristol addition.

Data from the National Drug Trade Index (1966) indicates that, in spite of the relatively restrictive labeling of the semisynthetic penicillins, these drugs were being widely prescribed for respiratory diseases, etc. Furthermore, the position of the Bureau has been based on the belief that liberalizing, instead of further restricting, the indications, would be followed by even more open promotion and use of these drugs as routine agents in general office practice for the treatment of common upper and lower respiratory tract infections. This would lead to a much more widespread use than has been the case in the past and could, therefore, contribute to the probability of a more rapid development of strains of staphylococci resistant to these agents. More recently, the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci.

Because of these facts and concerns, and because of the permissiveness of the labeling for several of these products, e.g., oxacillin and cloxacillin, it is the intent of the Bureau of Medicine to bring the labeling for all the semisynthetic penicillins, and other antibiotics where appropriate, into consistency with its Medical Advisory Board's recommendations, and the approved dicloxacillin labeling.

On March 27, 1968, the Director of the Bureau of Medicine telephoned the Vice President and Medical Director (Dr. Peltier) of Bristol Labs, to explain again the basis for FDA's so-called "restrictive" labeling for dicloxacillin. Dr. Peltier alleged that the labeling was discriminatory against this particular product.

Dr. Ley informed him that this was so only because it was the first reflection of a new policy, and promised him that the labeling of other semisynthetic penicillins, as well as that of other appropriate antimicrobial agents, was already under study for comparable revision.

Dr. Ley ended his telephone memo with this note, ". . . it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semisynthetic penicillins." It is, therefore, worthy of serious note that on March 28, 1968 Bristol turned from the scientific to the legal-administrative approach, developed the copy of the argument of that date, retained attorney Thomas Corcoran to present this to the Office of the Secretary on April 9, 1968.

Bristol, near the end of its March 28, 1968 position paper, suggests that the FDA apply the so-called "reserve drug therapy" evenhandedly or immediately discard it—this in spite of the assurance, on the day prior, of the Bureau Director that this was underway. Even more improperly, they end their paper with this misleading suggestion: "After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformally imposed or discarded."

It is misleading because it implies that the FDA reached its position in the absence of relying, in practical fact, on such an "advisory panel," which was known to Bristol not to be the case. It is misleading, also, because it was known to Bristol that the FDA, as part of its decision-making process in reaching the current position, already planned to reconvene the question after an appropriate interval allowed the collection of further evidence as to the potential danger represented by labeling these agents so that they might become in legal fact "Everyday penicillins."

TO BE SENT TO 55,000 RETAILERS AND 480 WHOLESALERS

To: All Wholesalers, Retail Pharmacists, Hospital Accounts
Request for embargo of Dynapen

The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and has requested that you hold on your shelf all supplies of Dynapen.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

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