



37



DRUG INDUSTRY ACT OF 1962

MONDAY, AUGUST 20, 1962

HOUSE OF REPRESENTATIVES,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The committee met, pursuant to recess, at 10:10 a.m., in room 1334, New House Office Building, Hon. Oren Harris (chairman of the committee) presiding.

The CHAIRMAN. The committee will come to order.

Today we resume the hearings on drug legislation and we expect to continue for the rest of this week until we have completed the hearings.

It will be our purpose to try to hear everyone who desires to appear and present information and testimony on this legislation.

I might remind everyone that the committee at this time will limit its consideration to the bill H.R. 11581.

It will be recalled that I introduced this proposal at the request of the administration and at the same time I introduced the companion bill, H.R. 11582, devoted primarily to cosmetic and therapeutic devices.

H.R. 11582 will not be pursued at this time because it is the desire of the committee to give full time and attention to the proposed drug bill. There has been some question as to the effect H.R. 11581 would have on the food industry. We have already held some hearings on that phase of the legislation.

The Chair does not feel it would be his responsibility to separate it at this stage of the hearings. It will be up to the committee to determine what it wishes to do in consideration of that phase of the proposal when the hearings are concluded.

These hearings were suspended some time ago in order that the committee could go into another important subject proposed by the administration, transportation legislation which required the attention of the committee.

At that time, I might say in all frankness, the long consideration that had been given by the other body of drug amendments seemed to have reached a point where it was doubtful that any formal action would be taken.

However, with recent events and reports that I have received, it is rather apparent that determined efforts should be made to get a bill.

In view of the changed events, I thought it was important for these hearings to be held this week.

I would also like to say to my colleagues I regret the fact that we seem to have been caught with the hearings this week, when the House is virtually in recess. Other Members of the House have been permitted to leave Washington and return to their districts.

171

However, since these hearings had been announced more than 2 weeks ago and so many people would again be inconvenienced if we did not go ahead, and since it would further delay the consideration of the bill after the brief recess, I decided that this was the most appropriate action that we should take.

I am sure my colleagues will understand the decision in this matter, and I think it is commendable that so many members decided to remain here this week and participate in these hearings. I personally want to think these members for it.

As I have stated publicly, it is my hope and desire that those who will participate in the hearings during the week will keep in mind not only the letter of the Legislative Reorganization Act of 1946, which is the procedure that guides hearings, and the rules of the House, but the spirit of that provision will be kept in mind.

I do not want to limit any witness. We have never pursued a course yet of limiting witnesses, but I might say I do not propose to sit during these hearings and listen to unusually long and repetitious statements.

I hope that will be kept in mind by everyone, with a full understanding of what we propose to do. We want to make a good record, a full and complete record, and the committee, I am sure, will help do that.

It will be recalled that we held 4 days of hearings in June. The committee received the cooperation from a number of witnesses, in addition to those representing the administration and the agencies involved. Since this matter has narrowed down to one bill, we should continue the hearings in an effort to develop the best possible record for the objectives sought.

Today we have the Pharmaceutical Manufacturers Association. There will be a number of witnesses representing that association, because that industry is primarily affected, along with the general public. There will be some others representing other phases of the industry.

The first witness this morning will be Mr. Eugene Beesley, who will present the general position of the Pharmaceutical Manufacturers Association on this legislation.

Mr. Beesley, we will be glad to have your testimony.

STATEMENT OF EUGENE N. BEESLEY, PRESIDENT OF ELI LILLY & CO., AND CHAIRMAN OF THE BOARD OF DIRECTORS OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION; ACCOMPANIED BY LLOYD CUTLER, ESQ., OF WILMER, CUTLER & PICKERING

Mr. BEESLEY. Thank you, Mr. Chairman.

I am Eugene N. Beesley, president of Eli Lilly & Co., of Indianapolis, a manufacturer of prescription medicines since 1876. I am testifying today as chairman of the board of the Pharmaceutical Manufacturers Association, whose 140 member companies produce more than 90 percent of the prescription drugs used in this country.

Recent tragic events involving a drug developed abroad have reminded all of us of the need for meticulous care in the introduction

and use of today's complex new medicines. It should reassure the American people that Congress, the executive branch of Government, and the pharmaceutical industry are constantly examining the many safeguards already in effect and searching for ways to strengthen them.

The fact is that safety checks on drugs have long been more effective in the United States than anywhere else in the world. But our job is to make certain that these safeguards are improved whenever possible and that we push on vigorously to fill present gaps in scientific knowledge, so that we can predict more accurately and completely the effects of new medical compounds on man.

Our association has already asked for stronger regulations governing our industry. It has supported measures to strengthen the food and drug laws in ways that will further the public health. We have opposed only those proposed measures which, in our judgment, would impair the ability of our industry to serve the public. We outlined our views to Congress in hearings before the Antitrust and Monopoly Subcommittee of the Senate Judiciary Committee in December 1961. The chairman of the subcommittee, Senator Kefauver, characterized our proposals at that time as "important steps forward," representing "industrial statesmanship of a high order."

We support a number of objectives which certain provisions of H.R. 11581 and the revised Senate bill S. 1552 are intended to achieve. We believe that these provisions modified to provide appropriate procedural safeguards and prevent unnecessary overregulation would be in the public interest.

All of us should be aware of one danger. In the emotional atmosphere which surrounds drugs today, there will undoubtedly be pressure from some for hastily conceived action which could produce more harm than good. The Congress and the administration must be careful not to let the pendulum swing too far. Unnecessary regulation can weaken and even destroy an industry which has been inventive and productive for the public good. We believe that this committee, with its long experience in complex health matters, will give new legislation the careful attention it deserves.

In these introductory remarks I shall briefly mention some basic principles which we hope will guide Congress as it considers new drug legislation. I shall also outline our recommendations in a very general way.

The other pharmaceutical industry witnesses who are here with me will discuss in detail the many complex provisions of proposed legislation. The committee has been supplied with a list of our witnesses and the sections of H.R. 1581 each will discuss.

HEALTH PROGRESS IN THE UNITED STATES

As we sit here today, we should not forget for one moment the tremendous advances that have been made in this country in the development of lifesaving medicines. Let us recall some startling facts:

About 4.5 million Americans are alive today who would be dead if the mortality rate of 25 years ago still prevailed.

Twenty-three years have been added to the lifespan of the average American since the turn of the century.

Since 1944 the death rate from influenza has dropped 90 percent; the rate from tuberculosis, 83 percent; acute rheumatic fever, 83 percent; syphilis, 79 percent.

The death rate among mothers in childbirth has declined by over 90 percent since 1940. The infant mortality rate has been cut almost in half.

The United States has made more important drug discoveries in the last two decades than all the rest of the world combined, and seven times as many as the next leading country.

Since 1949 the U.S. pharmaceutical industry has increased its own annual research and development expenditures for human medicines by more than 600 percent, from \$34 million to almost \$248 million. The percent of income invested in research and development by producers of medicines is almost three times the average for all industry.

The CHAIRMAN. Are you giving that on an annual basis?

Mr. BEESLEY. Yes, I am, Mr. Chairman.

The health professions as a whole are responsible for this heartening progress of man against disease, and prescription drugs have played a vital part.

GUIDELINES FOR NEW LEGISLATION

I hope we agree, therefore, that concern for the public health is to be the overriding element in considering new legislation. If a proposal serves to advance the health of the American people, it should be enacted; if not, it should be rejected.

In this respect, the Government has certain responsibilities. These are to approve the manufacturer's standards for production and quality of medicines; to conduct thorough inspections to insure adherence to these standards; and to punish those who ignore such standards. These are vital functions.

Industry, too, has vital responsibilities: To invest in a broad scientific search for new and improved medicines; to conduct thorough trials of new compounds to prove their safety and value before they are introduced; to establish and maintain proper quality controls at every step of manufacturing; to make medicines available wherever they are needed; and to maintain a constant flow of accurate and comprehensive scientific information about its products to the medical profession.

While Government regulation can prevent distribution of medicines which are below acceptable standards, no amount of regulation can, in itself, produce a safe and effective medicine. Safety and effectiveness must be built into a drug in the first place by the painstaking, step-by-step production and testing processes of the manufacturer. As members of this committee know, many producers of medicines strive for standards of excellence far higher than any which might be imposed by Government.

Moreover, Government regulation in itself can never create lifesaving drugs. This, too, depends in large measure upon the initiative and enterprise of industry.

It is important to public health, therefore, that Government regulations should not hamstring the medical advances produced by the industry. Disease and death can result from unnecessary delay in

permitting a lifesaving drug to reach the public, just as surely as they can result from inadequate Government regulation.

Let me illustrate. Penicillin has saved thousands of lives—perhaps hundreds of thousands—since it first became available. But penicillin can also cause loss of life or serious injury to a relatively few because of allergic reactions. However, if overcautious and restrictive Government regulation had blocked its testing and introduction 20 years ago, some lives would have been saved while a multitude of other lives would have been lost.

I am simply emphasizing, therefore, that the regulatory action of Government and the creativity, competitive initiative, and ultimate responsibility of industry both make very valuable contributions to public health. Public health will suffer if we concentrate on either factor alone and neglect or retard the other. Sound legislation in the public interest thus requires a wise and careful balancing of Government controls with private freedoms and responsibilities.

RECOMMENDATIONS OF THE PHARMACEUTICAL MANUFACTURERS
ASSOCIATION

In arriving at our recommendations on new legislation, we have tried to reach a wise balancing of all such considerations. Our objective has been to make possible the maximum contribution by both Government and industry in carrying out their respective responsibilities to protect and advance the public health.

Let me point out—before outlining our position—that many of the provisions of H.R. 11581 do not vest new power in the Food and Drug Administration. Rather, they clarify and, in some instances, enlarge and strengthen existing powers.

For instance, the effectiveness of drugs is already assessed by the FDA in passing on new drug applications and labeling claims. Experience has shown that under existing law the FDA can and does take the time needed to carefully evaluate new drug applications. Drug producers today maintain records for FDA inspection. FDA can remove unsafe drugs from the market and, through labeling requirements, can protect the public from unjustified claims of effectiveness. The FDA already reviews and passes on manufacturing and control procedures for new drugs. Under present law, false drug advertising is illegal.

Although it seems evident that FDA already has substantial authority in the areas covered in H.R. 11581, we endorse the following basic concepts of the bill in the belief that public health protection will be strengthened:

1. Before introducing a new drug, the manufacturer should be required not only to show the Food and Drug Administration that the drug is safe but also to present substantial evidence that it is effective in producing the results claimed.

2. FDA must have ample time to consider the safety and effectiveness of new drugs before they are introduced—but unnecessary delays in permitting valuable new medicines to reach the public must be avoided.

3. Manufacturers should be required to maintain records of experience with new drugs and other information bearing materially on safety and effectiveness and to make such information available to the FDA.

4. The FDA should have authority, after a hearing, to withdraw a new drug from the market if in the light of new evidence it is not shown to be safe or if there is a lack of substantial evidence that it has the effects claimed for it.

5. The inspection powers of FDA should be broadened to cover all facilities, controls, and records materially bearing on violations of the law.

6. FDA should be authorized to remove any drug from the market if the facilities or controls used in its manufacture are inadequate to assure the claimed identity, strength, quality, and purity.

7. A special program of controls and recordkeeping should be enacted to prevent illicit distribution of barbiturates and amphetamines.

8. FDA should be given standby authority, after a hearing, to designate an official, or generic, name for a new drug if a suitable name does not result from the existing voluntary procedures.

Furthermore, we believe that the public interest will be served if Congress goes even further than the present bill stipulates. Specifically, we propose that:

All manufacturers of drugs be required to register with the Food and Drug Administration, identifying their plants and their products to the agency responsible for inspecting and regulating their operations.

All manufacturers of drugs be subjected to mandatory inspection by FDA at least once every 2 years—and more frequently if unsatisfactory conditions make this advisable.

FDA's ability to deal with the serious health hazard of drug counterfeiting—the production and sale of drugs by fly-by-night operators who pass off their merchandise as the products of reputable manufacturers—be strengthened by including provisions specifically penalizing drug counterfeiters.

Additional and adequate funds be allocated to FDA. While we recognize that appropriations are not in the special province of this committee, it seems to us extremely important that FDA should be provided the necessary substantial expansion of staff, facilities, and funds to enable it to carry out effectively these broadened responsibilities.

There are certain provisions of H.R. 11581 which we oppose because, in our opinion, they would be detrimental to health progress. These include the unnecessary extension of cumbersome and expensive batch certification to all antibiotics; proposed regulations affecting biological drugs which would, without benefiting the public, add to the already complex and overlapping Government controls over biologicals; unrealistic requirements to present a complete drug treatise in each medical journal advertisement; and the provision authorizing the Secretary to withdraw a drug from the market before any hearing, without so much as prior notice to, and consultation with, the manufacturer. With respect to this last provision, we certainly agree that an unsafe drug should be promptly forced off the market if not removed voluntarily by the manufacturer—but the Secretary already has ample power for this purpose.

The program of legislation which we recommend will, we are confident, significantly strengthen public health protection. It will also preserve the opportunity for industry scientists to make their

own distinctive contributions to medical science. There are desirable changes in the legislative language of H.R. 11581 which need careful attention, and these will be discussed in detail by witnesses who follow me.

In concluding, Mr. Chairman, let us all be reminded that many of our health problems stem not from any inadequacy of law or law enforcement but from the limitations of present scientific knowledge of complex life processes and the ways in which drugs may affect them.

To add yet another scientific task force to help solve this basic problem, the Pharmaceutical Manufacturers Association has recently established a Commission on Drug Safety, composed of distinguished scientists. The commission will review the scientific information now available, and research being conducted, in an attempt to extend the frontiers of knowledge in the field of drug testing.

The chairman of the commission is Lowell T. Coggshall, M.D., a former Assistant Secretary for Medical Affairs in the Department of Health, Education, and Welfare. For many years he has directed medical activities and biological sciences for the University of Chicago. A list of the commission's members is attached to my statement.

However broad our present knowledge, ahead of us lies always the great unknown. We must move constantly forward toward understanding of the mysteries of life and life processes.

Our industry will continue to discharge, to the very best of its abilities, its responsibilities in research and production and widespread distribution of medicines that can save human lives and relieve human suffering. With your help, regulatory functions of Government can be strengthened to the same ends—and in such a way, we hope, that this Nation's leadership in medical affairs throughout the world can be maintained. Through dedicated effort on the part of all of us this Nation certainly can move forward to standards of health as yet undreamed of.

The CHAIRMAN. Mr. Beesley, I notice you have attached to your statement a brief statement of your own educational training, background, and experience.

Mr. BEESLEY. Yes.

The CHAIRMAN. This will be included in the record, together with the names and brief statement of each of the members of the Commission on Drug Safety.

(The documents referred to are as follows:)

EUGENE N. BEESLEY

Eugene N. Beesley, who is serving a second term as chairman of the board of directors of the Pharmaceutical Manufacturers Association, is president of Eli Lilly & Co. Born January 29, 1909, in Thorntown, Ind., he was graduated from Thorntown High School in 1925 and received a bachelor of arts degree from Wabash College in 1929. Later he attended law school at night and in 1943 received a bachelor of laws degree from the Indiana University Law School.

Beesley joined Lilly in June 1929. After several assignments as a salesman and as a district manager, he returned to the home office in 1941. In the following years he held executive positions in the fields of personnel, sales, and administration and was elected president of Eli Lilly & Co. in April 1953. He is the fifth president of the 86-year-old firm and the first president from outside the Lilly family.

In addition to serving on Eli Lilly & Co.'s board of directors, Beesley is chairman of the board of Eli Lilly International Corp. and a member of the boards of eight other Lilly subsidiaries in foreign fields. He is vice president and a

director of Lilly Endowment, Inc. He is also director of the United Fund of Greater Indianapolis, Inc., and the American Fletcher National Bank & Trust Co., Indianapolis.

He is a board member of the National Industrial Conference Board; a trustee of the National Fund for Medical Education, and the National Fund for Graduate Nursing Education; a director of the Radio Free Europe Fund, the American Arbitration Association, and the United States Rubber Co.; and chairman of the executive committee of the board of trustees of Wabash College. He is also a member of the American Pharmaceutical Association, the Indiana Pharmaceutical Association, the United States Committee of the World Medical Association, the American Bar Association, and the Indiana Bar Association.

DePauw University has conferred upon him an honorary doctor of laws degree; the University of Toledo, an honorary doctor of science degree; and Wabash College, an honorary doctor of laws degree.

He is married to the former Marian Crebore, of Elyria, Ohio. They are parents of two children: Mary Louise, who is married to Needham S. Hurst; and Mark C. Beesley.

STATEMENT OF PROFESSIONAL RECORDS OF MEMBERS OF COMMISSION ON DRUG SAFETY

Dr. Paul R. Cannon, 69, pathologist, retired as chairman of the Department of Pathology at the University of Chicago in 1957. He had served as department head for 17 years and was professor of pathology at the university for 25 years. Dr. Cannon has been editor of the American Medical Association's Archives of Pathology since 1954, and he is a former president of the American Society of Pathologists & Bacteriologists, the Association of Immunologists, the Chicago Pathological Society, and the American Society of Exploratory Pathology. The latter organization conferred the Burdick Award on him in 1948. He received his Ph. D. from the University of Chicago in 1921. He also was professor of pathology at the University of Mississippi for 3 years. He was a recipient of the Groedel Medal of the American College of Cardiology in 1958.

Thomas Francis, Jr., M.D., 62, has been professor of epidemiology and chairman of the Department of Epidemiology, School of Public Health at the University of Michigan Medical School since 1941. He earned his M.D. from Yale University in 1925. Dr. Francis is a past president of the Society of American Bacteriologists, the American Society for Clinical Investigation, and the American Epidemiology Society. He served as director of the Influenza Commission from 1941 to 1945, as a consultant to the Secretary of Defense, and as director of the University of Michigan poliomyelitis vaccine evaluation program. He was also professor of bacteriology and director of the bacteriological labs for New York University. Among his awards are the Howard Taylor Ricketts Medal, the Lasker Award of the American Public Health Association, and the American College of Physicians' James D. Bruce Memorial Medal.

Dr. Philip S. Hench, internationally known authority on arthritis and rheumatism, was awarded the Nobel Prize in physiology and medicine in 1950 for his work with hormonal drugs on arthritis and rheumatism. A native of Pittsburgh, Pa., Dr. Hench, 66, was also the recipient of the American Public Health Association's Lasker Award and the Page One Award of the Newspaper Guild of New York. He has been associated with the Mayo Foundation and Graduate School of the University of Minnesota since 1921 as professor of medicine there since 1947. Dr. Hench is a fellow of the American Medical Association and the American College of Physicians; a member of international, National, State, and local professional associations and societies; a foreign member or foreign correspondent for several professional associations; and chief editor of the American Rheumatism Reviews, published by the American Rheumatism Association. He has contributed about 200 articles to medical journals. A graduate of Lafayette College in 1916, Dr. Hench received an M.S. degree in internal medicine from the University of Minnesota, his medical degree from the University of Pittsburgh, and studied at the University of Freiburg and Ludwig-Maximilians-Universität, in Munich. Honorary degrees have been awarded him by Lafayette, the University of Pittsburgh, Washington & Jefferson College, Western Reserve University, the National University of Ireland, and Middlebury College.

Chester S. Keefer, M.D., 65, was a special assistant to the Secretary of Health, Education, and Welfare in 1946 and has been director of Boston University-Massachusetts Memorial Hospitals Medical Center since 1959. He has also been

Wade professor of medicine, Boston University School of Medicine since 1940. From 1940 to 1959, he was director of the Robert Dawson Evans Memorial Hospital and physician-in-chief at Massachusetts Memorial Hospital. During World War II Dr. Keefer was with the Office of Scientific Research and Development, where he was responsible for allocation of penicillin, then in critically short supply. He received his M.D. from Johns Hopkins University in 1922. Dr. Keefer has been instructor in medicine at Johns Hopkins and associate professor in medicine at both Peiping Union Medical College in China and Harvard Medical School. He has served as resident, visiting, and consulting physician at numerous institutions and is a regent and past president of the American College of Physicians. His work with HEW brought him the Medal of Merit.

Theodore G. Klumpp, M.D., 59, is a former Chief of the Drug Division, Food and Drug Administration (1936-41) and is now president and director of Winthrop Laboratories of New York City. He was instructor in internal medicine and assistant clinical professor at Yale University Medical School in 1932-36 and adjunct clinical professor of medicine at George Washington University in 1940-41. He serves the U.S. Department of Health, Education, and Welfare as a member of its Panel on Aging, and is also a member of HEW's Medical Advisory Committee, Office of Vocational Rehabilitation. Dr. Klumpp is a vice president and member, board of trustees of the U.S. Pharmacopoeia Convention. In 1961 he was chairman of the committee on rehabilitation of the American Heart Association. From 1955 to 1957 he was vice president of the National Health Council of New York City. He was chairman of the Medical Services Task Force of the Hoover Commission on Organization of the Executive Branch of the Government from 1953 to 1955. In 1951 he served as a director of the World Medical Association. During World War II Dr. Klumpp held membership on War Production Board committees concerned with the development of penicillin mass production and pharmaceutical manufacturing. His fellowships include the American Association for the Advancement of Science and the American Society of Clinical Investigation. A native of New York City, Dr. Klumpp is a graduate of Princeton University and the Harvard University School of Medicine.

John T. Litchfield, M.D., 49, is a specialist in pharmacology and drug safety evaluation. He is director of the experimental therapeutics research section of Lederle Laboratories, Pearl River, N.Y. Born in Minneapolis, he received his M.D. from the University of Minnesota in 1936 and was an assistant and later associate in pharmacology at Johns Hopkins University School of Medicine from 1937 to 1943. He studied under the famed physiologist-pharmacologist, Dr. E. K. Marshall, renowned for his work on the sulfa drugs and other agents. Dr. Litchfield returned to the University of Minnesota in 1943 as assistant professor, and did research there in various fields of chemotherapy. He joined American Cyanamid Co.'s Stamford, Conn., laboratory in 1945 as group leader in the chemotherapy department, leaving in 1954 for his present position. During 1944, he was with the Office of Scientific Research and Development, the Government agency that administered all scientific work associated with the war effort. Dr. Litchfield is a member of the Society of Pharmacologists, the Society of Experimental Biology, the American Chemical Society, and a fellow of the New York Academy of Chemotherapy.

Maurice R. Nance, M.D., 46, is an internist (specialist in diagnosis and non-surgical treatment of disease) with special training in pathology, the science of the origin, nature, and course of diseases. He is medical director of Smith Kline & French Laboratories in Philadelphia. A native of Reidsville, N.C., Dr. Nance graduated from the Medical College of Virginia in Richmond in 1941 and did his residency at Bryn Mawr Hospital, Pennsylvania, specializing in pathology. He was an associate in pathology there in 1947 and 1948 and was in private practice limited to internal medicine from 1946 to 1955. Dr. Nance first became associated with the Philadelphia drug firm in 1948.

Leonard A. Scheele, M.D., 53, for 23 years was a career officer with the U.S. Public Health Service, serving from 1948 to 1956 as the Surgeon General. He is now senior vice president of Warner-Lambert Pharmaceutical Co. of Morris Plains, N.J. He received his medical degree from Wayne State University in Detroit in 1934. Dr. Scheele's 8 years as Surgeon General were highlighted by the establishment of the Salk polio vaccine distribution system and development of the construction aid program for non-Federal hospitals and universities. He was responsible also for administration of the many specialized research facilities and programs of the National Institutes of Health. Beginning in 1937, and again after World War II service, he was assigned to the National Cancer Institute, becoming its director in 1947.

Among Dr. Scheele's professional offices and memberships are: Fellow, American Public Health Association; diplomate, American Board of Preventive Medicine; member, National Citizens Committee for the World Health Organization; Chief Delegate of the United States to the World Health Assembly for 7 years between 1949 and 1956; member, advisory committee, CARE, Inc.; governing member, Arthritis and Rheumatism Foundation; committee of sponsors, National Society for Crippled Children; visiting lecturer in public health, Harvard University School of Public Health.

Dr. Leon H. Schmidt, 53, a pharmacologist, has been research professor in biological chemistry at the University of Cincinnati College of Medicine since 1950. He has also been director of the Christ Hospital Institute of Medical Research since 1930. He received his Ph. D. from the University of Cincinnati in 1932. Dr. Schmidt is a consultant to the National Institutes of Health and the National Research Council Advisory Medical Board. He is a member of the executive committee of the Veterans' Administration Committee on the Chemotherapy of Tuberculosis. He serves on the editorial boards of a number of medical and technical publications and is a member of many organizations, including the American Association for the Advancement of Science, the World Health Organization, the American Academy of Microbiology, and the American Association for Cancer Research.

Austin Smith, M.D., 49, for 10 years was editor of the most widely read medical journal in the world, the Journal of the American Medical Association. During the same period (1949-58) he was editor in chief of all AMA scientific publications. From 1953 to 1959 he was executive editor of the World Medical Journal. He became president of the Pharmaceutical Manufacturers Association, a professional and trade organization of prescription drug manufacturers, in 1958. He was director of the American Medical Association's Division of Therapy and Research from 1946 to 1950, and secretary of AMA's Council of Pharmacy and Chemistry in 1942-49. He is author of various books and articles related to drugs. Dr. Smith is chairman of the board of directors, U.S. Committee, World Medical Association, and council emissary of the United States to WMA. He holds memberships in many organizations, including the Society of Experimental Biology and Medicine, American Society of Pharmacology and Experimental Therapeutics, and the American Therapeutic Society. Dr. Smith was born in Canada and received his doctorate in medicine from Queens University, Kingston, Ontario.

Thomas B. Turner, M.D., is a microbiologist and has been dean of the medical faculty of Johns Hopkins School of Medicine since 1957. An authority on spirochetal diseases and poliomyelitis, Dr. Turner, 60, is a consultant to the Surgeon General of the U.S. Army. He is a member of the general advisory committee and vice chairman of the committee on virus research and epidemiology of the National Foundation, as well as a member of the advisory committee on personnel for research of the American Cancer Society and the national advisory council of the National Institutes of Health. Born in Prince Frederick, Md., Dr. Turner received his B.S. degree from St. John's College in Annapolis, of which he is now a member of the board of visitors and governors, and he earned his M.D. degree at the University of Maryland. He is a fellow of the American Public Health Association, has been awarded the Legion of Merit, and is a member of the Association of American Physicians and the American Society of Clinical Investigation.

Josef Warkany, M.D., is noted for his research in endocrinology and prenatal deformities. A fellow of the Children's Hospital Research Foundation in Cincinnati, Dr. Warkany, 60, has been attending pediatrician at Children's Hospital since 1935. He is also professor of pediatrics research at the University of Cincinnati and attending pediatrician, pediatric and contagious divisions, Cincinnati General Hospital. Dr. Warkany is a diplomate of the American Board of Pediatrics and a member of the American Pediatric Society, the Society of Pediatric Research, the Ohio Medical Association, the Society for Experimental Biology and Medicine, and the Cincinnati Academy of Medicine. He was awarded the Mead-Johnson award in 1944 and the Borden award in 1950. A native of Vienna, Austria, he came to the United States in 1932 and was naturalized in 1938. He studied at the Real-Gymnasium in Vienna and received his medical degree from the University of Vienna in 1926.

The CHAIRMAN. I assume that does conclude your statement?
Mr. BEESLEY. It does, yes.

The CHAIRMAN. I should like to compliment you on a very fine statement, brief and concise, stating emphatically the views of your organization.

Mr. BEESLEY. Thank you.

The CHAIRMAN. Are there any members who have any questions?

Mr. FRIEDEL. Mr. Chairman, I want to compliment Mr. Beesley for his very fine statement.

Mr. BEESLEY. Thank you.

Mr. FRIEDEL. I remember visiting your plant.

Mr. BEESLEY. I recall your visit with pleasure.

Mr. FRIEDEL. I remember the research you were doing there, but there are a few question I would like to ask.

Do you presently need to get the approval of the FDA before distributing a drug to so-called experts for investigational or experimental use on human beings?

Mr. BEESLEY. No, we do not.

They have the power to require information to be supplied, and within the last 2 weeks regulations have been proposed which would inform FDA about the clinical work that is being done.

Those regulations—I think we have 60 days in which to give our opinions about the regulations.

The general purpose of the regulations, as I understand them, is to give FDA information about the clinical investigations that are going on.

Mr. FRIEDEL. Do you think that you need to have their approval?

Mr. BEESLEY. I beg your pardon?

Mr. FRIEDEL. Do you think you should have approval of the FDA before you distribute the drug to so-called experts?

Mr. BEESLEY. We feel that we should supply FDA with the information about clinical investigations.

We feel that responsible companies will carry on the investigations in a very satisfactory way, and that approval per se is not necessary.

Mr. FRIEDEL. Do you perform these tests on animals, including pregnant animals, before distribution?

Mr. BEESLEY. Before thalidomide?

Mr. FRIEDEL. Before distribution.

Mr. BEESLEY. I think there is a very widespread movement now to test all drugs, or virtually all of them, at least, in pregnant animals.

I do not know the extent of those tests prior to some of the recent happenings.

Dr. Keefer and Dr. Scheele, who will follow me as witnesses, are well qualified to testify in this field.

Mr. FRIEDEL. Let me ask these questions, and I hope they will be pursued.

Mr. BEESLEY. Yes.

Mr. FRIEDEL. Just two more questions.

Are these experts required to advise the person to whom they intend to administer an investigational drug that the drug is investigational or experimental and has not been approved by the FDA?

What I mean by that:

Do they have to get the permission of a person to use it before it is approved by the FDA?

Mr. BEESLEY. No, they do not, and we feel that this should be left to the discretion of the physician. It should not invade the traditional physician-patient relationship.

And I think that, as a matter of general practice, probably most physicians would tell the patient that a drug that is in an investigational phase is being used.

However, there are situations where probably it would not be wise for the physician to tell the patient that an investigational drug is being used.

We feel that it should remain the prerogative of the physician to determine whether it is wise to tell the patient that an investigational drug is being administered in that patient's case.

Mr. FRIEDEL. For the record, I would like to have your reasons why in some cases a patient should not be told.

Mr. BEESLEY. Dr. Keefer will go into this in great detail, if you want to wait just a few moments for his testimony.

Mr. FRIEDEL. Thank you, Mr. Chairman.

That is all the questions I have at this time.

The CHAIRMAN. Mr. Bennett?

Mr. BENNETT. Mr. Beesley, is the law applied differently in respect to the testing of a new drug as distinguished from putting it on the market for general sale?

As I understand it, in the area of a drug that is regarded as experimental, manufacturers put it out on a clinical test basis rather than putting it out for general distribution.

Mr. BEESLEY. Yes.

Mr. BENNETT. Does the law have different requirements with respect to the procedure you follow in testing a drug and in putting it out on the market?

Mr. BEESLEY. The present law exempts investigational drugs from regulation.

Mr. BENNETT. Exempts the test of drugs?

Mr. BEESLEY. Exempts the testing, but it is subject to regulations to be promulgated by the Secretary.

Mr. BENNETT. What are the requirements of the law with respect to a new drug that is put out for general distribution?

Mr. BEESLEY. That new drug applications must be submitted with very extensive information about the experience with the drug, and that information, of course, is reviewed by the Food and Drug Administration.

Mr. BENNETT. While that is being reviewed, do you go ahead and sell it?

Mr. BEESLEY. No, indeed.

According to the food and drug law, not until the Administration has either 60 or 180 days in which to review this information, and either they ask for more information or permit the new drug application to become effective. That is the present law. Or they disapprove it; one or the other.

Mr. BENNETT. Do you file notice that you are going to put the drug on the market or desire to put the drug on the market, say, in 60 days, and if the Food and Drug does nothing, at the end of that time, do you then have authority to put it on the market?

Mr. BEESLEY. If the Food and Drug Administration does nothing, that is correct.

The CHAIRMAN. Will the gentleman yield?

Mr. BENNETT. Yes.

The CHAIRMAN. Maybe I misunderstood you, Mr. Beesley, or I am a little confused about it.

You say in testing under the law it is exempted?

Mr. BEESLEY. That is correct.

The CHAIRMAN. Then you say but it is subject to regulation.

If it is exempted, how can it be subject to regulation?

Mr. BEESLEY. Mr. Chairman, the Department of Health, Education, and Welfare just about 2 weeks ago for the first time issued regulations in this field.

I have here a statement that was issued by the Department of Health, Education, and Welfare which gives the objectives of these regulations.

First, the regulations require that the Food and Drug Administration be notified and given complete details on distribution of drugs for investigational use.

Second, the manufacturer is required to satisfy Food and Drug Administration that the investigations will be based on preclinical, chemical, and animal studies of such a nature as to assure safety for patients.

Third, the clinical studies would have to be properly planned, executed by qualified investigators and FDA kept fully informed of the progress of these investigations.

Now, that is a capsule statement of very long, detailed regulations.

Our association favors the general purposes of these regulations.

Mr. DINGELL. You say you favor the general purposes. Do you object to the regulations in any way?

Mr. BEESLEY. These regulations issued on August 9?

Mr. DINGELL. Yes. Do you have objection to the regulations?

Mr. BEESLEY. We have 60 days in which to try to study these regulations and present our views.

Now, then, we have not yet had time to thoroughly appraise and assess the implications of the individual regulations. I think that we probably will have some suggestions to make for changes.

Mr. DINGELL. In other words, you will have some objections to those regulations?

Mr. BEESLEY. Some of the details in them, I think we will have, yes, sir.

The CHAIRMAN. I am not getting into a discussion of the regulations. That is not our purpose at this time.

Mr. BEESLEY. Yes.

The CHAIRMAN. But how can they issue a regulation of this kind executively, if it is exempt under the law?

Mr. BEESLEY. May I ask Mr. Cutler to comment on that?

The CHAIRMAN. Maybe you had better let Mr. Cutler identify himself for the record.

Mr. BEESLEY. Mr. Cutler is a member of the law firm of Wilmer, Cutler & Pickering of Washington, and counsel for the Pharmaceutical Manufacturers Association.

The CHAIRMAN. Yes, if you could clear that up.

Mr. CUTLER. Yes, Mr. Chairman. Under section 505 of the present law, a so-called new drug, that is, one whose safety is not yet generally accepted, may not be introduced into interstate commerce until an

application has been filed with the Food and Drug Administration and the period of time Mr. Beesley referred to, which is either 60 or 180 days, has passed, and the Food and Drug Administration has either let the application become effective or has disapproved it, in which case, of course, the drug could not be marketed.

That section 505 has an exception in subparagraph (i) that permits the introduction into interstate commerce of new drugs for experimental purposes only, subject to such regulations as the Secretary shall issue governing the distribution of such drugs for experimental purposes.

The CHAIRMAN. Then it is not exempted?

Mr. CUTLER. It is not.

The CHAIRMAN. That is what I have been trying to get down to.

Mr. CUTLER. It is not exempted, that is correct.

The CHAIRMAN. All right. That is the answer I wanted.

Mr. BENNETT. Is it exempted under the present law, or are you speaking now—

Mr. CUTLER. Under the present law. Under the present law drugs may only be introduced into interstate commerce for experimental use under regulations issued by the Secretary.

Mr. BENNETT. What are those regulations presently?

Mr. CUTLER. Under the present regulations—

Mr. BENNETT. I do not mean the ones that were issued 2 weeks ago.

Mr. CUTLER. Yes. Under the present regulations the manufacturer is required to obtain a certificate from the clinical investigator, the distributor or whoever else it may be, certifying that he is qualified by training and experience to evaluate the safety of drugs, and the manufacturer is required to keep records of the distribution of drugs for experimental use. That is essentially the scope of the present regulations. The new, proposed regulations are much broader.

Mr. BENNETT. Let us not get into that for a minute or two.

Under the existing law and regulations, can the Food and Drug Administration refuse to permit a drug to be marketed for experimental testing purposes?

Mr. CUTLER. They are not marketed for this purpose, Mr. Bennett. They are distributed. But under the present regulations the Food and Drug Administration does not forbid the marketing for this purpose. Presumably it could.

Mr. BENNETT. I am asking you: Do they have the authority under the present law?

Mr. CUTLER. Under the present law?

Mr. BENNETT. To forbid.

Mr. CUTLER. They have the authority to forbid it, except under such conditions as they might choose to authorize.

I do not think you could read the present law so as to permit them to absolutely forbid any experimental work with new drugs, but they are entitled to set conditions that would adequately protect the public health.

Mr. BENNETT. Presently—and I am not speaking of the recent drug regulations—but, presently, does Food and Drug require you to obtain any affirmative approval from them before testing new drugs?

Mr. CUTLER. No, sir.

Mr. BENNETT. What you are required to do is to file the information that you talked about a few minutes ago and then you go ahead and do the testing?

Mr. CUTLER. You are required to maintain certain records under the present law, that is all.

Mr. BENNETT. Then in testing a new drug, you wish to leave it to the discretion of the physician, who has the drug in his possession, to determine whether or not it is not safe for the patients to use?

Mr. CUTLER. Yes, sir. And if I can turn for a moment to the proposed new regulations, the Food and Drug Administration now desires to be currently informed so that if they would disagree as to the safety of the proposed use, they could take measures.

Mr. BENNETT. They want to bring it within this discretion?

Mr. CUTLER. That is correct.

Mr. BENNETT. Rather than the discretion of the physician?

Mr. CUTLER. Right.

The CHAIRMAN. Mr. Jarman?

Mr. JARMAN. Mr. Beesley, you make a recommendation on page 9 that all manufacturers of drugs be subjected to mandatory inspection by FDA at least once every 2 years.

Mr. BEESLEY. Yes.

Mr. JARMAN. What is the situation at the present time as to inspection?

Mr. BEESLEY. It is to a large extent discretionary. There is no time interval that is specified.

I believe that the inspections occur, perhaps, all the way from an interval of once every 6 months up to perhaps once every 5 years—something of that kind.

This recommendation ties in with our proposal that all drug manufacturers be required to register, because there are supposed to be, according to the census of business, some 1,200 drug manufacturers in the country, and it seems to us that the identification of all of these manufacturers to the Food and Drug Administration and the inspection of all of the manufacturers would be in the public interest.

Mr. JARMAN. When an inspection is made by FDA, how thorough is the inspection? How much time is usually taken for an inspection?

Mr. BEESLEY. Well, our people tell me that it is very thorough; that when an inspector comes to visit us, he is likely to be there several days.

Mr. JARMAN. Thank you.

I think that is all.

The CHAIRMAN. Mr. Schenck?

Mr. SCHENCK. Thank you, Mr. Chairman.

I would like to commend Mr. Beesley for his excellent statement.

Mr. BEESLEY. Thank you.

Mr. SCHENCK. I recall a very helpful and instructive visit we made to your laboratory several years ago.

Mr. BEESLEY. Thank you.

We certainly were happy to have the members of the committee visit us.

Mr. SCHENCK. All of us, Mr. Beesley, received a great deal of helpful information at that time, and we appreciated the very diligent care you observe in your plant to make sure of quality control at all steps of manufacture.

Mr. BEESLEY. Thank you.

Mr. SCHENCK. Now, Mr. Beesley, perhaps this is not a question you would care to answer, I do not know, but if you do not, it is quite all right.

Does Eli Lilly & Co., for example, spend a substantial amount of money in research on new drugs each year?

Mr. BEESLEY. Indeed, we do. This is information that we publicize in our annual report and other places, so I have no hesitancy in revealing the figures.

This year our research budget will be between \$20 and \$21 million, which is approximately 10 percent of our total sales.

In other words, we spend approximately 10 cents out of each sale's dollar in financing research.

Mr. DINGELL. How much do you spend on advertising out of each sales dollar?

Mr. BEESLEY. I do not have the figures in mind.

Mr. DINGELL. Will you submit it for the record?

Mr. BEESLEY. Indeed, I will.

Mr. DINGELL. Would you say it was equal to the 10 cents you spend on research?

As a matter of fact, it exceeds the 10 cents you spend on research, does it not?

Mr. BEESLEY. My opinion is that it does not, but I do not have the figures in mind, and I would prefer not to give a definite opinion on that.

(The requested information was subsequently received for the record:)

ELI LILLY & Co.,
Indianapolis, August 29, 1962.

HON. OREN HARRIS,
Chairman, Committee on Interstate and Foreign Commerce,
House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: At page 271 of the transcript of my testimony before the Committee on Interstate and Foreign Commerce, I was asked by Congressman Dingell to submit for the record a statement of the number of cents out of each sales dollar our company spent on advertising during the last year.

During its calendar and fiscal year 1961, Eli Lilly & Co. and its subsidiaries spent approximately 3.2 cents out of each sales dollar on advertising. As pointed out in my testimony, this compares with about 10 cents of each sales dollar spent in financing research.

Respectfully yours,

EUGENE N. BEESLEY, President.

The CHAIRMAN. Mr. Schenck, any further questions?

Mr. SCHENCK. Yes, Mr. Chairman.

In the matter of research and the \$20 to \$21 million that you spend, which is a very substantial sum, it is spent by your company for the purpose of developing the best method of manufacture and also to improve the necessary quality control of both old and new drugs in the best public interest and safety.

Mr. BEESLEY. That is correct.

Mr. SCHENCK. And this is true of all the testing of new drugs?

Mr. BEESLEY. Yes.

Mr. SCHENCK. Now, Mr. Beesley, while I think you said that all of this is a part of your cost of manufacture—

Mr. BEESLEY. Indeed.

Mr. SCHENCK (continuing). As you develop new methods of manufacture, then I assume that these lower costs are reflected in and make lower prices possible?

Mr. BEESLEY. Yes.

We in our company maintain an index of prices, and in the last 10 years the index, which includes all of the drugs that we have, is now approximately 86 percent of the figure that it was at the beginning of the 10-year period.

Mr. SCHENCK. I have in mind, Mr. Beesley, that when insulin was first introduced, your company, I believe, was one of the key manufacturers of insulin?

Mr. BEESLEY. That is right.

Mr. SCHENCK. At that time it was quite expensive, was it not?

Mr. BEESLEY. Yes, it was.

Mr. SCHENCK. And it is now very much less in cost to the patient is it not?

Mr. BEESLEY. Yes.

It has been, I think, about 40 years since we first introduced insulin. We have had 13 price reductions during that period, and I believe the current price is about 6 percent of the price that prevailed in 1922.

Mr. SCHENCK. So that the users of the drugs manufactured do benefit, as you have increased your ability to develop drugs at lower cost?

Mr. BEESLEY. Indeed, that is correct.

Mr. SCHENCK. Now, I have one other series of questions here.

It has been suggested, Mr. Beesley, that the pharmacists, in filling a prescription, should somehow or other indicate on the prescription label itself the kind of drug that is in that prescription.

Is it not true that pharmacists buy drugs in, let us say, large quantities of a thousand, or so as an example, of a certain kind of tablet?

Mr. BEESLEY. Yes.

Mr. SCHENCK. They fill a physician's prescription for perhaps 25, 30, or 50 tablets and put them in a small container.

Now, the pharmacist then puts on that small container his own prescription number and the doctor's name, the date and the dosage.

Would it be a difficult proposition to require the pharmacist also indicate on the prescription label the generic of the drug that was included?

Mr. BEESLEY. I suppose it could be done, but I think it would be unwise and certainly would not be in keeping with the wishes of the great majority of the medical profession, because most patients are not familiar with the actual characteristics of the drug that the physician may think it advisable for them to take, and it is in the nature of the relationship of the physician with his patient and the relationship between the patient and the pharmacist that the physician and the pharmacist should have the information about the drug that is being used, being prescribed by the physician, but I would doubt the wisdom of putting that name on the actual label of the prescription package, sir.

Mr. SCHENCK. In some cases that would be difficult, anyhow, would it not, because of the very long and involved chemical name?

Mr. BEESLEY. Indeed.

Mr. SCHENCK. Or the generic term?

Mr. BEESLEY. It certainly would.

Mr. SCHENCK. There also are times when the pharmacist removes the label from the small container and merely puts on the prescription label, is that not true?

Mr. BEESLEY. That is correct.

Mr. SCHENCK. Is there any way for a pharmaceutical manufacturer to identify the capsule, the tablet, or what have you, so that in the event the patient becomes ill while he is away from his own home community and home physician, that another physician would know what he had been taking?

I am thinking of something for a heart condition or something for a respiratory condition, or something of that nature?

Mr. BEESLEY. I think the way that most physicians prefer to have this handled is for the pharmacist to give the patient a copy of the prescription, and the patient then carries the copy of that prescription with him regularly.

The manufacturer would be able, in most instances, to determine if it was that manufacturer's own product that had been used, but sometimes it would not be readily apparent without a chemical analysis.

Mr. SCHENCK. Mr. Beesley, I want to commend you for your splendid statement.

Mr. BEESLEY. Thank you.

Mr. BENNETT. The Chair asked me to recognize Mr. Dingell next. Do you have any questions, Mr. Dingell?

Mr. DINGELL. Thank you, Mr. Chairman.

Mr. Beesley, I want to compliment you on a very fine statement. We are honored to have you with us this morning.

Mr. BEESLEY. Thank you, Mr. Dingell.

Mr. DINGELL. I would like to go through briefly with you, if I may, to see what sections of the administration's bill you endorse and what you oppose, and then we will try and find out specifically why.

Mr. BEESLEY. Mr. Dingell, may I suggest that you have before you the list of witnesses, and they are going to discuss each of these sections in detail.

It was our hope that in order to handle the hearing expeditiously, that they might be permitted to discuss the appropriate provisions.

Mr. DINGELL. I see. Let me ask you this: Do you oppose the amphetamines and barbiturates section?

Mr. BEESLEY. No, we do not.

Mr. DINGELL. You endorse that?

Mr. BEESLEY. Indeed.

Mr. DINGELL. I see. Very good. So in our consideration of the bill we can dispose of those as being agreed upon by the industry, am I correct, those two sections?

Mr. BEESLEY. I think there are a few minor problems on language, but certainly nothing of substantial importance.

Mr. DINGELL. All right. Now, you mentioned penicillin has saved thousands of lives.

I think this is one of the great things. As a matter of fact, I happen to be living because of penicillin, too, but I was wondering about this: Penicillin is one of the drugs which is approved on a lot or a batch-by-batch basis, is it not?

Mr. BEESLEY. Yes.

DRUG INDUSTRY ACT OF 1962

189

Mr. DINGELL. There are five of these antibiotics which are endorsed or, rather, which are approved on a batch-by-batch basis. Those are the five that were named in the original statute, am I correct?

Mr. BEESLEY. That is correct, yes.

Mr. DINGELL. Subsequent to that time, there have been a number of new antibiotics which have come on the market?

Mr. BEESLEY. Yes.

Mr. DINGELL. The statute, of course, was silent on these and these are just treated as ordinary drugs as opposed to antibiotics, am I correct?

Mr. BEESLEY. That is correct.

Mr. DINGELL. The administration bill proposes to expand the treatment of antibiotics to cover all of these.

Now, do you endorse or do you oppose that section?

Mr. BEESLEY. We would oppose the extension of that certification.

Mr. DINGELL. On what ground?

Mr. BEESLEY. May I give a little background here, which I am sure you are quite familiar with, but I would like to recall it to lay the groundwork.

You will recall that batch certification was put in the act about the middle of World War II, and this was right in the beginning of the time when antibiotics were being used.

Certainly fermentation and the purification procedures were not at that time an exact science, and it was during that time that our industry cooperated with the Government in getting legislation enacted that would require the certification of at that time just penicillin, and later the other antibiotics were added.

However, since that time the whole thing has changed. Fermentation has become very much more an exact science, and today manufacturers can produce antibiotics with the same skill and definiteness that any other drug can be produced with, and, as a consequence, we do not feel that batch certification should be extended to include other antibiotics.

Mr. DINGELL. Then, as a matter of fact, you feel that batch certification should be stricken insofar as the five which have this requirement, am I correct?

Mr. BEESLEY. That is my personal opinion, yes.

Mr. DINGELL. Why do you feel this should be done, because it is costly?

Mr. BEESLEY. Costly and duplication, unnecessary.

Mr. DINGELL. Basically, though, it is cost, is that it?

Mr. BEESLEY. Yes. And it uses the time of highly skilled people, a group of individuals who are certainly in short supply.

Mr. DINGELL. The thing that concerns me is here I note that in 1962 penicillin had to be recalled, or one batch had to be recalled because it was contaminated with sulfonamides.

Apparently there was need for batch-by-batch certification in that particular case, was there not, because they found that one particular lot of penicillin was contaminated with sulfonamides?

This would indicate that there is some need for batch-by-batch certification, at least in the case of penicillin, and I would assume that these other newer antibiotics are really not much different in the method of preparation. Am I correct on this?

Mr. BEESLEY. Was that batch of penicillin certified?

Mr. DINGELL. I would assume that it was, if they are supposed to. I would assume that it had been. I do not know whether it was or not, but I assume it was supposed to have been.

Mr. BEESLEY. Do I understand that this was a recall of penicillin contaminated with sulfonamides by FDA from the market, is that correct?

Mr. DINGELL. That is correct. That is my understanding.

Mr. BEESLEY. Now, that would indicate, then, that batch certification did not do the job.

Mr. DINGELL. It would indicate that, but it would indicate we were better off with batch certification than without it, am I correct?

Mr. BEESLEY. The penicillin apparently here was certified. It was produced, and then certified by FDA?

Mr. DINGELL. Yes.

Mr. BEESLEY. Now, apparently—I am just guessing, now—I assume from the statement you have made that there was a contamination with sulfonamides in the tableting or whatever it was of the pharmaceutical form, so that we might get back to factory inspection or something like that.

Mr. DINGELL. I think this is also a good case for factory inspection.

Mr. BEESLEY. I agree.

Mr. DINGELL. Is it not?

Mr. BEESLEY. I would agree, yes.

Mr. DINGELL. But, to continue on this, you object to this because it is costly, am I correct, in the case of antibiotics?

Mr. BEESLEY. It is a duplication of effort.

Mr. DINGELL. But basically it is costly?

Mr. BEESLEY. Yes.

Mr. DINGELL. Duplication of efforts boils down to simply economic costs?

Mr. BEESLEY. That is right.

Mr. DINGELL. Does it not?

Mr. BEESLEY. That is right.

Mr. DINGELL. If I told you this costs a twentieth of a cent a dose, would you say that that was costly, a twentieth of a cent to certify the batch, a twentieth of a cent a dose? This is Food and Drug figures.

They say it costs a twentieth of a cent a dose to certify a prescription antibiotic.

Now, would you say that this is costly?

Mr. BEESLEY. It is just one more added cost.

Mr. DINGELL. I know, but let us compare this with advertising.

It is a great deal less than the amount of the advertising cost per dose of prescription antibiotics, is it not?

Mr. BEESLEY. May we carry this one step further?

Mr. DINGELL. Let us stay right where we are first, and then we will go a step further.

Mr. BEESLEY. All right.

Admittedly, of course, one-twentieth of a cent, in itself, per dose, is not much, but it is just that additional expense. Now, we might say that everything ought to be certified. That certainly would be a duplication and a costly procedure.

Our point, Mr. Dingell, is that we do not believe that antibiotics are in any different category than most other drugs.

Mr. DINGELL. For 5 years we have had certification on batch-by-batch basis on five.

Mr. BEESLEY. That is right.

Mr. DINGELL. And apparently it has worked well.

Mr. BEESLEY. Yes, but—

Mr. DINGELL. Apparently it has afforded protection to the people, and we have five which do have this protection that is standard to users, and then we have the balance of these antibiotics which have no similar protection extended to users.

Mr. BEESLEY. And may I point out that, so far as I know, there has been no difficulty that certification could have prevented with the balance of the antibiotics.

Mr. DINGELL. Let us talk factory inspection a little bit.

Do you oppose any additional factory inspection authority in the Food and Drug Administration?

Mr. BEESLEY. Now, may I point out that Mr. Connor will go into this in great detail.

Mr. DINGELL. I understand that, but I want to query you on it, too.

Mr. BEESLEY. General support for the provision.

Mr. DINGELL. You support the provision of factory inspection?

Mr. BEESLEY. In general, yes.

Mr. DINGELL. In general. Now, that means you have some specific reservation. Would you care to enumerate them briefly?

Mr. BEESLEY. As I pointed out in point No. 5, I think that is in my statement, Mr. Dingell, inspection powers should be broadened to cover all facilities, controls, and records that have a material bearing on violations of the law.

Mr. DINGELL. Then you do support expansion of the factory inspection provisions in the law?

Mr. BEESLEY. Expansion, yes, with certain reservations.

Mr. DINGELL. Last of all, do you support the requirements for adequate controls of manufacture?

Mr. BEESLEY. Yes.

Mr. DINGELL. Which is 101?

Mr. BEESLEY. Yes, we do.

Mr. Connor also will speak to that.

Mr. DINGELL. Thank you very much, Mr. Chairman.

The CHAIRMAN. Mr. Younger?

Mr. YOUNGER. Thank you, Mr. Chairman.

I do want to join in complimenting you, Mr. Beesley.

Mr. BEESLEY. Thank you.

Mr. YOUNGER. For a very fine statement.

I have only one question.

In the experience of your company, how many drugs have been removed from the market by the FDA?

Mr. BEESLEY. Of our company?

Mr. YOUNGER. Yes.

Mr. BEESLEY. We have had none.

Mr. YOUNGER. In your entire history you have had none?

Mr. BEESLEY. To the best of my knowledge, we have had none, that is correct.

We have had maybe one, two, or three voluntary recalls of a particular batch of a drug, but, as far as taking off the market by the Food and Drug Administration, we have had none as long as the Food and Drug Administration has been supervising the manufacture of drugs.

Mr. YOUNGER. For general information, do you know how many from other companies, or have you heard of how many have been withdrawn?

Mr. BEESLEY. I believe Mr. Connor has detailed statistics on that question.

I do not recall the figures specifically.

Mr. YOUNGER. Thank you, Mr. Chairman.

The CHAIRMAN. Mr. Moss, do you have any questions?

Mr. MOSS. I have no questions at this time, Mr. Chairman.

The CHAIRMAN. Mr. Rogers?

Mr. ROGERS of Florida. Thank you, Mr. Chairman.

Mr. Beesley, your testimony has been helpful, and I think it is fine that the drug industry has set up a Commission on Drug Safety.

On page 8, your item No. 4, you mentioned that the FDA should have authority, if an item is not safe, to withdraw it after a hearing.

Is it not true that if an item is not safe now, that FDA can remove it from the market?

Mr. BEESLEY. Yes. Yes.

Mr. ROGERS of Florida. What additional authority is necessary?

Mr. BEESLEY. We fully support the position that a manufacturer's product should do what it is claimed to do. We feel, however, that the test should be whether or not there is substantial evidence that the drug will do what it is claimed to do.

I believe that answers the question.

Mr. ROGERS of Florida. What about your statement that in the light of new evidence it is now shown to be safe? That refers where there is a substantial doubt that it is safe?

Mr. BEESLEY. May I defer to Mr. Cutler?

Mr. CUTLER. Mr. Rogers, under the present law, the Food and Drug Administration may remove a drug from the market after hearing if the Food and Drug Administration can carry the burden of showing that the drug is not safe.

In other words, they must prove unsafety.

The proposed amendment would establish substantially the same test that exists when the drug is first allowed on the market, when the manufacturer must prove that the drug is shown to be safe, and we agree that the law should be amended so that in a recall case, a suspension case, the manufacturer must bear the same burden he had to bear in the first instance of proving in the light of new evidence that the drug is still shown to be safe.

That is the distinction.

Mr. ROGERS of Florida. So if there is a substantial doubt, then, on the part of FDA, once a drug has been approved and it is on the market, if there is substantial doubt, then, FDA could say:

"We want to remove this," have a hearing, as you propose?

Mr. CUTLER. Yes.

Mr. ROGERS of Florida. And the burden is then on the manufacturer?

Mr. CUTLER. Yes.

Mr. ROGERS of Florida. Before the drug would be removed?

Mr. CUTLER. Before the drug would be removed, yes, sir.

Mr. ROGERS of Florida. In other words, they must have a hearing before the drug would be removed?

Mr. CUTLER. Yes.

Mr. ROGERS of Florida. Suppose there is sufficient evidence to show it is not safe.

Could not FDA go ahead and remove it immediately without a hearing?

Mr. CUTLER. Under present law they could obtain a preliminary injunction in a court to remove it under those conditions, yes.

Mr. ROGERS of Florida. So that they do have some way of removing it?

Mr. CUTLER. Yes.

Mr. ROGERS of Florida. If it is not safe?

Mr. CUTLER. Yes.

And, of course, they are always free to notify the medical profession that they regard it as unsafe, which amounts to removal.

Mr. ROGERS of Florida. Yes.

Thank you, Mr. Chairman.

The CHAIRMAN. Carrying that one step further, the Administrative Procedures Act would have to be complied with in the course of the hearing, would it not?

Mr. CUTLER. Yes.

The CHAIRMAN. I am talking about with reference to withdrawing something that has been on the market.

Mr. CUTLER. Yes, that is correct, Mr. Harris.

Now, there is a provision in this bill which would allow the Food and Drug Administration to withdraw a drug from the market before a hearing, and without consultation with the manufacturer, if the Food and Drug Administration finds what is called an imminent hazard to the public health.

The CHAIRMAN. Do you support that?

Mr. CUTLER. We do not support that provision, sir.

We think that that provision gives the Food and Drug Administration more authority than it needs.

We think it already has ample power to remove a clearly unsafe drug from the market immediately, and that there should not be discretionary power, except in this one case of a clearly unsafe drug, where they already have all the power they need.

The CHAIRMAN. In other words, under present law you contend that the Food and Drug Administration can take any drug off the market that it determines to be unsafe?

Mr. CUTLER. Yes, sir, immediately, by going to a court and getting a preliminary injunction.

The CHAIRMAN. But they would have to go to a court to do it?

Mr. CUTLER. To get a preliminary injunction, yes sir, or under present law they could hold a hearing and determine, as a result of the hearing, that the drug was unsafe and remove it from the market.

Mr. BENNETT. Will you yield just to clarify that?

What is the difference between the present law, then, and the change that is being proposed here?

Mr. CUTLER. You are speaking now of the power to remove?

Mr. BENNETT. What you are talking about.

Mr. CUTLER. Because of the imminent hazard to the public health without a hearing?

Mr. BENNETT. You got me confused, and I think you have the chairman confused, too, about where the authority lies.

You say, on the one hand, that the Food and Drug has authority to remove an unsafe drug by going into court and getting an injunction; and, on the other hand, they can hold a hearing and enter an order themselves.

Mr. CUTLER. Yes, sir. They have the power—

Mr. BENNETT. Do they have those dual powers under the present law?

Mr. CUTLER. Yes, under the present law they have the power.

Mr. BENNETT. The dual power?

Mr. CUTLER. The power to hold an administrative hearing and, after the hearing, remove a drug administratively from the market as unsafe, or they have the power before an administrative hearing to go right to a court and get a preliminary injunction removing the drug from the market as unsafe.

Mr. BENNETT. All right.

Now, what additional or different authority would this bill give them?

Mr. CUTLER. This bill would give them the power by an order which the Secretary could sign this morning, without a hearing, without notice to the manufacturer, just ordering the drug removed from the market.

Mr. FRIEDEL. Mr. Chairman, will the gentleman yield?

Just one question on the same point.

You say that they have a right to have a hearing and then take a drug off the market?

Mr. CUTLER. Yes, sir.

Mr. FRIEDEL. Suppose they refuse. What happens?

Mr. CUTLER. It would be a criminal violation of law.

Mr. FRIEDEL. In other words, they would not have to go to court, then, to get a preliminary injunction?

Mr. CUTLER. No, sir.

Mr. FRIEDEL. That is all, Mr. Chairman.

The CHAIRMAN. I will go into that a little later.

Mr. Sibal?

Mr. SIBAL. Thank you, Mr. Chairman.

Mr. Beesley, on page 8 of your statement, the second point, FDA must have ample time to consider the safety and effectiveness of new drugs before they are introduced, but unnecessary delays in permitting valuable new medicines to reach the public must be avoided.

I think everybody would agree with that statement, but, on the other hand, there are interpretations which could differ substantially.

What is the present procedure if at the end of 60 days the FDA does not feel it is able to form an opinion as to the safety and efficacy of a drug?

Mr. BEESLEY. Then that time is extended to 180 days.

Mr. SIBAL. And suppose at the end of 180 days they still do not feel that they are qualified, considering the tremendously broad area of public health involved here, to have an opinion?

Mr. BEESLEY. They can turn it down on the grounds that there is not enough evidence of safety to permit the drug to go on the market.

Mr. SIBAL. Does the industry have any legal rights to require a decision anywhere along the line?

In other words, what right does the industry have to protect itself against perhaps dilatory treatment of its application?

Mr. BEESLEY. There is a provision giving the manufacturer the right to have a hearing after the verdict of the FDA, after the opinion has been formed.

Mr. SIBAL. You have a hearing before the FDA examiner?

Mr. BEESLEY. That is correct.

Mr. SIBAL. What happens then if the FDA is still uncertain?

Mr. BEESLEY. After the hearing it could be carried to the courts on appeal.

Mr. SIBAL. Has this ever happened?

Mr. BEESLEY. To the best of my knowledge, it has not.

Mr. SIBAL. Do you consider these 60- and 180-day provisions realistic?

Mr. BEESLEY. It has been proposed that the 60 days be extended to 90 days, and we have no objection to that, but, otherwise, we think the 90 and 180 days would be quite realistic.

Mr. SIBAL. Do you, based on your long experience in dealing with the FDA, feel that it has the personnel to meet these arbitrary deadlines, so to speak, without perhaps reducing the attention the personnel can give these drugs?

Mr. BEESLEY. Our association has long supported additional funds for Food and Drug Administration in order that they can have more personnel than they now have.

Mr. SIBAL. Do you feel they need it?

Mr. BEESLEY. Yes, indeed, we do.

Mr. SIBAL. Now, in these experimental cases which were referred to earlier in the testimony and also in the questioning of some of the other members, has there been any history of harmful effects in the past?

I am not talking about the immediate past which we are all aware of, but over the years, which resulted from the use of experimental drugs?

Mr. BEESLEY. I would answer that by saying that I think the record has shown that the present procedure is quite satisfactory, and it has only been in the last few weeks that there has ever been, so far as I am aware, any serious cloud thrown on the present procedure.

But Dr. Scheele, who is the former Surgeon General, and Dr. Keefer will follow me as witnesses, who can speak with more authority on that subject than I can.

Mr. SIBAL. Now, this procedure, as I recall, with the physician—would you mind repeating your testimony concerning what a physician must do when he is using a drug which has not been approved, but which is in an experimental stage?

Mr. BEESLEY. The physician signs an investigational use form which the manufacturer must keep on file. That is the present procedure.

The manufacturer has the responsibility of selecting careful, satisfactory investigators.

Now, then, the Food and Drug Administration just on August 9 issued the regulations that we have referred to earlier. Would you like for me to repeat the objectives of those regulations?

Mr. SIBAL. No, I recall them.

Mr. BEESLEY. Yes.

Mr. SIBAL. I was more interested in the actual mechanics of how it is done.

Mr. BEESLEY. Yes. I think that that is the extent of the present regulation.

Mr. SIBAL. The physician fills in a form and returns it to the manufacturer?

Mr. BEESLEY. And, of course, all records and reports that are submitted to the manufacturer then on subsequent investigations of the drug are retained.

They are available for inspection by the Food and Drug Administration.

Of course, most of this material is included in the new drug application that is eventually submitted if the manufacturer feels that the drug is worthy of such submission.

Mr. SIBAL. How long a period of time does this experimental phase last?

Mr. BEESLEY. Well, of course, it will vary from drug to drug. Perhaps as long as 5 years in some instances; sometimes as short a period as 1 year, perchance. Very seldom would it be less than 1 year.

Mr. SIBAL. There is no regulation which controls this. This is entirely at your discretion?

Mr. BEESLEY. There is no current legislation in force. There would be regulations under the proposal issued on August 9.

Mr. SIBAL. How do you feel about that?

Mr. BEESLEY. As I stated earlier, we are in favor of the objectives. We have 60 days from August 9 in which to develop our considered opinions, and we think we will have some suggestions for changes on specific language.

But we certainly are in accord with the general objectives of the regulation.

Mr. SIBAL. Now, is there any indication as to the breadth of your use of experimental drugs or the amount, the number of physicians, for example?

Mr. BEESLEY. There is no present statutory regulation or regulation promulgated by HEW or Food and Drug Administration that would limit that.

Mr. SIBAL. Including the August 9 proposed regulation, there is nothing in there?

Mr. BEESLEY. As I understand the regulations, there are no specific limitations in that field.

The manufacturer would be required to submit information to Food and Drug Administration on the extent of the investigation, and if the Food and Drug Administration is not satisfied with the amount of information that is being obtained, then the FDA has the power to ask the manufacturer to improve his test, and if the manufacturer does not do so, the regulation then states that if the conditions of exemption are not immediately met, the Commissioner shall notify the sponsor of the termination of the exemption.

But there is another specific point that perhaps we should mention in this connection, and may I just quote it:

The sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug pursuant to section 505(b) of the act or a statement that the investigation has been discontinued and the reasons therefor.

Mr. SIBAL. Is that in the present regulation?

Mr. BEESLEY. That is the proposed regulation, yes.

Mr. SIBAL. So that would tend, I suppose, to eliminate these five cases?

Mr. BEESLEY. Here let us take a cancer drug, for example, that would, very likely, be under investigation for a long time before it is ever put on the market, if ever, and quite properly so, and I am sure the Food and Drug Administration would agree in such case.

Mr. SIBAL. I just have one more question.

What must you show the FDA, or is there any requirement that you must show the FDA, before you use a drug in this experimental phase?

I mean is there a minimal amount of research which you must show?

Mr. BEESLEY. You mean currently or under the proposed regulation?

Mr. SIBAL. Currently.

Mr. BEESLEY. No, there is nothing.

Mr. SIBAL. So, theoretically—I know you are a company of repute which would not do this, but, as a matter of theory—a drug could be distributed to physicians in this country under the experimental phase of the law which had not actually had much research done on it, is that correct?

Mr. BEESLEY. I think that is correct.

I do not believe it would happen, but I think there would have been adequate tests performed, but technically I think you are entirely correct.

Mr. SIBAL. This is in the responsibility of the manufacturer?

Mr. BEESLEY. That is correct.

Mr. SIBAL. Do you think this is sound?

Mr. BEESLEY. This is the sort of thing that would be corrected under the regulations just proposed on August 9. That is one of the reasons why we support the objectives of these regulations.

Mr. SIBAL. Thank you very much, Mr. Beesley.

Thank you, Mr. Chairman.

The CHAIRMAN. I just want to pursue for one moment this question of withdrawing the drug when it is determined that it is unsafe.

In the past, when it was determined that a drug was unsafe and it was suggested that it be withdrawn, has the industry cooperated?

Mr. BEESLEY. That is right.

The CHAIRMAN. You will recall the figures in connection with the polio vaccine?

Mr. BEESLEY. Yes.

The CHAIRMAN. You will recall the concern created then, and of course there is the recent publicity having to do with thalidomide which caused great interest throughout the world.

I want to now recognize the presence of Dr. Kelsey. We appreciate Dr. Kelsey's interest in this program and we are glad to have you with us in these hearings today.

But thalidomide was never put on the market?

Mr. BEESLEY. No.

The CHAIRMAN. There were certain amounts of it that were given to doctors.

In other words, any manufacturer may develop a drug and then provide as much of it as he wants to doctors for experimental purposes?

Mr. BEESLEY. That is correct.

Mr. CUTLER. The statute, Mr. Harris, gives the FDA full power to set the terms and conditions on which drugs will be distributed for experimental use.

Until recently the FDA had not fully exercised that power.

The CHAIRMAN. In other words, there is plenty of authority?

Mr. CUTLER. Correct.

The CHAIRMAN. To deal with that insofar as the law is concerned?

Mr. CUTLER. Yes, sir.

The CHAIRMAN. But until a few days ago, the FDA has never taken such steps to control that particular phase of it?

Mr. CUTLER. They had taken some steps, but they had not utilized their full authority until the last few weeks.

The CHAIRMAN. In other words, under the law—and I think this should be made very clear and specific because of all the publicity that has been given to it—the agency does have authority to make certain requirements even for the dispensation of a new drug for testing purposes to physicians?

Mr. CUTLER. Yes, sir, section 505(i) of the present law.

The CHAIRMAN. And if the Department had utilized the authority it has under the statute, then thalidomide, which was given to certain doctors of the country, could have been withheld?

Mr. CUTLER. Whenever the Food and Drug Administration had wanted to withhold it.

The CHAIRMAN. Yes, that is what I am talking about.

Mr. CUTLER. The Food and Drug Administration would have had full and current information.

The CHAIRMAN. In other words, not only under present law does the Department have authority to withhold the drug thalidomide from being put on the market, but had it utilized fully the provisions of law and taken precautions which are authorized by law, they could have controlled the dispensing of thalidomide to the doctors?

Mr. CUTLER. Yes.

The CHAIRMAN. I wanted to make that very clear and definite.

Now, back to the present authority and what is proposed with reference to withdrawing a drug if it should be determined unsafe, after approval had been given.

A good many years ago, a polio vaccine had been approved and was dispensed to the general public. After a certain length of time there were reports as to the effect it had on certain people throughout the country.

Now, had not the industry cooperated by voluntarily withdrawing it or trying to withdraw it from the market—that was Salk vaccine then, was it not?

Mr. BEESLEY. That is correct.

The CHAIRMAN. Incidentally, I do recall the visit we had to your company back in those days.

DRUG INDUSTRY ACT OF 1962

199

Mr. BEESLEY. We were very privileged to have you, sir.

The CHAIRMAN. The visit was very revealing from the standpoint of the committee at that time.

Now, if the company had not cooperated—and I do not believe it was your company that was involved in that, either, was it?

Mr. BEESLEY. It was another company, sir.

The CHAIRMAN. If it had not cooperated, then before the Food and Drug Administration could have required it to be withheld, under the law it would have been necessary to have a hearing, No. 1, and the Administrative Procedures Act would have had to be followed, or else the FDA would have had to go to court to get an injunction?

Mr. BEESLEY. First, as you will recall, this is a biological product that you are referring to, and is under the jurisdiction of the Department of Biological Standards of the National Institutes of Health, and it is a different statute. But assuming the same circumstances, the rules are the same.

The CHAIRMAN. Now, you know, as one lawyer to another, although I have been removed from that practice for a good many years and would not maintain that I am on a par, but it requires time to process a case under the Administrative Procedures Act, does it not?

Mr. CUTLER. Yes, sir.

The CHAIRMAN. It could require a lot of time?

Mr. CUTLER. Yes, sir.

You could have an expedited hearing, if you follow the administrative hearing course. I would think you could have a hearing within a period of several months, but it would take at least several months.

The CHAIRMAN. It would take several months, and possibly much longer?

Mr. CUTLER. Right.

The CHAIRMAN. Now, you go into court and ask for an injunction. That would require some time?

Mr. CUTLER. That might require, at best, 48 hours, I would think, Mr. HARRIS.

The CHAIRMAN. Yes.

And if the judge had some questions in his mind as to what to do with it, it could require a longer time?

Mr. CUTLER. If you were on the bench and the Food and Drug Administration came to you requesting an injunction for what they deemed to be a clearly unsafe drug, I would think you would grant the preliminary injunction while you looked into the matter.

The CHAIRMAN. I would certainly consider it.

Mr. CUTLER. If I were on the other side, I do not know how we could stop you.

The CHAIRMAN. I was trying to develop and pinpoint the difference here—although it is somewhat technical—about the attitude of the industry toward temporary suspension of the use of the drug by injunction, and the request of the Administration to have this temporary authority within the agency.

Mr. CUTLER. We are asking, sir, only that there be some check on the arbitrary authority of one man without hearing and without even discussion with the manufacturer.

The CHAIRMAN. Even if that one man is the Secretary, himself?

Mr. CUTLER. Yes, sir.

He at least ought to be able to satisfy a judge in a court within 24 to 48 hours. He has any number of remedies available. He can notify all physicians immediately that he suspects the drug, and that will really do more by way of stopping immediate use than any kind of recall procedure.

He has plenty of weapons during the period while he has to check his judgment with somebody and give some kind of a hearing.

The CHAIRMAN. I think you should give serious consideration as to the result.

Now, let us go back and take the experience of withdrawing cranberries from the market several years ago, and see what happened throughout the country.

I suppose there is still debate going on whether that should have been done or should not have been done.

I am not going to ask you to comment on it, and I am not going to comment on it either.

But, using that as an example, you know, as a matter of fact, it did create a great deal of uneasiness and concern all over the country among business people, particularly those who had it on the shelves and others. Then a search went out to get the cranberries off the shelves.

In the case of experimental drugs sent to doctors the distribution would not be as wide but if it were to get to drugstores throughout the country, it seems to me there would be about the same turmoil.

It seems to me that serious consideration should be given to meet this problem without getting involved in such a public turmoil, which scares everybody to death.

Now, there are quite a lot of doctors in the country that had thalidomide dispensed to them. How many doctors have we got in the country?

Mr. BEESLEY. About 175,000 to 180,000.

The CHAIRMAN. 180,000 in the United States.

Well, with all the publicity that is given, I do not suppose there is any way of telling how many expectant mothers in the country were just put in a very, very unstable mental condition.

And I know and you know, as a matter of fact, thousands upon thousands of young mothers have been in terrible mental anguish during this stage of expectancy. It does seem to me that there should be some way to avoid that kind of a situation.

Thank you very much.

Mr. MOSS. Mr. Chairman?

The CHAIRMAN. Mr. MOSS.

Mr. MOSS. I have just a couple of questions. One, I would like to have some clarification of this authority of the Secretary in the matter of investigative or experimental use of drugs. He may not deny the right to a drug for investigative or experimental purposes, may he?

Mr. CUTLER. I think that in an extreme case he probably could, Mr. MOSS.

Mr. MOSS. The law says that he shall promulgate such rules and regulations for its use.

Mr. CUTLER. Yes.

Mr. MOSS. For this purpose.

Mr. CUTLER. Yes, but if the information which he required be furnished to him showed such a clear case of danger and lack of safety, perhaps he could even stop it under those circumstances.

Mr. MOSS. That is a question that is unresolved at the moment.

Mr. CUTLER. It has never been attempted, but I don't think it could be challenged.

Mr. MOSS. Now I am interested in the objection to granting the Secretary the authority to summarily remove, after approval, a drug where there is an imminent hazard to the public health. You indicate that in all probability a judge would grant a temporary order. He might not, however. It isn't totally inconceivable that he might not.

Mr. CUTLER. I think it would depend on the strength of the Secretary's case.

Mr. MOSS. It is like the question I asked just a few moments ago. This is one of those things that is unresolved.

Mr. CUTLER. Yes.

Mr. MOSS. What is so onerous about the language which requires, one, that there be an immediate notice upon the suspension of approval, and that the order state the finding upon which it is based?

Now if it were capricious, certainly you could go into court at that point on the basis of the order and challenge the action of the Secretary, could you not?

Mr. BEESLEY. May I comment on the question, Mr. Moss?

Mr. MOSS. Certainly.

Mr. BEESLEY. We have here a situation where a manufacturer has a substantial investment in a product, usually millions of dollars in the research, in the development of that product, and here the manufacturer has launched it on the market again, with an investment of a lot of money. It seems to us that before a virtual death sentence can be passed on that activity, that the manufacturer should have a hearing for a temporary suspension is virtually a death sentence, because with the publicity that would be attendant to taking that product off the market temporarily, it would in effect be killing the drug completely.

Now if it is warranted, that is fine, but if it isn't warranted, then we think that that is really an arbitrary use of the power that is unjustified.

Mr. MOSS. What would be the effect of the Secretary seeking a temporary injunction? Wouldn't there be the attendant publicity, and from the standpoint of a death sentence just about the same effect?

Mr. BEESLEY. Well, that could be, but at least a court of law would have to pass on the question.

Mr. MOSS. Here we are discussing the finding of an imminent hazard to the public health.

Mr. BEESLEY. Yes.

Mr. MOSS. Now if for that finding—and I would trust that it would not be capriciously made.

Mr. BEESLEY. Indeed.

Mr. MOSS. If the evidence is such as to convince the Secretary, and of necessity before he is convinced the staff of the Food and Drug Administration must also be convinced that there is an imminent hazard, then we are talking about a most unusual case rather than the routine: are we not?

Mr. BEESLEY. Yes.

Mr. MOSS. And at that point, having convinced the agency and the Secretary, shouldn't we be then concerned with the immediate protection of the public? There must be fairly persuasive evidence at hand for that conclusion to be reached.

Mr. BEESLEY. Mr. MOSS. I would like to submit that in my judgment these occasions do not require such precipitate action.

Now then, may we take the recent unpleasant situation? I have no personal information on this, but judging from the newspaper reports, it is my understanding that the alleged connection between thalidomide and deformities has been known for some 8 months. In fact, one magazine of national circulation, aside from the articles that had appeared in the medical journals, one lay magazine of national circulation published this in late February.

Mr. MOSS. Mr. Beesley, we are not talking about the type of case that would be involved here. We are talking here of a preparation previously approved. Thalidomide was not in that category. Approval was withheld on thalidomide because of the vigilance of a member of the staff of the Food and Drug Administration.

Mr. BEESLEY. Correct, that which was marvelous.

Mr. MOSS. Here we are discussing one where approval has been given, and on a broader use undoubtedly some development has emerged, in its totality, that must be very persuasive if the Secretary is to make a finding of an imminent hazard to the public health.

Mr. BEESLEY. Well, may I allude to another recent example that has been in all, or was in all, of the newspapers for several days, the preparation Enovid, made by a company with which I am not associated, but the company is a member of this association.

It is a marketed product. I am sure that company had made tremendous investment in the research that went into the development of this product. It has been, in the view of very competent clinicians, a worthwhile product.

Yet there was some publicity in medical journals and in newspapers and lay journals which would perhaps have given rise to the belief that this drug should be summarily taken off the market. Now fortunately the Food and Drug Administration did not reach that conclusion.

Mr. MOSS. It acted with great restraint.

Mr. BEESLEY. Indeed, that is correct.

Mr. MOSS. And with a very fine sense of responsibility for the role it plays.

Mr. BEESLEY. That is correct. May I point out, however, that in another country, Norway, the drug was actually taken off the market.

Now then, fortunately, here the Food and Drug Administration acted with great restraint, and I think acted very wisely. Yet I submit that the decision might have gone the other way, and if they had had this power—

Mr. MOSS. And had it gone the other way, my point is that going in and seeking the temporary restraining order would have been just as damaging as the procedure here, the difference being that if they guessed right, in moving to remove it, that from the moment of a guess the product is off the market.

Mr. BEESLEY. We are laying great stress on judicial review.

Mr. Moss. Well, it is provided here inherently.

Mr. CUTLER. After the fact.

Mr. BEESLEY. After the fact, though. We are talking about before the fact.

Mr. Moss. Of course, counsel indicated that all the judges would very quickly respond to the request of the Secretary and grant the temporary restraining order.

Mr. CUTLER. Mr. Moss, it seems to me this is a matter of your philosophy. We can all think of cases where administrators should be allowed to act without hearings, without talking to the people whose lives and businesses they are affecting, and without going to any court first. But that hasn't been the philosophy of our Government. Whenever we can, we have always provided for some sort of review by a court or a hearing procedure on the discretion of one man.

Mr. Moss. No.

Mr. CUTLER. That is all we are asking for here.

Mr. Moss. I would say that there are any number of instances in administrative agencies, touching in my judgment upon less critical area than the public health, where the agency can move summarily, and the review is after, not before the fact. I chaired a subcommittee on the Home Loan Bank Board. They can seize a solvent institution and then provide for hearings, seize it whenever they have made certain determinations not as far reaching as the determination which must be made here, and there, because they are not subject to the Administrative Procedures Act, some of the review authority inherent here is not present.

So I don't think it goes to philosophy, because the history in some of these administrative agencies has already created a philosophy. I think the philosophy here is how far do we have to go to prudently protect the public health, at the same time maintaining a proper balance.

Mr. CUTLER. Yes.

Mr. Moss. Which does not destroy the industry.

Mr. CUTLER. Part of our problem here, Mr. Moss, is that of a standard of "imminent hazard to the public health." Now what is that? Is it such a clear case of unsafety that it is dangerous to permit the time necessary for a hearing. That would be one thing. But all of us could fill in the content of "imminent hazard to the public health" in different ways.

Mr. Moss. I would so interpret the use of the term "imminent hazard to the public health" to require a very clear showing of an immediate hazard.

Mr. CUTLER. I would think, sir, that the differences between us could well be resolved by further and more careful definition of the phrase we are talking about, the standard to be applied.

Mr. Moss. I think that is quite possible, and I don't think this would be violative of any philosophy or principle of government to which we both adhere.

Mr. CUTLER. Yes, sir.

Mr. Moss. That is all the questions I had, Mr. Chairman.

The CHAIRMAN. Mr. Beesley, thank you very much again for your presentation here this morning. The committee will be in recess until 2 o'clock, at which time Dr. Chester S. Keefer, will be the first witness.

(Whereupon, at 12:05 p.m., the committee recessed, to reconvene at 2 o'clock on the same day.)

AFTERNOON SESSION

The CHAIRMAN. The committee will come to order.

The first witness this afternoon is Dr. Chester S. Keefer.

Dr. Keefer, we are pleased to have you and we will be glad to have your testimony.

STATEMENT OF CHESTER S. KEEFER, M.D., SENIOR MEMBER, EVANS MEMORIAL DEPARTMENT OF CLINICAL RESEARCH AND PREVENTIVE MEDICINE AT MASSACHUSETTS MEMORIAL HOSPITALS

Dr. KEEFER. Thank you, sir.

My name is Chester S. Keefer. I am senior member of the Evans Memorial Department of Clinical Research and Preventive Medicine at Massachusetts Memorial Hospitals, and am also Wade professor of medicine at Boston University School of Medicine. I have held both of those posts for more than 20 years.

It may be a matter of special interest to this committee that during the early 1940's I was in charge of the nationwide collaborative clinical trials of penicillin and streptomycin, and that I served in 1953-55 as Special Assistant for Health and Medical Affairs to the Secretary of Health, Education, and Welfare. A more complete statement of my background has been submitted for the record.

For the past several years I have served on the board of directors of Merck & Co., Inc.

I do not appear before this committee as a representative of that company or of the drug industry, but as a doctor and professor of medicine.

I have been asked by Dr. I. S. Ravdin, vice president for medical affairs of the University of Pennsylvania and one of our most distinguished surgeons, to present for the record of these hearings a statement with respect to the legislation under consideration. That statement has been endorsed by 16 other outstanding physicians and surgeons, whose curricula vitae is furnished to the committee to be attached to this statement.

All of the sponsors of the statement hold or have held positions of responsibility in medical schools, in medical societies, and in hospitals throughout the country. I am pleased to join with them in their statement and ask that it be included in the record at this point.

This committee is today hearing testimony on legislation to amend the laws with respect to new drugs. The widespread publicity on congenital malformations in infants—malformations which have been attributed to the drug thalidomide—has intensified public interest in our drug laws.

While we can be glad that our present system worked to prevent the general introduction of the drug into this country, we should heed the warning implicit in the tragedy and conscientiously examine the laws and regulations under which we operate.

This committee has demonstrated in its long experience with drug legislation an ability to deal in such sensitive areas with perspective

and perception. Those qualities are urgently needed today if we are to have legislation which will in fact advance the interests of the health of the Nation without at the same time jeopardizing the steady flow of new and improved drugs which enable the medical profession to carry on its never-ending battle against the critical and crippling diseases for which we now have no adequate prevention, treatment, or cure.

I have recently been asked by Dr. Lowell T. Coggeshall, a vice president of the University of Chicago, to serve with him and other scientists on a commission for drug safety.

The purpose of the commission is to advance scientific knowledge of the predictability of action in human beings of new pharmaceuticals, and I am confident that its work will result in increased safety in clinical testing.

The need of advances in testing procedures for the safety of new drugs, while always a matter of concern, has been dramatized by the reports that the drug thalidomide has been associated with the death or deformity of newborn babies in Germany, in England, and in other countries where the drug was released for general use.

Historically, pharmacological testing of new drugs in animal experiments has been quite a reliable yardstick in determining whether the drug is sufficiently safe to warrant clinical testing in human beings.

However, the need for tests to detect the possible relationship between therapeutic use of the drug and the occurrence of congenital malformations had never before been generally recognized.

That can be classified as a gap in scientific knowledge.

Even after the fact, no one knows the precise nature or extent of the relationship between the drug and the deformities. As has been stated by Senator Humphrey:

All we know is we do not know enough.

Among the purposes of the commission on drug safety will be to study ways of improving pharmacological testing so that the risks in clinical investigation may be minimized.

Although the bill before this committee deals with drugs in general use and does not deal specifically with the investigational use of drugs, I wish to say a word at this point to help lay at rest a distortion that has crept into the current discussion of the testing of drugs.

That is the human guinea pig concept, a term that lends itself to abuse and misunderstanding. Every advance in science requires trial and experimentation.

The law requires that prior to marketing, a drug be extensively tested for its effect on human beings. Before that is done extensive pharmacological testing on animals is required.

There is, however, no substitute for the trial of drugs in man. I think it should be emphasized, as stated by Mr. Larrick and Dr. Kelsey of FDA, that the responsibility for the administration of drugs to a patient, whether the drugs are on the market or in an experimental stage, is that of the physician.

It is most important to see the thalidomide tragedy in perspective, and to act with knowledge and understanding of that perspective.

During the past several decades, tremendous progress has been made in drug therapy. This has been due in large measure to the dynamic

research programs of the American drug industry. Countless lives have been saved.

Millions have been helped to live happier, more productive lives. But there is no such thing as absolute safety or absolute effectiveness. And progress does not come without the payment of some price.

We have been extremely fortunate in this country in the low price we have paid for tremendous progress in drug therapy. I think the Food and Drug Administration and the drug industry deserve tremendous credit for the advances which have been achieved under our present laws as compared with the almost minimal occurrence of serious side effects.

I think the Food and Drug Administration has been improperly criticized for permitting certain drugs to be marketed which later were recalled.

Medicine is at best an uncertain science. There is no way of putting a new drug application through a computer and knowing what adverse side effects may occur. Despite this fact the safety tests for new drugs in this country have proven remarkably effective.

In the past 4 years, according to the records of the Food and Drug Administration, approximately 784 new drugs have been marketed and only 15 have been withdrawn (generally on the basis of information as to side effects provided by the manufacturer).

The combined incidence of unwanted effects of all of those 15 drugs did not approach the incidence of effect associated with thalidomide. That seems to me to be an exceptional record of responsibility, rather than one which merits censure for the handful of withdrawals.

I recognize in the legislation presently under consideration by this committee an effort at a constructive approach to some of the problems faced by the drug industry and the FDA.

Since they are at the same time problems of American medicine and of the American people, I know this committee will approach them objectively and will not recommend legislation which would unduly obstruct research in new drugs which are vitally needed by the doctors and the people of the country.

Today tuberculosis, pneumonia, and other scourges of the recent past are no longer among the top 10 killers, due largely to breakthroughs in drug therapy.

But we are still confronted with the scourge of diseases such as heart disease, cancer, mental illness, neurological disorders and many others.

I am sure no one of us would wish to retard much-needed research leading to new drugs or in any way to delay the availability of existing drugs for cancer and other uncured ailments. Keeping a useful drug off the market or unduly delaying its marketing may frequently in itself be a great detriment to public health.

Today we regard the drugs of 1942 as outmoded. It is to be hoped that the doctors of 1982 will consider the drugs of 1962 just as outmoded. That can be accomplished only by continuation of the present dynamic drug research program.

My concern is that there is danger in the present legislation of over-regulating the drug industry, the research it conducts and the clinical investigation it fosters. I am also concerned that it should not place so much authority and responsibility for recordkeeping and review in the Food and Drug Administration as to weaken and perhaps destroy its ability to carry out its assigned tasks.

DRUG INDUSTRY ACT OF 1962

207

As this committee is well aware, legislating in the area of new drugs requires objective perspective and mature judgment. The drug industry, the FDA, and the conscientious physician are all vitally interested in the discovery, development, and applications of new and useful drugs. They are also interested in making new drugs accessible to all patients who need them as promptly as possible—because drugs are for patients who need them.

I should like to read the statement by Dr. Ravdin, if I may.

STATEMENT OF DR. I. S. RAVDIN

The subscribers to this statement are doctors of medicine. We hold, or have held, positions of responsibility in medical schools, in medical societies, and in hospitals throughout the country. We represent one or more of the many fields of medicine, and for this reason we feel a responsibility to comment on H.R. 11581.

The tragic thalidomide experience of recent weeks has understandably focused attention on drug research as a whole. Improvements, particularly in the areas of clinical investigations, may be made through the strengthening of certain regulations.

However, broader legislation conceived in an emotional atmosphere must be viewed in the light of its possible detriment to independent and creative research by the pharmaceutical industry of this country.

In our opinion, H.R. 11581 raises a serious medical issue by providing that, in addition to showing that a new drug is safe, a manufacturer must also prove to the Food and Drug Administration that it is "efficacious." Proof of efficacy is desirable only if the "efficacy" requirement is taken to mean that a manufacturer should produce substantial evidence that a drug has the effect the manufacturer claims for it.

If proof of efficacy is interpreted as meaning more than this, then there is a serious danger that this provision of the bill would keep many valuable new medicines from the American people.

We ask the committee to consider the following points:

(1) Medicine is in part an uncertain science. There is at the present time no precise method for determining absolute efficacy or effectiveness. Such a determination must frequently be based upon medical opinion, and medical opinion is not always unanimous.

(2) Physicians very often have differing opinions about the usefulness of an agent in treating a particular disease. Many eminent physicians, for example, favor the use of the corticosteroids in the treatment of rheumatoid arthritis, but others believe that the corticosteroids are not the drug of choice for this purpose.

Under such circumstances, it is difficult, if not impossible, to determine the exact effectiveness of the corticosteroids in treating rheumatoid arthritis. It would be an appalling development to have the FDA, directly or indirectly limiting the rights and responsibilities of a prescribing physician by determining, for example, the corticosteroids should not be marketed because of the FDA's opinion that they lack efficacy.

(3) Drugs are not uniformly effective in individual patients even with the same disease. In the case of epilepsy, some of the available drugs are useful in treating perhaps only 20 percent of the patients suffering from this disease.

But we believe it would be wrong to deny a drug to this 20 percent because that drug is ineffective in the treatment of the remaining 80 percent of those suffering from epilepsy.

If a drug company should be required to submit a preponderance of evidence as to the effectiveness of a new drug, it is highly doubtful that any drug which is effective in treating a limited percentage of patients would ever be marketed.

(4) To be truly effective, the medical profession needs an expanded and improved arsenal of drugs. We have confidence that the American prescription drug industry, if permitted to operate in an atmosphere of freedom, can supply that need.

In our judgment, both the industry and the medical profession—and ultimately the American people—would suffer if Government were to require anything more than substantial evidence that a drug is effective for the use claimed for it. By "substantial" evidence we mean that the clinical testing data submitted to the FDA should be performed by truly competent and qualified clinical investigators and that the medical evidence supporting the claim of effectiveness should be significant.

(5) To require a drug company to submit a preponderance of evidence as to the effectiveness of a new drug is, in our judgment, unreasonable. It is a well-known fact that the majority of expert opinion has at first often been opposed to what later was proven to be valuable new discoveries in medicine.

Yet such discoveries have, in the long run, greatly benefited our people. Under this bill, a finding by the FDA that a company has not submitted a preponderance of evidence as to the effectiveness would for all practical purposes keep that drug—possibly a lifesaving one—from being marketed.

We believe that the Food and Drug Administration should continue as the protector of public safety. When a new drug is under consideration, we think it should insist that substantial evidence of effectiveness be demonstrated before the product is released for marketing. But we believe it is the physician's responsibility, and his alone, to decide whether a drug will be effective in treating his patients.

There is one other major provision of the bill that we feel is not in the public interest—that relating to trademark names.

It is our opinion that trademarks are of great value to the physician. It is often said that all prescribing should be done by generic names, but such a suggestion overlooks the realities of medical practice.

In the course of his experience, the physician gradually builds up confidence in certain pharmaceutical firms because he knows that they will supply him with drugs of reliable quality. He identifies certain trademark names with the firms he favors, and these names serve as a shortcut for writing prescriptions.

Moreover, there is evidence that the same generic-name drug, produced by two different companies, may react quite differently in a patient. This occurs not because of differences in the active ingredients, but because of variations in the inert ingredients used. For this reason, the doctor comes to rely on trademark names.

In our opinion, therefore, the provision of H.R. 11581 that calls for generic names to take precedence over trademark names on the label will, we believe, only complicate normal procedures in the day-to-day practice of medicine.

This statement, Mr. Chairman, has been signed by Dr. Henry Bockus, of Philadelphia; Dr. Wallace M. Yater, Yater Clinic, Washington, D.C.; Dr. William A. Sodeiman, dean, Jefferson Medical College, Philadelphia; Dr. William A. Altmeier, Cincinnati, Ohio; Dr. Loyal Davis, Northwestern Medical School, Chicago, Ill.; Dr. Reed Nesbit, University of Michigan Medical School, Ann Arbor, Mich.; Dr. George E. Armstrong, New York University School of Medicine, New York, N.Y.; Dr. Julian P. Price, Florence, S.C.; Dr. Francis Wood, Philadelphia, Pa.; Dr. Michael E. DeBakey, Baylor University, Houston, Tex.; Dr. Harold Glendon Scheie, University of Pennsylvania, Philadelphia, Pa.; Dr. Howard Mahorner, director, Mahorner Clinic, New Orleans, La.; Dr. Clifford Barborka, Chicago, Ill.; Dr. Joseph Marchant Hayman, Jr., dean, Tufts University School of Medicine, Boston, Mass.; Dr. Cecil J. Watson, University Hospitals, Minneapolis, Minn.; Dr. Alton Ochsner, New Orleans, La.; Leroy E. Burney, M.D., vice president of health sciences, Temple University School of Medicine, Philadelphia, Pa.; Warren Henry Cole, M.D., professor and department head of surgery, University of Illinois, Research and Educational Hospital, Chicago, Ill.; Thomas Morton Durant, M.D., Temple University School of Medicine, Philadelphia, Pa.; William M. M. Kirby, M.D., University of Washington Medical School, Seattle, Wash.; George Widmer Thorn, M.D., Peter Bent Brinham Hospital, Boston, Mass.; Barnes Woodhall, M.D., dean, Duke University, School of Medicine, Durham, N.C.; Paul Dudley White, M.D., Boston, Mass.; and myself.

Thank you very much, sir.

The CHAIRMAN. Thank you, Doctor, for your statement, and the statement from other well-known medical people in the country.

I am sure the committee appreciates your concern with reference to the problem as you have very appropriately outlined in your statement to the committee. I am certain that the committee will give very careful and close attention to these problems, keeping in mind our objective in this legislation, which is to provide the appropriate authority, without doing irreparable harm, to the continued research and development of drugs and that will alleviate human suffering.

Any questions of the committee?

Mr. DINGELL. I have several but I would be happy to yield to Mr. Schenck.

The CHAIRMAN. Mr. Schenck.

Mr. SCHENCK. I listened with great interest, Mr. Chairman, to the statement of Dr. Keefer, and I know that Dr. Keefer is very distinguished, able and a highly recognized member of the medical profession.

Dr. KEEFER. Thank you, sir.

Mr. SCHENCK. And, therefore, the statement is very important to this committee.

Of course, I am not a trained person in medicine, pharmacology or any of the allied fields. I am wondering, Dr. Keefer, as a member of the medical profession, whether or not you know if the pharmaceutical companies are using a great deal of care in the selection of the doctors to whom they allot certain quantities of a drug to be tested?

Do the drug manufacturers carefully select those men or women?

Dr. KEEFER. Mr. Schenck, I would say that they used extraordinary care in selecting highly trained clinical investigators when they attempt to place an important drug on the clinical trial basis. There are a number of highly qualified clinical investigators in the United States. In fact, there is a 50-year-old society known as the American Society of Clinical Investigation, and these young men, I say young men, because they must join the emeritus list at the age of 45, have all been highly trained in our university and hospital clinics in the techniques of clinical investigation.

So, that I would say that in my own experience these investigators have been selected with great care and with great critique.

Mr. SCHENCK. That is very reassuring. Dr. Keefer, do these investigators make a rather careful case study of the patient prior to prescribing of new drugs?

Dr. KEEFER. Yes, sir.

Mr. SCHENCK. Is that a general procedure?

Dr. KEEFER. Yes, sir. They certainly do, and they prescribe such an investigational drug only to patients to whom they feel might be benefited by such a drug.

They take a careful history and decide after physical examination, whether or not such a drug would be suitable for clinical trial in that individual patient.

Mr. SCHENCK. As you have pointed out, Dr. Keefer, in your statement or in this additional statement from others which you presented here, that different individuals react differently to the same drug.

Dr. KEEFER. Yes, sir.

Mr. SCHENCK. And also the inert or filler part of the medicine is quite often a determining factor.

I am told that the drug which has been recently discussed in the press as one of the contraceptives, as having developed some thrombophlebitis, that that situation would be likely to occur if the patient had had a rheumatic type injury or illness to his or her heart.

Therefore, such condition or other conditions should be shown up in the history of the patient if the investigating or the clinical doctor had made a very careful case study of that, is that true?

Dr. KEEFER. That is true, sir.

Mr. SCHENCK. So it may well be that thrombophlebitis cases which have developed because of inadequate case histories, perhaps?

Dr. KEEFER. No, sir. I don't think that that necessarily follows, because thrombophlebitis is a very common disorder and can occur under a wide variety of circumstances, and is certainly one of the major problems in the study of diseases of the blood vessels and particularly the veins.

So that occasionally—some patients, whether they are taking drugs or not, will develop thrombophlebitis, and it is particularly true if they have an illness and are confined to bed or have some slight injury to an extremity. These factors must all be taken into account when a patient develops thrombophlebitis. It may not be related to any medicines that the patient has been taking at all.

It is only when a side effect, or an unwanted effect or a complication arises during the treatment of a patient which appears with regularity and frequency, and is unrelated to anything other than what one may determine as drug therapy, that one is justified in drawing the conclusion that the drug therapy itself has promoted the development of the thrombophlebitis.

Mr. SCHENCK. Mr. Chairman, I have just two brief questions.

It has been suggested that the pharmaceutical companies must include in their advertising in medical journals all of the side effects and contraindications. Do you feel that would be necessary or proper or helpful?

Dr. KEEFER. Sir, Mr. Cain is going to discuss this matter this afternoon.

Personally, I do not think that it is necessary to include all of those facts in advertising, because it would really mean that so much space would be devoted to repeating what is in the usual package inserts or the monographs of drugs that advertising would lose its effectiveness, particularly since advertising is mainly for reminding the doctor of products.

Mr. SCHENCK. Each of the physicians then, Dr. Keefer, do receive rather complete monographs or the information packaged with the drug, do they not?

Dr. KEEFER. Yes, sir.

Mr. SCHENCK. And that is rather complete?

Dr. KEEFER. And these are all approved by the Food and Drug Administration.

Mr. SCHENCK. And that is required by the Food and Drug Administration?

Dr. KEEFER. Yes, sir; it is.

Mr. SCHENCK. All right. Now, just this one final question, Dr. Keefer.

On page 4 of Dr. Ravidin's statement, and endorsed by others, line 2 and later down, he uses the same word again, you discuss the preponderance of evidence as to the effectiveness of the new drug.

Now, are you interested only in the effectiveness or are you also interested in the safety?

Dr. KEEFER. Well, sir, we are very much interested in safety as well as effectiveness.

Mr. SCHENCK. Wouldn't you feel then that this statement might well be revised to that extent that you might include "effectiveness" and "safety"?

Dr. KEEFER. Yes, indeed. The reason it was not included in the statement, sir, was that we took this for granted, really, that we are concerned primarily with safety as well as effectiveness.

Mr. SCHENCK. Thank you very much, Dr. Keefer.

Thank you, Mr. Chairman.

Dr. KEEFER. Thank you.

Mr. DINGELL. Doctor, you indicate in your statement that you feel it is unwise to require a drug to be labeled with the generic name, is that your position?

Dr. KEEFER. No. No—

Mr. DINGELL. You say:

There is one other provision of the bill that we feel is not in the public interest—that relating to trademark names. It is our opinion that trademarks are of great value to the physician. It is said that all prescribing should be done by generic names

Where in the bill does it appear that all prescribing should be done by generic names?

Dr. KEEFER. Well, it does not appear in the bill.

Mr. DINGELL. It does not appear in the bill.

Dr. KEEFER. No, sir.

Mr. DINGELL. Then you have no objection to the bill on its language dealing with generic names?

I assume you have read the bill and are familiar with it, aren't you, Doctor?

Dr. KEEFER. Yes. I am familiar with the bill. It says here:

In our opinion the provision of H.R. 11581 that calls for generic names to take precedence over trademark names on the label we believe will only complicate normal procedures in the day-to-day practice of medicine.

Mr. DINGELL. All right.

Let's take a look at that.

If this bill is passed, you will get a bottle with a label first of all giving the generic name and then the trademark name, am I right?

Dr. KEEFER. Yes.

Mr. DINGELL. All right.

How is that going to complicate the practice of medicine?

Dr. KEEFER. Well—

Mr. DINGELL. You will still be able to prescribe by trademark name if you are so minded, wouldn't you?

Dr. KEEFER. I hope so.

Mr. DINGELL. All right.

You will have available to you one additional piece of information, will you not? You will have available to you not only the trademark name but you will also have the generic name available to you, isn't that right?

Dr. KEEFER. The doctor has that information available before he writes the prescription.

Mr. DINGELL. I am aware of that, but that will be on the label of the commodity that he prescribes. What is bad about that?

Dr. KEEFER. Well, I don't think there is anything bad about it.

Mr. DINGELL. All right.

So you then have no objection to it?

Dr. KEEFER. It is just required by law. All right.

Mr. DINGELL. But you have no objection to it then because it is not bad?

Dr. KEEFER. No.

Mr. DINGELL. Then your statement with regard to this point you might like to revise at this point by indicating to the committee that you have no objection to this section then?

Dr. KEEFER. I have no objection, it is a matter of precedence.

Mr. DINGELL. I see. But you have no objection to it?

Dr. KEEFER. No.

Mr. DINGELL. As a matter of fact, you do not feel then that this section is not in the public interest, as you have indicated on page 4 of your statement?

Dr. KEEFER. It is largely a question in my mind and in the mind of the committee—

Mr. DINGELL. Just a minute, Doctor. You are an intelligent man, you are schooled in pharmacology, and I assume you are schooled in the drug trade and also in medicine.

I am a layman, but I am able to read a statement and you are, too. You state this is not in the public interest and then you state you have no objection. Which of the two is true?

Dr. KEEFER. It is simply a matter of precedence.

Mr. DINGELL. But you have no objection to it, as you indicated?

Dr. KEEFER. No, I have no objection.

Mr. DINGELL. I would like to talk to you a little here about efficacy; you devoted a great deal of your statement to efficacy.

Do you feel the drug industry should be able to market new drugs with claims that are not supported by medical evidence?

Dr. KEEFER. No.

Mr. DINGELL. You don't think that is sound or in the public interest?

Dr. KEEFER. No, I do not.

Mr. DINGELL. All right.

It has been said up to 20 percent of the new drugs studied by the AMA's Council on Drugs since 1956 are being promoted by one or more claims unsupported by reliable evidence.

In your view is this a situation that should remain unchanged by this new legislation?

Dr. KEEFER. Who says this?

Mr. DINGELL. I just say—well, let's make first of all, the assumption, let's just say for purposes of the argument then, that this statement is true [laughter] do you think that this [laughter] do you think that this situation should continue?

Dr. KEEFER. Why, no; I don't think it should continue.

Mr. DINGELL. I think, by the way, if you would check the Celler hearings, I think you will find something to this effect in there. All right.

Now, is what you are saying that the drug manufacturer should be allowed to claim that his drug will prevent heart attacks if he has medical study to support it even though the preponderance of evidence shows the claim is false?

Dr. KEEFER. Certainly not. If the preponderance of evidence would show that the claim is false he certainly should not be justified in saying that it was true.

Mr. DINGELL. I see. Would he be justified in marketing a drug where the preponderance of the medical evidence showed that his claims of efficacy were not true?

Dr. KEEFER. Well, this is a matter of opinion, and a question on the part of the experience of a doctor who uses these drugs as to whether or not, in his experience, it has prevented heart attacks or not.

Mr. DINGELL. All right. Well, then, you say—you say, then, that the drug manufacturer should be allowed to market a drug based on claims of efficacy even though the preponderance of sound medical evidence shows that the drug has no efficacy?

Dr. KEEFER. Well, if the evidence is substantial that it has prevented, let us say, heart attacks in 20 percent of cases over a period of 5 years compared to a group who have not received similar therapy, I think that that is substantial evidence.

Mr. DINGELL. Let's go one notch further here. Which one of the manufacturers do you work for as a consultant?

Dr. KEEFER. I don't work for any manufacturer.

Mr. DINGELL. You don't work for any of them at all.

Let's assume you were a manufacturer and you had an unfair labor practice case before the NLRB, and you said that there was an unfair labor practice and the union said there was not.

Would you regard it as appropriate that the NLRB should find against you because there was some substantial evidence on the other side even though you presented a preponderance of evidence?

Dr. KEEFER. Mr. Dingell, I am not a lawyer and I am not an expert in labor relations, so I don't know how I could answer that question adequately.

Mr. DINGELL. Well, now, you see, here we are, we are going to say we can market these drugs even though we can say there is only substantial evidence.

Yet you will concede that circumstances under your testimony will arise in the course of events whereby the preponderance of evidence will say that the drug has no efficacy, and where you say, or rather where the person who wants to market it has only some substantial evidence to show that the drug has efficacy, is it your feeling that all of these where the preponderance of the evidence shows there is no efficacy should be marketed even though there is just some substantial evidence to show that the drug does have efficacy?

Dr. KEEFER. Well, I think that this is a matter of relative judgment and experience with the department of any drug, and I don't think that drugs are ever marketed that have been in clinical trial that have no efficacy.

Mr. DINGELL. How many drugs are marketed for the treatment of arthritis?

Dr. KEEFER. Well, I wouldn't know, but I would say that there are a great many.

Mr. DINGELL. A great many. How many of these actually have efficacy in the treatment of arthritis?

Dr. KEEFER. Well, this is a matter of opinion and statistics developed by the doctor who observes the patient and follows the course of his illness, who knows the patient and knows the course of the disease.

So that some drugs are much more effective in the treatment of arthritis than others. It depends upon the stage and type of the arthritis.

Mr. DINGELL. Do you think that a drug ought to do what the manufacturer says when he goes to put it on the market?

Dr. KEEFER. I do.

Mr. DINGELL. All right. If we take this as being the test of efficacy, do you think that the efficacy should be supported just by substantial evidence or should it be supported by the preponderance of evidence?

Dr. KEEFER. I think it should be supported by substantial evidence.

Mr. CUTLER. Mr. Dingell, if I can break in for a moment, sir, Dr. Klumpp has some 10 pages of detailed discussion on this precise point which we would be reaching very precisely.

Mr. DINGELL. I see. I had read this gentleman's testimony and it was my impression he was here speaking on efficacy.

Mr. CUTLER. He is speaking as a doctor; Dr. Klumpp is speaking as a manufacturer and as a doctor.

Mr. DINGELL. Thank you, Mr. Chairman, no further questions.

The CHAIRMAN. Mr. Younger?

Mr. YOUNGER. Thank you, Mr. Chairman.

It has been suggested that a doctor should notify his patient if he is administering the drug in an experimental manner.

What is your feeling on that?

Dr. KEEFER. Well, Mr. Younger, I would say in my own experience that the vast majority of physicians inform patients that they are using an investigational drug, and since he is not able to prescribe that drug, and the patient is not able to buy it, he usually gives it to the patient and informs him. If he happens to be an ambulatory patient, he instructs the patient how to take it, and then gives him all the instructions and tells him usually what it is. Also he asks the patient to report any symptoms that may be considered to be unwanted, and also observes this patient to determine what effect the drugs have actually had.

For example, if it is a new drug for the treatment of hypertension, usually he prescribes it, the patient takes it, and he takes his blood pressure periodically, patients often take their own blood pressure at home, and then they return. Patients often keep very good records in the form of a diary, and bring it to the doctor for examination.

If the patient is being treated in the hospital, similar records are kept, so that they can be examined thoroughly and unwanted symptoms looked for, and also determine what the action of the drug has been in the patient.

Mr. YOUNGER. As you know, when you go to the hospital for an operation you sign a statement that you consent to the operation, and so forth.

What would be the attitude of the doctors, perhaps, of having some kind of a statement signed by the patient acknowledging that this drug was administered to him for experimental purposes?

Dr. KEEFER. Well, Mr. Younger, this is a suggestion that has been made on a number of occasions and I believe that some doctors make it a practice to get such a statement from the patient. It is not universal.

Mr. YOUNGER. On page 5 of your statement, one more question, you mention about 15 incidents where the drug has been withdrawn.

Dr. KEEFER. Yes, sir.

Mr. YOUNGER. Was that withdrawal by the order of the Food and Drug or was that a voluntary withdrawal or what were the circumstances, do you recall in these occasions?

Dr. KEEFER. Mr. Younger, that is usually a voluntary withdrawal after discussion with the Food and Drug Administration.

Mr. YOUNGER. Those are not the cases, as you recall, I asked Mr. Beesley this morning and he could give no incidence of where the drug was withdrawn by order of the FDA.

Dr. KEEFER. Well, I do not know of any, sir.

Mr. YOUNGER. That is all, Mr. Chairman.

The CHAIRMAN. Mr. Sibal.

Mr. SIBAL. Dr. Keefer, I hesitate to examine you on Dr. Ravdin's statement, but I don't know how else to approach this. He discusses on page 5 of his statement the fact that there is evidence that the same generic drug produced by two different companies might react differently on a patient because of differences in the inert ingredients used.

Could you expand on that a little bit so that those of us who are laymen in this field follow that a little better?

Dr. KEEFER. Well, by insert ingredients is usually referred to the binder or the chemical substances that make a tablet so that it is more soluble, or less soluble depending upon its desired effect after, let us say, a tablet is taken. These binders are different, and have been developed through pharmacy research so that some of these ingredients which are inert as far as having some unwanted effects are concerned, may in some instances cause the drug not to dissolve so it will not be absorbed.

Others will have other side effects. This subject has been studied extensively by the profession of pharmacy and I believe that this is going to be discussed later this afternoon in greater detail.

Mr. SIBAL. Well—

Mr. SCHENCK. Mr. Chairman, will the gentleman yield?

Mr. SIBAL. Yes.

Mr. SCHENCK. As I understand some of these active ingredients are in such a small quantity that unless some so-called inert material is added as a filler you couldn't even handle it?

Dr. KEEFER. Yes, sir.

Mr. SIBAL. I understand that, but the point I am getting to is, does the Food and Drug Administration, in the licensing of a drug, take into consideration the binder, if you will, which is used with the drug?

Dr. KEEFER. With every new drug; yes, sir.

Mr. SIBAL. In other words, when an application is made and a testing goes on and ultimately approval is given by the FDA it is given to the whole package?

Dr. KEEFER. Right.

Mr. SIBAL. Including the inert material, if you will, and the manufacturer is required thereafter, is he not, to continue to use the same inert material along with the active material; in other words, he does not have the leeway of changing his binder or changing—

Dr. KEEFER. That is correct, sir.

Mr. SIBAL. In effect, then, the point that Dr. Ravdin makes is that so far as the reaction of the patient to a particular generic drug it might be quite different between trade names?

Dr. KEEFER. Yes. That is correct.

Mr. SIBAL. So the trade name becomes important as well as the generic name as the doctor prescribes?

Dr. KEEFER. That is correct, sir.

Mr. SIBAL. Thank you very much.

The CHAIRMAN. What should be used, the trade name, the generic name, or both?

Dr. KEEFER. I beg your pardon, sir?

The CHAIRMAN. What should be used, the generic name, or the trade name, or both?

Dr. KEEFER. Well, sir, I think that this is a matter of the judgment of the physician.

Very often he can prescribe with a generic name and place after it which company he would like to have provided, whose product he would like to have provided.

The CHAIRMAN. You are talking about prescription drugs now?

Dr. KEEFER. Yes, sir.

The CHAIRMAN. What about proprietary drugs?

Dr. KEEFER. Well, I think that all, practically all of those drugs are sold under a trade name.

The CHAIRMAN. Thank you very much, Dr. Keefer.

Mr. SCHENCK. Mr. Chairman, I would like to say just one other thing here. Brand names are important in many, many different things other than medicine, are they not?

Dr. KEEFER. I would say they were most important, sir.

Mr. SCHENCK. You buy food and you buy automobiles and you buy suits and you buy everything else by brand names, do you not?

Dr. KEEFER. Yes, sir.

The CHAIRMAN. Dr. Leonard A. Scheele.

Dr. Scheele, let me, on behalf of the committee, welcome you back to the committee. We recall your numerous appearances in the past.

I see that you are a member of the Warner Lambert Pharmaceutical Co.

STATEMENT OF DR. LEONARD A. SCHEELE, MEMBER, BOARD OF DIRECTORS, WARNER LAMBERT PHARMACEUTICAL CO.

Dr. SCHEELE. Mr. Chairman, and members of the committee, it is indeed a pleasure to be back here after 5 years and to see several friends and new friends.

I am a member of the board of directors of Warner Lambert Pharmaceutical Co., which is our parent, and in addition I work with the research program of our company and with the ethical drug operation which is Warner-Chilcott Laboratories.

As you know, I am a physician, having graduated from Wayne State University, the medical school of that university. I joined the U.S. Public Health Service and spent 23 years as a career officer in that service, serving from 1948 until I retired in 1956 as Surgeon General.

I am here today, as you know, on behalf of the Pharmaceutical Manufacturers Association directing my comments to section 103 and section 106 of H.R. 11581. Those sections would require reporting by drug manufacturers on new drugs being placed in clinical trial and during their trial period prior to the filing of a new drug application, as well as after a new drug application has become effective.

These sections have attracted particular attention, Mr. Chairman particularly in the light of the intense public interest that is now being focused on the testing of a new drug, and the steps that are being taken to protect the public health while new drugs are being tested.

This committee is keenly aware of the major disease problems of our country and the world. You have held many hearings and issued many excellent reports on the toll of our major diseases, their causes, prevention, and control. And, of course, you have dealt over the years with the creation of laws which enable the health agencies of the Department of Health, Education, and Welfare to play major roles in improving man's health.

We recognize, Mr. Chairman, that it is at once the strength and the weakness of a democratic society that it takes crisis to give impetus for major legislative change. We recognize that since we discover, develop, test, produce, and market drugs that have a direct bearing on the physician's ability to save life and protect health, we have special responsibilities to accept regulation and to regulate ourselves.

We believe we have met our responsibilities well in the past, and that our record of accomplishment is one of which we and the Nation we serve can be proud. The industry is constantly striving to make more uniform throughout the industry those practices which now characterize the best of the industry.

You are aware, as I am, that dramatic progress has been made in controlling some diseases, especially those caused by bacteria, but that, like an iceberg with seven-tenths of its mass submerged, the large-scale cripplers and killers, including the chronic afflictions which plague our senior citizens more and more, as the lifespan increases, are still very much untouched. Too frequently we are limited to relief of symptoms and lack knowledge and drugs to prevent more illnesses and provide more cures.

Amendments to the Food, Drug, and Cosmetic Act should be designed to close existing gaps while at the same time assuring maximum effort by the Public Health Service, the National Science Foundation, in its grants program, and the Nation's private laboratories, including those in universities, pharmaceutical companies and elsewhere, to continue and, for that matter, speed the flow of new, safe, and useful drugs.

In general the pharmaceutical industry has been the principal producer of new drugs while other laboratories have been producing much of the flow of basic knowledge which enables us better to understand body processes in health and disease and makes it easier to produce needed drugs.

One example of the Congress recognition of this is the support you give to cancer research through provision of large numbers of grants to universities and others to do general research and through provision for contracts with pharmaceutical companies to produce drugs for testing in animals which, hopefully, can lead to testing in humans.

This committee has demonstrated its awareness of the problem of shortages of physicians, dentists, and clinical investigators in many ways. One of the most recent was its consideration and action on H.R. 4999, to provide for grants to medical and related schools for the creation of new facilities for medical education. An expression of PMA's interest in this legislation was submitted to this committee by letter dated February 2, 1962.

A recent Public Health Service program, which the Congress has also fostered, is directed to improving our capacity for sound clinical investigation by awarding grants to assist in the construction, staffing and operation of clinical research centers in medical schools and leading research hospitals across the country.

These and many other actions taken on many fronts suggest that the long-range solution to the problem of clinical investigation is to improve clinical research facilities, increase the number and broaden the competence of clinical investigators, and accord more general stature and recognition to those whose lifework is centered in the selection, testing, and evaluation of new therapeutic agents.

It is of fundamental importance that new drugs, before being used widely in research and being marketed, should be adequately tested for safety. Of equal importance is the fact that there be a continuous flow of new and improved drugs. Any legislation on this subject, therefore, needs to strike a fine balance. On the one hand, it properly seeks to broaden and strengthen controls over drugs both new and old, to protect the public interest. On the other hand, it must encourage rather than obstruct the continuing flow in the number and kind of new drugs that are needed for better health. It is with this goal in mind that I wish to address myself to the provisions of H.R. 11581, which I mentioned earlier.

Certainly the pharmaceutical industry and its Government do not disagree on the objectives that underlie section 103(b) and section 103(a) of the bill. The objective of section 103(b) is to permit the Food and Drug Administration to obtain information about the investigational testing of a new drug so as to enable them to evaluate its safety and efficacy in the event a new drug application should be filed. The objective of section 103(a) is to provide the FDA with continuous and current information on the safety of a drug after it is released.

We share these objectives, Mr. Chairman.

I do wish to point out that Secretary Celebrezze and Commissioner Larrick. I am sure on advice of departmental counsel, apparently feel the Department already has the legislative authority to pursue the objective of section 103(b). As the committee knows, it was referred to by Mr. Beesley this morning, the Department on August 9 announced that it would exercise its existing authority to issue proposed new regulations covering the investigational use of drugs, and on August 10 published an extensive series of proposed amendments.

DRUG INDUSTRY ACT OF 1962

219

Under established procedures, 60 days are allowed for comments, and after that comment is taken into account, the regulations are published in final form. I submit herewith a copy of the proposed regulations for the record.

The CHAIRMAN. Let it be received.
(The document referred to follows:)

[Published in the Federal Register of August 10, 1962]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

[21 CFR Part 130]

NEW DRUGS FOR INVESTIGATIONAL USE

NOTICE OF PROPOSAL TO AMEND REGULATIONS

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 701, 52 Stat. 1052, 1055; 21 U.S.C. 355, 371) and under the authority delegated to him by the Secretary of Health, Education, and Welfare (25 F.R. 8625), proposes to amend the new-drug regulations (21 CFR 130.3) as hereinafter set forth. The Commissioner hereby offers an opportunity to all interested persons to submit their views in writing with reference to this proposal to the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue S.W., Washington 25, D.C., within 60 days from the date of publication of this notice in the FEDERAL REGISTER. Views and comments should be submitted in quintuplicate.

It is proposed to amend § 130.3 to read as follows:

§ 130.3 New drugs for investigational use; exemptions from section 505(a).

(a) A shipment or other delivery of a new drug shall be exempt from section 505(a) of the act if all the following conditions are met:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use."

(2) The person seeking the exemption has filed with the Food and Drug Administration a completed and signed "Notice of Claimed Investigational Exemption for a New Drug" in triplicate, with the following information:

"Form FD 1571.

"Department of Health, Education, and Welfare,
"Food and Drug Administration.

"NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

"Name of sponsor _____

"Address _____

"Name of investigational drug _____

"TO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,

"For the Commissioner of Food and Drugs,
Washington 25, D.C.

"DEAR SIR: The undersigned _____ submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3.

"Attached hereto are:

- "1. Name of drug and description of dosage form.
- "2. Complete list of components of drug
- "3. Complete statement of quantitative composition of drug.
- "4. Description of source and preparation of any new-drug substances used as components, including the name and address of each supplier or processor, other than the undersigned, of each new-drug substance.
- "5. A brief statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and main-

tain appropriate standards of identity, strength, quality, and purity as needed to give significance to clinical investigations made with the drug. If any of these operations are performed by a person other than the undersigned, each such person is identified and his signed statement covering the part of the operations he performed is attached.

"6. Adequate information about the preclinical investigations, including studies made on laboratory animals, which show that it is reasonably safe to initiate clinical investigations with the drug. Such information should include identification of the person who conducted each investigation; identification and qualification of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug; and an explanation of where the investigations were conducted and where the records are available for inspection. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of proposed clinical testing such as, for example, whether the drug is for short- or long-term administration or whether it is to be tested or used in infants, children, pregnant women, premenopausal women, or geriatric patients.

"7. Five copies of all informational material to be supplied to each investigator. This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigations. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side effects, and precautions suggested by prior investigations and experience with the drug for the information of clinical investigators.

"8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind the pharmacological action of the drug and the conditions of use contemplated by the plan of clinical investigation.

"9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) of this paragraph and that the investigator is qualified by scientific training and experience as an appropriate expert to investigate the safety of the investigational drug under the criteria outlined in section 8 of the 'Notice of Claimed Investigational Exemption for a New Drug.'

"10. An outline of the planned clinical investigations of the drug including the following:

"(a) Planned stages of investigation, if any, that will be completed and evaluated prior to determining whether the next stage or stages will be initiated.

"(b) The names of the investigators to be engaged in each stage and kind of investigation.

"(c) The specific nature of the investigations to be conducted in each stage, together with the specific information or forms showing the scope and detail of the clinical observations and clinical laboratory tests to be made and reported.

"(d) The approximate number and any specific criteria as to the selection of patients by age, sex, and condition, to be employed in each stage of the investigation.

"(e) The estimated duration of the clinical investigation by stage, and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration. (This part of the statement may be limited to the plan for one or more stages of the investigations, provided that shipments or deliveries of the drug for use in additional stages of the investigations are not made until a supplemental statement recording results of the prior investigations and outlining the plan for following stages of investigations has been submitted to the Food and Drug Administration.)

"Ordinarily a plan of investigation will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain complete case histories of an adequate number of patients, designed to record observations and permit evaluation of any and all discernible effects of the drug on each individual treated, and comparable records on any

individuals employed as controls. These records shall be individual patient records maintained to include full information pertaining to each individual, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all clinical observations and laboratory examinations made, full information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

"11. A statement as to whether or not the drug will be sold; and if so, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not effective.

"Very truly yours,

 (Sponsor)

 "Per -----

 (Indicate authority)

(3) Each shipment or delivery is made in accordance with the commitments in the "Notice of Claimed Investigational Exemption for a New Drug."

(4) The sponsor maintains complete records showing the investigator to whom shipped, date, quantity, and batch or code mark of each such shipment and delivery, until 2 years after a new-drug application becomes effective for the drug; or, if an application does not become effective, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration has been so notified. Upon the request of any officer or employee of the Department at reasonable times, the sponsor makes the records referred to in this subparagraph and in subparagraph (2) of this paragraph available for inspection, and upon written request submits such records or copies of them to the Food and Drug Administration.

(5) The sponsor closely monitors the progress of the investigations and currently evaluates the evidence relating to the safety of the drug as it is obtained from the investigators. Accurate progress reports of the investigations and significant findings shall be submitted to the Food and Drug Administration at reasonable intervals, not exceeding 1 year. All reports of the investigation shall be retained until 2 years after a new-drug application becomes effective for the drug; or, if an application does not become effective, until 2 years after shipment and delivery of the drug for investigational use is discontinued. Upon request of any officer or employee of the Department, at reasonable times, these reports shall be made available for inspection, and on written request copies of these reports shall be submitted to the Food and Drug Administration.

(6) The sponsor shall immediately report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest hazards, contraindications, side effects, and precautions pertinent to the safety of the drug.

(7) If the investigations adduce facts showing that there is substantial doubt that they may be continued safely, the sponsor shall promptly discontinue the investigation, notify all investigators and the Food and Drug Administration, recall all stocks of the drug outstanding, and furnish the Food and Drug Administration a full report of the reason for discontinuing the investigation.

(8) The sponsor shall discontinue shipments or deliveries of the new drug to any investigator who fails to maintain or make available complete records or reports of his investigations.

(9) The sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug pursuant to section 505 (b) of the act or a statement that the investigation has been discontinued and the reasons therefor:

(i) With reasonable promptness after finding that the results of such investigation appear to establish the safety of the drug; or

(ii) Within 60 days after receipt of a written request for such an application from the Commissioner of Food and Drugs.

(10) Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any labeling, advertising, public relations statements, or news releases, representing the drug to be safe or useful for the purposes for which it is offered for investigation.

(11) The sponsor shall not commercially distribute nor test-market the drug until a new-drug application has become effective pursuant to section 505(b) of the act.

(12) The sponsor shall obtain from each investigator a signed statement in the following form:

"Form FD 1572.

"Department of Health, Education, and Welfare, Food and Drug Administration.

"STATEMENT OF INVESTIGATOR

"Name of investigator-----

"Date-----

"Name of drug-----

"To supplier of drug:

"Name-----

"Address-----

"DEAR SIR: The undersigned----- submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of the regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.

"1. The following is a statement of my education and experience:

"a. Colleges, universities, and medical schools attended, with dates of attendance, degrees, and dates degrees were awarded.

"b. Post-graduate medical training: Dates, names of institutions, and nature of training.

"c. Teaching or research experience: Dates, institutions, brief description of experience.

"d. Experience in medical practice: Dates, institutional affiliations, nature of practice.

"e. Medical publications: Titles of articles, names of publications and volume, page number, and date.

"2. The following facilities will be used for investigating the safety of the new drug (including a statement of hospital, institutional, and clinical laboratory facilities, etc., which are available and will be employed in connection with the investigation)-----:

"3. The investigational drug will be used by the undersigned or under his supervision in accordance with the plan of investigation described as follows:

"(Outline the plan of investigation, including approximation of the number of patients to be treated with the drug and the number to be employed as controls, if any; clinical uses to be investigated; characteristics of patients by age, sex, and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain a complete record of the observations and test results obtained.)

"4. The undersigned understands that the following conditions, generally applicable to new drugs for investigational use, govern his receipt and use of this investigational drug:

"a. The sponsor is required to supply the investigator full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

"b. The investigator is required to maintain complete records of the disposition of all receipts of the drug, including dates, quantities, and use by patients.

"c. The investigator is required to prepare and maintain complete and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

"d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports at appropriate intervals not exceeding 1 year. Any adverse effect associated with

use of the new drug shall be reported to the sponsor immediately. A complete report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

"e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application becomes effective for the drug; or if the application does not become effective, until 2 years after the investigation is discontinued. Upon the request of any officer or employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying.

"Very truly yours,

 "(Name of Investigator)"

 "(Address)"

(b) A shipment or other delivery of a new drug that is being imported or is offered for importation into the United States shall be exempt from the requirements of section 505(a) of the act if the following conditions are complied with:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use";

(2) The importer of all such shipments or deliveries is an agent of the foreign exporter residing in the United States, which agent and exporter have prior to such shipments and deliveries completed and submitted signed copies to the Food and Drug Administration of the "Notice of Claimed Investigational Exemption for a New Drug"; and

(3) The agent acts as the sponsor of the clinical investigation to assure compliance with the conditions prescribed by paragraph (a) of this section; or

(4) The drug is shipped directly to a scientific institution with facilities and qualified personnel to conduct the investigation and is intended solely for investigational use in such institution.

(c) Whenever there is submitted to the Commissioner the name of an investigator who has previously failed to comply with the conditions of these exempting regulations, the Commissioner will notify the sponsor that the investigator is not entitled to receive investigational-use drugs, and such investigator shall not be supplied any investigational-use drug until adequate assurance is provided to and accepted by the Commissioner that the conditions of the exemption will be met.

(d) If the Commissioner of Food and Drugs finds that:

(1) The submitted "Notice of Claimed Investigational Exemption for a New Drug" contains an untrue statement of a material fact or omits material information required by said notice; or

(2) The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigations with the drug; or

(3) There is substantial evidence to show that the drug is unsafe for the purposes for which it is offered for investigational use; or

(4) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed to give significance to clinical investigations made with the drug; or

(5) The plan for clinical investigations of the drug described under section 10 of the "Notice of Claimed Investigational Exemption for a New Drug" is not a reasonable plan in whole or in part, solely for a bona fide scientific investigation to determine whether or not the drug is safe for use; or

(6) The clinical investigations are not being conducted in accordance with the plan submitted in the "Notice of Claimed Investigational Exemption for a New Drug"; or

(7) The drug is not intended solely for investigational use, since it is or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the investigation; or

(8) The labeling submitted for the drug as required by section 7 of the "Notice of Claimed Investigational Exemption for a New Drug" or any other labeling of the drug disseminated within the United States by or on behalf of the person who signed such notice fails to contain an accurate description of prior investigations or experience and their results pertinent to the safety and possible usefulness of the drug, including all relevant hazards, contra-

indications, side-effects, and precautions; or any labeling, advertising, public relations statements, or news releases disseminated within the United States by or on behalf of the sponsor contains any representation or suggestion that the drug is safe or that its usefulness has been established for the purposes for which it is offered for investigations; or

(9) The person who signed the "Notice of Claimed Investigational Exemption for a New Drug" fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or

(10) The person who signed the "Notice of Claimed Investigational Exemption for a New Drug" fails to promptly inform the Food and Drug Administration and all investigators of newly found serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug;

he shall notify the sponsor and invite his immediate correction. If the conditions of exemption are not immediately met, the Commissioner shall notify the sponsor of the termination of the exemption.

(e) Where drugs are under investigation on man on the date of publication of this notice of proposed rule making, the sponsor shall, within 60 days after these regulations become effective, submit the completed "Notice of Claimed Investigational Exemption for a New Drug" to the Food and Drug Administration. Failure to do so shall automatically terminate the exemption.

(f) A shipment or other delivery of a new drug for laboratory research or animal tests only shall be exempt from section 505(a) of the act if it is labeled: "Caution: New drug—Limited by Federal (or United States) law to laboratory research and tests on animals. Not for human use." No animals used in such tests shall be used for food purposes.

Dated: August 7, 1962.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

Dr. SCHEELE. I do not propose here to comment on those regulatory proposals. Both my company and the industry are studying them carefully and will make our views known to the Department after our study is completed. But the proposed changes in regulation are relative to the consideration of H.R. 11581 since section 103(b) appears to be directed to giving the Department powers it already has.

The clinical trial process involves practicing physicians and patients. The investigational use of a new drug is an integral part of the practice of medicine and of health sciences. It should, therefore, be noted that the views of the clinical investigators themselves, who will be directly affected by the proposed regulations, should carry a great deal of weight, and I say, they probably should carry a great deal more of weight than the opinions of those of us who are administrators in the pharmaceutical industry.

Since the proposed changes in section 103(b) appear to us to be directed at giving the Department powers it already has, we urge the committee to study the existing law and proposed new regulations in order to ascertain whether or not the amendment proposed in section 103(b) is necessary.

In the event this committee should decide that the present law of the FDA requiring recordkeeping and reporting on new drug investigations is inadequate, we urge the committee to consider adding the proviso contained in section 7(a)(3) of S. 1552 to section 103(b) of H.R. 11581. That proviso reads:

Provided, however, That regulations issued under this subsection and under subsection (j) shall have due regard for the professional ethics of the medical profession and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations are applicable, of similar information received or otherwise obtained by the Secretary.

That proviso is necessary in order to insure a proper regard for the confidential relationships of the medical profession and its patients and also to provide, under certain conditions, for examination by those to whom the regulations apply of similar information received or otherwise obtained by the Secretary, or by the Department.

When regulating on the complex subject of recordkeeping and reporting by clinical investigators, the touchstone should be to place as few additional recordkeeping and reporting burdens on the clinical investigators as are absolutely required to insure a reasonable degree of safety.

Section 103(a) of H.R. 11581 would add a new subsection 505(j) to the act which would permit the Secretary to have access to data of manufacturers containing clinical results from the use of new drugs which are on the market pursuant to new drug applications. We favor this amendment in principle, but again suggest the adoption of the proviso contained in the Senate bill which I previously quoted, which also applies to subsection (j).

The comments in this statement on section 103 (b) and (a) of H.R. 11581 apply equally to sections 106 (b) and (a) of H.R. 11581, which relate to recordkeeping and reports about investigational use of antibiotics and clinical data for antibiotics which have been certified or released. Sections 106 (b) and (a) of H.R. 11581 would amend sections 507 (d) and (g) of the act.

My experiences lead me to the conclusion that the public health of this Nation has been well protected under the existing drug and biological laws.

I hope that the committee, should it report out a bill, will in its report call attention to the urgent need for a continuing flow of new and useful drugs and will emphasize the importance of requiring only those records and reports that are necessary to help assure safety without overburdening clinical investigators with nonessential paperwork.

Finally, members of the Pharmaceutical Manufacturers Association wish to cooperate fully with the FDA in providing essential information with respect to the investigation of new drugs and reports on already approved drugs, and we wish to assure the greatest possible safety for all people for whom drugs are prescribed.

The CHAIRMAN. Doctor, thank you very much for your statement on these two sections of the bill. We are very glad to have your advice and your suggestions.

Mr. Dingell, any questions?

Mr. DINGELL. No questions, Mr. Chairman, thank you.

The CHAIRMAN. Mr. Schenck.

Mr. SCHENCK. Thank you, Mr. Chairman.

I appreciate seeing Dr. Scheele again and having him before our committee.

Dr. Scheele, there is one aspect of your statement which bothers me a little, and that is at pages 6 and 7 you seem to emphasize that reporting should be kept to the basic necessary minimum.

All of us who have had a great deal of experience with the law of various and sundry reports that have to be made at various times, and they do require a tremendous amount of time, yet it would seem to me it is quite essential, and I do not know how you can determine which is nonessential paperwork. I do not know whose judgment

will decide nonessential paperwork, and it would seem to me that it would be very important to have full and complete reports in order to evaluate some of the experiences with these drugs.

Dr. SCHEELE. I agree with you, Mr. Congressman.

Actually, of course, the amount of recordkeeping that will be required is going to be determined by the Food and Drug Administration.

I think our plea here is to them not to develop a lot of, say, pro forma reporting which may not be applicable to a drug on trial of a certain type and in a certain kind of field.

The kind of records required, the kind of reports on patients will vary depending on the disease being treated or the patient being treated.

It would not be appropriate, for example, to ask for a chest X-ray on every person being treated with a new drug.

Our plea, Mr. Congressman, here is for the exercise of scientific reason and requiring only those things necessary to enable the Food and Drug Administration to make a judgment on the safety aspects of a drug, and the other aspects they wish to consider.

Mr. SCHENCK. Dr. Scheele, we have been hearing a discussion about inadequacy of information going back and forth between various nations of the world in the development of drugs and the treatments.

Now, is not the World Health Organization supposed to be an organization to improve, encourage, and do this sort of thing? Weren't you very closely connected with that operation?

Dr. SCHEELE. Yes, sir; I was. I served as chairman of the U.S. delegation to that Organization's annual meeting for many, many years.

The World Health Organization, of course, could play a role. I think all of us here would have to say that something does remain, something is desired, in communication as between countries, as between physicians in countries, as between pharmaceutical companies in various countries, and as between health departments and the World Health Organization in that same role.

I think that the recent events on thalidomide will certainly help everyone now be more acutely aware of this problem, and I think in the future we will see a lot more flow of information.

On the other hand, I must point out that information develops in a sort of scattered way. We may have a drug which seems completely safe, and after using this in very large numbers of patients, a physician may see a certain kind of side effect which no one else has paid much attention to or maybe nobody else has seen. He probably will not pay much attention to it either because he sees many side effects that are not side effects of the drug. He knows that people on sugar pills have side effects.

So until someone becomes acutely enough aware to recognize that there may be some drug relatedness, no word is spoken. The company does not know, other physicians do not know.

In the ordinary course of events, one or two or three people may become suspicious, they may compare notes. At this point it becomes apparent that several factors are coming up in common.

Then again depending on the interests of that physician or those physicians, this may come into open medical records, shall we say, or it may not.

If they are men who feel they must make a public report of this, that is to the medical profession, they may go before a scientific society, they may send a letter to a journal, and by this device the effect may be reported.

So there is a timelag in this process, but I think that the job is to minimize that timelag and is to exchange as much information as we can.

Mr. SCHENCK. You have to develop a better common denominator.

Dr. SCHEELE. That is right. There are dangers, however, of course, that must be recognized, too, in trying to find a lot of side effects and communicating a lot, too.

Many times there may be what are thought to be side effects in a drug which are not or which may be unimportant, and a great deal of harm can be done. We can take away from the patient some of the confidence the patient has in his physician and drugs.

We can make patients afraid even of good things and things without serious side effects.

We must also recognize—and this is something I said to a House appropriations subcommittee quite a few years ago when a certain tranquilizing drug was developed—that as we go forward in treating and curing some of man's serious illnesses, it is going to be very difficult to find ideal drugs which will operate only on that one condition.

The body is a very complex biochemical mechanism. There are a multiplicity of reactions which go on in a very short time. The body can take basic building chemicals, building blocks, and pass them through various chemical processes literally by the hundreds, literally in seconds, literally in minutes that in test tubes may take hours, days and weeks to do. So it is not very likely that ideal things will come along that will not cause some side effects.

So this is why it is very difficult sometimes to explain these things to the public or to the patient.

These are very highly complex scientific matters, and when we say side effects, we always have to say on which drug, treating which condition.

As a matter of fact, the very drug that I am referring to that I mentioned to the appropriations subcommittee a number of years ago, was a drug that was at first rejected by a series of pharmaceutical companies in the United States. It was developed overseas to be an antihistamine, and they found that it was not enough better than, in fact, it seemed to be inferior to, antihistamines then available on the U.S. market for physicians to use, hence they rejected it.

It turned out that a side effect of the drug, a tranquilizing effect, a drowsiness-causing effect, was accidentally discovered by two French clinicians who were testing it for the other purpose on mental patients in two mental institutions, one in Paris and one adjacent to Paris, and showed the great virtues of this drug as a tranquilizer. Suddenly there was born a whole new field of medical drug therapy which has kept the number of beds and patients in mental hospitals from growing.

So we cannot—we have to be very careful about this absolutism of all black and all white. There are many shades of gray and this, I think, is what Dr. Keefer was referring to as judgmental matters. This is why, I know, it is very difficult for this committee in a sense to set up all the safeguards necessary to assure absolute protection.

You cannot legislate out all side effects. We may want to use them as methods of therapy.

We may sterilize our progress in the United States, in part, if we work too hard to make everything safe. So we have to depend then on the judgment of competent scientific people, competent physicians, who understand clinical investigation, understand the application of biostatistical procedures and on our folks in the Food and Drug Administration to arrive at these judgments soundly and scientifically.

Mr. SCHENCK. Thank you very much.

The CHAIRMAN. Mr. Younger?

Mr. YOUNGER. Thank you, Mr. Chairman.

Just one question, Doctor.

We are glad to see you back.

Dr. SCHEELE. Thank you, sir.

Mr. YOUNGER. On page 6, the proviso that you propose, will you enlarge a little bit on "shall have due regard for the professional ethics of the medical profession"?

What do you mean by that?

Dr. SCHEELE. In the relationship between a physician and a patient, even as in the relationship between an attorney and his client, certain matters are confidential. We take a drug to a group of clinicians and we ask them to test it on patients on a protocol, a study design, and we ask them then to send us detailed clinical records on those patients.

Those records will probably contain the name of the patient, age of the patient, the vocation of the patient, data on where the patient lives, a lot of information on the patient.

Some patients, of course, would not mind having all this information become fairly public. Others would prefer to have things they tell the doctor remain confidential.

So this, in a sense, would be an instruction in the law to the Commissioner of Food and Drugs, to whom we give these data or who ask for these data in the preclinical testing period, to hold that as confidential, even as today, under the Food and Drug Act and under the Biologics Control Act, the Food and Drug Administration and the Public Health Service are forced to hold any data they get on manufacturing processes, and so forth, as confidential.

We primarily want this patient data to remain confidential as far as actual names go.

That is what the safeguard is that is asked for here, sir.

Mr. YOUNGER. If you had an agreement with the patient to start with, where he knew that he was a guinea pig in taking an experimental drug, would it be any easier to get that confidential information made available?

Dr. SCHEELE. Mr. Younger, the reason I am smiling is because if the patient is a perfectly healthy patient and all he has is a headache and that is what the physician is trying the new drug for, I am sure he probably would not care.

But if the patient, in addition to that, had a certain kind of illness, if his illness might, if it became public information, cause him to lose his job or somebody not promote him, or whatever it might be, it might embarrass him among his friends, he might prefer not to be identified.

Many patients do not like to even admit that they have cancer, for example. If we are trying a drug for something else, and the patient

has cancer of the lip or tongue or rectum, or whatever it may be, is it not in the best interest of the patient not to have his name made public with the clinical report?

To the Food and Drug Administration giving the record without a name is all right.

Mr. YOUNGER. Thank you, Doctor.

The CHAIRMAN. Doctor, thank you very much. It is a pleasure to have you back with us.

Dr. SCHEELE. Thank you. It is a pleasure being here.

The CHAIRMAN. Dr. Theodore G. Klumpp?

STATEMENT OF THEODORE G. KLUMPP, M.D., PRESIDENT OF WINTHROP LABORATORIES, AND A MEMBER OF THE BOARD OF DIRECTORS OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION; ACCOMPANIED BY LLOYD CUTLER, ESQ.

Dr. KLUMPP. Mr. Chairman, I will not take your time to recite my training and experience.

That is here on this mimeographed form, except to add that since this was mimeographed, President Kennedy announced my appointment to his Health Resources Advisory Committee.

The CHAIRMAN. Your background and experience will be printed in the record at this point.

(The biographical sketch referred to is as follows:)

THEODORE G. KLUMPP, M.D.

Born May 15, 1903. Married 1934, four daughters, two sons.

Bachelor of science from Princeton; doctor of medicine, Harvard; honorary doctor of science from Philadelphia College of Pharmacy and Science and New England College of Pharmacy; honorary doctor of laws, University of Chattanooga.

Internship at Peter Bent Brigham Hospital, Boston. Residency at Lakeside Hospital, Cleveland. Served in various capacities with New Haven Hospital and as instructor in internal medicine at Yale, prior to joining Food and Drug Administration in 1936 as Chief, Drug Division.

Joined staff of American Medical Association in 1941 as director of drugs, food, and physical therapy and secretary of council of pharmacy and chemistry. In 1942 became president and director of Winthrop Laboratories; is now in addition director and vice president, Sterling Drug, Inc.

Has served or is now serving Federal governmental bodies as member, Medical Advisory Committee, Office of Vocational Rehabilitation, Department of HEW; chairman, Medical Services Task Force, Hoover Commission; member, Study Committee on Federal Aid to Public Health, Commission on Intergovernmental Relations; chairman, Task Force on Employment of the Handicapped (Office of Defense Mobilization).

Service to private and civic organizations includes: vice president, U.S. Pharmacopeia Convention, Inc., and member of its board of trustees; member of the board of directors of Pharmaceutical Manufacturers Association; member committee on rehabilitation, American Heart Association; various committees of the American Medical Association; director, World Medical Association; member, board of directors, American Foundation for Tropical Medicine; numerous other organizations.

My name is Theodore G. Klumpp. I am president of Winthrop Laboratories, and a member of the board of directors of the Pharmaceutical Manufacturers Association. I was graduated from the medical school of Harvard University in 1928 and practiced at various hospitals in Boston, Cleveland, and New Haven, where I was on the faculty of the Yale University Medical School. I was adjunct professor of clinical medicine at the George Washington University

Medical School and attending physician at the Gallinger Municipal Hospital from 1938 to 1941. In 1936 I was appointed Chief Medical Officer and in 1938 became Chief of the Drug Division of the U.S. Food and Drug Administration and served in this capacity until 1941. I was vice president of the U.S. Pharmacopeia from 1950 to 1960 and was reelected to a second term, running from 1960 to 1970. I also served as Chairman of the Medical Service Task Force of the Hoover Commission and am presently a member of the Medical Advisory Committee of the Department of Health, Education, and Welfare's Office of Vocational Rehabilitation. In addition, I was Chairman of the Office of Defense Mobilization's Task Force on Employment of the Handicapped. I am a member of the Panel on Aging of the Department of Health, Education, and Welfare, and Chairman of its Subcommittee on Physical Fitness. I am a director of the U.S. Committee of the World Medical Association, a director of the American Heart Association, and chairman of its Committee on Rehabilitation. I am a fellow of the American College of Physicians and the New York Academy of Medicine.

Dr. KLUMPP. Mr. Chairman, I would also like to say at the outset that I recognize that this statement is long. It is the longest that you will be confronted with, so far as I know, today.

We regret that very much, and my collaborators and I have gone over this thing to chop it down and try to reduce it to its least common denominator, but, as it stands here, the thread of reasoning is such that we could see no way in which it could be further shortened except that, as I go along, I will try to eliminate some of the examples and extemporaneously try to shorten it.

I shall testify in behalf of the Pharmaceutical Manufacturers Association concerning section 102 (a) and (b) and section 104 (a) and (b) of H.R. 11581, which relate to the safety and effectiveness of new drugs, the definition of "new drugs," the filing of new drug applications and their suspension or withdrawal.

By way of introduction, let me say that the new drug provisions of the present Food, Drug and Cosmetic Act which were enacted in 1938 were drafted in close collaboration with the Food and Drug Administration. As Chief Medical Officer I participated in the discussions and councils that led to the adoption and enactment of these provisions. As Chief of the Drug Division I also participated in the formulation of the administrative policies and regulations by virtue of which the "new drug" and other sections of the law were enforced. I have had, therefore, the somewhat uncommon experience of working closely with the food, drug, and cosmetic law from two points of view: first, that of a law enforcement official, as Dr. Scheele was; and then as chief executive officer of a company whose responsibility it was and is to comply with this law and the administrative rulings pertaining to it.

Under the current law and system the drug industry has made great strides, particularly since World War II, and its discoveries have helped materially to make the health of the American people unequalled in the world. We of the drug industry accordingly believe that the matter of any changes should be approached with care, with full understanding of the philosophy of existing law, and with appreciation of the implications and consequences of proposed changes. At the same time, we recognize our public responsibilities and are not opposed to change as such, so long as it is constructive and maintains a proper balance between needed regulation and industrial freedom which together make up the public interest, the balance to which Mr. Beesley has referred. It is in this light that I intend to discuss the amendments proposed in sections 102 (a) and (b) and 104 (a) and (b) of the bill.

In substance and effect these provisions of H.R. 11581 broaden the definition of the term "new drug" to include drugs not generally recognized as efficacious; require that a new drug application must be affirmatively approved by FDA before it can become effective and before the new drug can be marketed; grant FDA the authority to reject a new drug application if the manufacturer has not convinced FDA that the drug is efficacious for use; and, give FDA the power to withdraw an effective new drug application if FDA entertains a substantial doubt as to the drug's safety or efficacy—such withdrawal to be effective in advance of a hearing if FDA feels that the drug presents an imminent hazard to the public health.

Let me state very clearly—these are radical, even revolutionary, proposals. The basic philosophy of our food and drug laws—the philosophy that was incorporated in the first Pure Food and Drug Act of 1906 and consistently and repeatedly reaffirmed ever since by the Congress, and particularly by this committee—is changed by these provisions of H.R. 11581 concerning "efficacy," "substantial doubt," and "affirmative approval."

That the Pure Food and Drug Act of 1906 did not seek to establish the Government as the arbiter of scientific or medical opinion was expressly stated in 1911 by Justice Oliver Wendell Holmes in *United States v. Johnson* (221 U.S. 488 (1911)). In holding that the 1906 act did not give the Executive power to decide questions of therapeutic efficacy, Justice Holmes stated for the Supreme Court: Congress—

was much more likely to regulate commerce in food and drug with reference to plain matter of fact * * * than to distort the uses of its constitutional power to establishing criteria in regions where opinions are far apart. (P. 498)

Again in 1916 with respect to the 1912 amendments to the Pure Food and Drug Act the Supreme Court stated, this time through Justice Charles Evans Hughes: "Congress deliberately excluded the field where there are honest differences of opinion between schools and practitioners (concerning therapeutic efficacy) * * *." *Seven Cases v. United States* (239 U.S. 510, 517 (1916)).

The great and extensive amendments of 1938 likewise reaffirmed this basic philosophy. As one court summed it up in 1944: "Plainly, therefore, the subject of regulation in the 1938 act, as in its predecessors, is matter of fact, not matter of opinion"—referring to the report of this very committee. *United States v. 7 Jugs, etc., of Dr. Salisbury's Rakos* (53 F. Supp. 746, 758 (D.C.D. Minn. 1944)).

This basic philosophy will be changed if the provisions of H.R. 11581 concerning "efficacy," "substantial doubt," and "affirmative approval" are enacted. Although these provisions have an attractive and apparent simplicity, the pharmaceutical industry faces a rule of men, not our traditional rule of law, if these provisions are adopted without change. Each of them shares this fatal flaw: they give to FDA authority to decide for industry, for practicing physicians and, therefore, for the public itself, complicated questions of scientific opinion rather than of fact, concerning what drugs should be available, and without application of objective and clear criteria or other safeguards. These provisions, in their present form, will upset the system which has played such a responsible role in this country's unmatched progress in medicine, and will impede the development of

CT

of
1938
ion
na-
om
ree
ory
of
use
ber
ind
U.S.
art
of

set
ou

me
on
ch
x-
les

is-
nd
w
a-

of
in
d-
is-
ge
he
ue
d.
k-
of
id
it
gs

at
re
d
ie
n-
n-
ie
p-
is
m
r.
ie
)

new products which are essential to that progress. Accordingly, we are opposed to these provisions of H.R. 11581 as they stand and, while we are in sympathy with the objectives sought by some of them, we believe that certain modifications are essential if they are to be adopted, as I shall now discuss in detail.

THERAPEUTIC EFFICACY

Let me first discuss section 102(b) of the bill, which would require new drugs to be cleared by FDA for efficacy, in addition to safety as at present. We fully endorse the principle that a drug should be effective—that it should have the effects which its manufacturer claims for it—and we are not opposed to having this principle properly reflected in the statutory provisions applicable to new drugs, although under section 502(a) of the act it was and is a crime to market a drug that is not effective as claimed. Obviously, drugs should be effective as well as safe. While the present new drug sections of the law deal only with safety, FDA nevertheless does consider effectiveness when passing on new drug applications. If FDA desires confirmation of its power to pass on the effectiveness of new drugs, we have no objection, so long as appropriate safeguards are included in recognition of the difficult problems involved in determining efficacy. I will discuss these problems first to show why safeguards are necessary, and then state what safeguards we believe should be added if the concept of efficacy is included to the law.

Efficacy has a deceptively simple and attractive sound, but it raises a host of problems which I feel need to be discussed in some detail so that this committee may have a full understanding of the matter. In the entire realm of medical science nothing is more difficult and more subject to honest differences of qualified opinion than the determination of the therapeutic effectiveness of drugs in human beings. The Supreme Court of the United States recognized this truth as early as 1902 in the famous *McAnnulty* case (187 U.S. 94 (1902)), and, as I pointed out earlier, our food and drug laws have been based upon this premise from their inception right up until today.

Despite advances in scientific techniques, therapeutic representations and claims remain essentially matters of opinion. Different schools of thought with respect to the proper treatment of various diseases are prevalent and sometimes completely contradictory. Not infrequently, it takes years and sometimes decades of widespread clinical experience to evaluate the true or relative merit of a drug in given conditions. From such long experience, a medical consensus generally emerges but even then some qualified physicians refuse to go along with their colleagues.

History teaches that authoritarian bodies have often been guardians of orthodoxy rather than champions of progress. Medical experts rejected Jenner's smallpox vaccine, Pasteur's anthrax vaccine, Lister's theory of antiseptics and Semmelweis' discovery of the cause of child-bed fever. Cod liver oil was rejected as worthless by the Council on Pharmacy and Chemistry of the American Medical Association. When Prontosil, the first sulfa drug, was introduced in the United States, it was greeted as another quack remedy by the outstanding American authority on infectious diseases and chairman of the U.S.

Army's Commission on Infectious Diseases. In the early 1930's, the same authority, unfortunately, dismissed early English reports on penicillin as incredible and refused to employ for clinical testing a culture of penicillium that had been brought to him by one of his associates, and that culture was poured down the sink.

The Committee on Medical Research of OSRD, faced with the problem of allocating a short supply of penicillin to the treatment of the most serious diseases for which penicillin was then known to be effective, refused to release penicillin for the treatment of sub-acute bacterial endocarditis because the initial dosage used experimentally by physicians had not proved to be effective, although subsequently when material became more readily available and larger dosage was applied, this drug proved to be a cure for what was until then a 100 percent fatal disease.

I would like to interpolate that before the outbreak of World War II, our military rejected Atabrine as a safe and effective treatment for malaria.

They scrambled to build up a stockpile of quinine, even recalling the small dribbles that lay on the druggists' shelves.

Atabrine subsequently proved to be not only safe and effective, but actually superior to quinine.

Dr. Keefer discussed the differences of medical opinion with respect to the drugs employed for the treatment of rheumatoid arthritis. He also referred to epilepsy, and the curious fact that one drug will be effective on a small proportion of cases and not at all useful in other cases. He also referred to the fact that if such a drug, effective in 20 percent of the cases, was submitted to the Food and Drug Administration, how would the Food and Drug Administration react toward it?

At the present time, there are sharply opposed views among experts concerning the proper treatment of many common diseases. Rheumatoid arthritis is such a condition. There are highly qualified physicians who favor the use of corticosteroid drugs. There are others who feel that the employment of the corticosteroids does more harm than good and that the only meritorious drug is aspirin. Still others are proponents of, respectively, Butazolodin, gold salts and antimalarial drugs such as quinacrine, chloroquine and hydroxychloroquine. The use of pyramidon, or large doses of vitamin D, still has adherents, and particularly among clinicians in foreign countries. The reaction of experts to any new drug offered for the treatment of rheumatoid arthritis will inevitably be conditioned by the school of thought to which they happen to adhere. By whose advice is FDA to be guided in the evaluation of a new drug for this condition?

Epilepsy is an affliction for which a variety of drugs is available. For reasons not now understood, any one of these drugs may be effective in some cases of epilepsy and worthless in others. If a new drug were found to fail in 80 percent of the cases in which it was tested and successful in the remainder, would it be released by FDA as "efficacious," or would the clinical testing required be so extensive and costly that no manufacturer could afford to carry through such a program for the possibility of gaining only 20 percent of a limited and already highly competitive market? If this were to happen, it might deprive a number of unfortunate epileptics of a drug uniquely

ngly, we
id, while
hem, we
adopted,

l require
afety as
ould be
facturer
roperly
lthough
t a drug
effective
the law
ffective-
res con-
ugs, we
uded in
efficacy.
e neces-
dded if

t raises
etail so
er. In
d more
rmina-
t. The
arly as
d, as I
l upon

esenta-
fferent
arious
Not
spread
t drug
sensus
use to

rdians
xperts
ister's
child-
ouncil
ation.
nited
nding
U.S.

effective in their particular cases. Much the same situation prevails today with the antihistamines. There are now over 30 different substances with antihistamine activity on the market. While they all share a basic antihistamine activity, yet the fact is some work for some patients while others work only for other patients. If H.R. 11581 were the law, how many antihistamines would we have?

Mucous colitis is a disease, the cause of which is still unknown. For almost a century, it was considered to be due to intestinal infection from an organism as yet unidentified. In 1924, Barger of the Mayo Clinic reported the isolation of a bacterium from cases of mucous colitis. This discovery was hailed as the revelation of the culprit responsible for the disease. It gave impetus to the use of antiseptic agents and later sulfa drugs and antibiotics in the treatment of the condition. Unfortunately, no drug was found to be uniformly successful and as a result other theories were advanced to explain the nature of the disease and to provide a rational basis for its treatment. Reputable surgeons, concluding that no drugs are effective, still remove large segments of the bowel. More recently, psychiatrists became convinced that the condition was due to emotional disturbances and represented nothing more than an extension of the well-known diarrhea of fear and fright. At the present time, these and other divergent schools of thought adhere to their theories. With all the various forms of treatment, some cases improve and others go on to death. Here again the attitude of medical officers of FDA, if given the authority to decide for all doctors the effectiveness of new therapies, will be conditioned by the theories which they happen to favor.

There is no known cure for the common cold. Many physicians are convinced that nose drops with vasoconstrictors, or antihistamines, or sulfa drugs, or antibiotics are helpful. Others believe that they do no good and may even be harmful. Some feel that a cold vaccine is effective in preventing a cold. Others consider such vaccines utterly useless. Who is to say which view is correct and impose his particular bias on the 180,000 practicing physicians who are sharply divided on the proper management of the common cold?

Spinal anesthesia with drugs of the procaine series is widely employed by anesthesiologists.

Here, again, we have a serious difference of opinion. One investigator reported the successful use of this form of anesthesia in over 50,000 cases. Numerous anesthesiologists have had similar and perhaps even more extensive favorable experience. However, some equally expert anesthesiologists have found that unexplained and serious side effects occasionally result, and they do. The majority of the investigators favor the use of these drugs because they believe their superior effectiveness offsets the risk of occasional serious side effects. Other investigators will not use them. They think the dangers outweigh the benefits. What will be the fate of a new drug application for a drug of this kind, if the medical officers of FDA happen to share the view of the latter school of thought?

The above specific illustrations are only a few of the many that can be cited to show that—

(a) The determination of the effectiveness of a drug is always difficult and sometimes cannot be achieved except by the test of time and widespread use.

ails
ub-
all
me
581

rn.
ec-
the
of
he
of
nt
ly
he
nt.
re-
es
rn
er
he
to
in
a-
r.
is
s,
lo
ie
t-
is
y

(b) Therapeutic representations are essentially matters of opinion.

(c) Differing schools of thought frequently exist concerning therapeutic issues, and the school which favors one theory as to the nature and treatment of disease tends to be skeptical of the drugs advocated in opposing schools. Moreover, medical opinions as to effectiveness of a particular drug can differ widely among equally qualified physicians because of basic differences in opinion relating almost entirely to questions of diagnosis and preferred method of treatment, as well as differences as to the comparative efficacy of one member of a class of drugs in relation to others or the mode of action of a particular drug in the complex body mechanism.

I might also add that the present law recognizes specifically two systems of medicine: the homeopathic system and the allopathic system, and provides different textbook standards for each of those systems of medicine.

(d) Initial authoritative opinion concerning the effectiveness of new drugs has often proved to be wrong.

(e) Where a drug is useful for only a small number of patients, or where the incidence of a disease is small, the expense of extensive clinical trials to provide conclusive evidence of usefulness may deprive patients of such drugs.

The foregoing examples and considerations point up the difficulties and the danger inherent in giving FDA the authority to pass explicitly on "efficacy." They serve to explain why it has been decided on previous occasions that FDA should not have such authority. As a former official of FDA who participated in the councils of FDA concerning the Federal Food, Drug, and Cosmetic Act in 1938—especially the new drug provisions—I can state that FDA at that time did not want to assume the awful power of deciding this complex question. FDA then felt that it was best and wisest for all concerned to leave these decisions to the physicians of the world who in the final analysis must be assured this freedom if they are to practice their profession in a rational and responsible manner. In this connection it must be kept clearly in mind that FDA then and now has full authority to rid the market of products whose claims are not supported by honest, reputable medical opinion. FDA has consistently and successfully invoked this power thereby protecting the public health and responsible manufacturers.

The question of including "efficacy" as a standard in the law was also considered by the Congress as late as in 1951 in connection with the Durham-Humphrey amendment to the Food, Drug, and Cosmetic Act and was rejected.

The majority report No. 700, issued by this committee, dated July 16, 1951, which accompanied H.R. 3298, included the following statement:

The standard which the bill, as amended, would write into the law (subparagraph (B) (1) of the amendment) contains the words "efficacy" and "efficacious." The use of these words has given rise to some apprehension . . . that the Federal Security Administration—

which was then the parent organization—

might have the power to determine which drugs are "efficacious" or "effective" and which are not. It may be stated unequivocally that this provision is not in-

tended to grant any such power to the Administrator, nor does it lend itself in any way to such an interpretation. (P. 11.)

On the floor of the House, when the bill was being discussed, a distinguished member of this committee, Mr. Roberts of Alabama, who, I am pleased to note, is still a member, stated as follows:

Mr. Chairman, when this bill was being considered in committee there was quite a difference of opinion as to the meaning of the word "efficacy" and the meaning of the word "efficacious." Webster's Dictionary defines efficacious to mean possessing the quality of being effective. Many of us feel perhaps that it is too broad, and in fact many of us voted to strike those words out in committee. I feel the bill will be just as good and will accomplish the same purpose and will answer some of the objections being made along the line that we are giving too much power to the Administrator.

Mr. Roberts' motion was passed on the floor and the efficacy provisions were stricken from the bill thus keying the standard of what drugs must be sold on prescription to those that are not safe for self-medication. This, I submit, after 24 years, has been a satisfactory and workable standard.

Now I come to the safeguards which we think are essential if FDA is given the power to pass on the efficacy of new drugs. In the light of the problems and considerations I have mentioned, we believe that the following should be reflected in any amendment on the subject:

(1) The terms "effective" and "effectiveness" should be used instead of "efficacy" and "efficacious". The latter terms tend to connote a curative result. The test should be whether the drugs will have the effects—the biological or pharmacological activities—claimed by their producer, which a physician may desire even though they may not find it possible to cure the patient.

(2) It should be clearly provided or understood that the test for effectiveness is whether a drug produces an effect in the body or is inert, not whether the effect is or is not desirable in the treatment of a given class of patients where medical opinion may differ according to basic differences in schools of medical opinion and thought.

(3) It should be clearly provided that a drug meets the test for effectiveness if there is substantial (but not necessarily preponderant) evidence that it has the effect claimed, and it should be understood that the authority to pass on effectiveness does not include the authority to consider the relative efficacy of one drug over another.

(4) There should be a specific provision that the new requirement of "effectiveness" shall not apply to old drugs already on the market or to new drugs which were cleared before the amendment, and such new drugs should be subject to withdrawal or suspension only on safety grounds.

In our view, the foregoing modifications are essential if we are to preserve the physician's freedom to prescribe as he sees fit and to encourage the development of new products. It would be perilous to rational medical practice and the public welfare to require that, before a drug can be marketed, its therapeutic effectiveness must be supported by all investigators or even by a preponderance of opinion. It should be enough if responsible and qualified clinicians have found that the new drug produces the claimed effect, although equally responsible and qualified clinicians have not yet found it to be effective or believe it to be ineffective. FDA should not be the arbiter of such conflicting views which necessarily involve large elements of subjective

opinion by qualified clinicians. Otherwise, we face the serious danger to medical progress inherent in a central authority where conflicting viewpoints in medicine will be indirectly resolved, as they are under a totalitarian system, and we run the very grave risk of recasting our system in a sterile, foreign mold and denying to physicians drugs which they may want to have for their patients.

What I am saying is equally relevant to the problem of research and development of new materials. It has been the experience of my company that the cost of development of a new drug for marketing is approximately \$5 million. I might add that the cost of other major pharmaceutical houses is about the same as ours. If it is made more difficult and more costly to bring new drugs to market because of added redtape and restrictions—if a new drug can be barred because of conflicting views, honestly held—but involving subjective judgments on its effectiveness—research is seriously threatened and indeed may be effectively foreclosed in the case of drugs for serious diseases which are not highly prevalent. It is vitally important that development of new products of potential public health significance not be shut off for such reasons, for the result will be to hamper seriously progress in the conquest of disease and the prolongation of life.

So we urge that, if "effectiveness" is added to the law, the safeguards I have outlined should be written in.

DEFINITION OF NEW DRUG

I come now to section 102(a) of the bill which would amend the definition of new drug to include drugs which are not generally recognized as "efficacious". We are opposed to this amendment as confusing and unnecessary. For almost 25 years the touchstone of whether an article is a new drug has been whether it is generally recognized as safe. That has been a satisfactory and workable standard. Under it, industry and FDA have been able to conclude, with reasonable certainty, what is, and what is not, a new drug. The proposal to add "efficacy" to this standard would cause confusion without benefit and would substantially destroy the workability of the standard. The conflicting views, often involving subjective judgment, which are frequent on the matter of "efficacy," would make it virtually impossible to determine what drugs are generally recognized as efficacious, and for a manufacturer to know when a "new drug" became an old drug, and therefore was no longer subject to the new drug procedures. Many unquestionably safe "old rugs" would have to be processed by FDA as "new drugs" to determine their "efficacy," and would probably have to be withdrawn from the market until FDA had cleared them. This would be wasteful, and would needlessly deprive patients of some drugs which they have been using for years. Such a situation could be catastrophic to them as well as to the manufacturer. It would also, and this is important, bog down FDA and industry with needless new drug applications.

They are having difficulty enough in handling the applications under the present provisions of the law.

As the Senate Report No. 1744, on S. 1552, dated July 19, 1962, points out, this would be unsound. No question of safety would be involved, and FDA presently has ample power, including seizure,

to proceed against any old drugs of unquestioned safety for which unsupported claims of effectiveness are made.

It is also unnecessary to amend the definition of new drug in order to give FDA specific authority to consider the effectiveness of new drugs, which we have conceded they should have. By retaining the present definition FDA will be assured of having submitted to it for clearance under the new-drug procedures all genuinely new drugs, because as to them there will necessarily be a question as to safety. When the required new drug application is submitted—either for a new product or for a new use of an existing product which is not generally recognized as safe—FDA can pass on the question of the drug's effectiveness if that power is given to it. That is the power FDA seeks—the specific authority to consider effectiveness in passing on new drug applications—and that is all that should be given to FDA. It is accordingly unnecessary to amend the definition of new drug to include "effectiveness," and such amendment should not be made because it would only produce needless confusion as I have pointed out above. We agree with the Senate Report No. 1744, on S. 1552, dated July 19, 1962, which states at page 17—

that there is no basis for the concern which has been expressed that if the definition of new drug is not amended to refer to effectiveness, a drug once cleared for the market under the new drug procedures as a tranquilizer, for example, could subsequently be marketed for some other use without going through the new drug procedures as to such use.

As that report points out, this is not true under existing law and would not be true under the law if it is amended to give FDA specific authority to consider effectiveness. Any such new use would have to be submitted under a supplemental new drug application and would have to be cleared for safety under existing law, and also for effectiveness if that power should be added to the law.

AFFIRMATIVE APPROVAL AND TIME LIMITS

Section 104(a) of H.R. 11581 would make two basic changes in existing law. It would require FDA to affirmatively approve new drug applications, instead of letting them become effective unless the FDA disapproves them. It would also extend the time limits for action.

We are opposed to requiring affirmative approval of NDA's. It shifts the responsibility for products from the manufacturer to FDA, it places a very heavy burden of decision on the personnel of FDA, and the inevitable result will be undue delay in the introduction of new drugs. The consequences of that are serious indeed. We have heard much about making sure that dangerous drugs do not get on the market inadvertently, a situation which in 24 years has not arisen in practice. Just as important, however, is the drug that wasn't there—the drug which has been delayed from coming on the market by misplaced caution and which, if it had been available, would have saved lives.

As an official of FDA at the same time the present law was adopted, I can say that the present procedure is what FDA itself wanted. It was then the considered opinion of FDA that it would be unwise for FDA to be placed in a position of having to affirmatively approve each application. FDA recognized then and for many years that this

was unwholesome prior censorship, that it placed an impossible burden of decision and responsibility on the individual employee involved, and that the result would be needless delay and misplaced caution. This conclusion was reinforced by the view that if FDA had affirmative approval power its exercise would be interpreted by the physicians and the public as Government endorsement of each new drug placed on the market.

FDA's position on the matter in 1938 sprang from its realization of his historic and intended role as an agency of Government which saw to it that manufacturers produced pure products, properly labeled, and adequately tested and not an agency which established or enforced "official" medical or scientific opinion. Moreover, FDA was mindful of its early experience under the Pure Food and Drug Act of 1906. That act required that a manufacturer make to the trade certain guarantees that his product complied with the act. Shortly after the act went into effect, a custom arose of manufacturers placing prominently on their package a statement to the effect that the product was "guaranteed under the Pure Food and Drug Act of 1906." When segments of the public took these statements to mean that the Government had approved the product when actually it had not, FDA issued a regulation forbidding such statements from appearing in labeling. This experience with the favorable reaction of the public to any product that seems to be approved by the Government convinced FDA personnel that if FDA actually had such authority the consequent responsibility and demands of the public would be unbearable burdens. I see no reason to suppose that the public would react any differently or expect any less today if FDA were granted the power of affirmative approval. Likewise, I fail to see why FDA should now have the power which all along since 1906 FDA believed was unwise for it to have when the new drug provisions were enacted in 1938.

The drug manufacturers do not want to hide behind the skirts of Government approval. We are prepared to continue to be responsible for our products. If every new drug has to be affirmatively cleared by the FDA, pharmacists, physicians and patients will inevitably tend to relax their vigilance, and rely more strongly on the FDA approval. At the same time, FDA will become increasingly cautious over extending approval, and there will be inevitable delays. In an area where the safety of a product is not, and never will be, susceptible to absolute conclusions, and will vary from time to time, depending upon new knowledge and new conditions, it seems quite evident that many new drugs of enormous potential will be withheld from use for increasingly long periods. I cannot repeat enough how serious this will be.

I might also add that when new facts are found that show that a drug once considered safe is no longer safe, it makes the FDA look very foolish, having positive, affirmative approval.

So far as time limits are concerned, we have no objection to the provisions of section 104(a) of the bill which would lengthen the time for initial consideration of NDA's to 90 days and allow a total of 180 days for the Secretary to act or give notice of hearing. Actually, the time limits of existing law have not operated to deprive FDA of whatever time it thinks necessary to consider an NDA. Such

limits have not been a problem because of FDA's practice of requiring more information when it is unsatisfied, and industry's record of cooperation. For example, preliminary results of an industry questionnaire indicate that in 1961 about 60 percent of the NDA's filed took more time to process than the 60-day initial period fixed by present law. So far as we know, there are no instances in which a new drug application has become effective before FDA has satisfied itself as to the drug's safety for the asserted uses.

And I might add that if our experience is any criterion, our notice at the end of 60 days has not always arrived at the end of that period, and nobody had any question about going on the market.

However, we do object to the failure of section 104(a) of the bill to specify a time for beginning the hearing which the Secretary is to give notice of at the end of the 180-day period if he believes the application should not become effective. We urge that provisions be included requiring the hearing to begin within a specified period after notice, say 30 days or such further time as the Secretary and the applicant may agree upon, and also requiring that the hearing be conducted on an expedited basis. FDA should not be permitted to temporize and delay action or hearing indefinitely.

Commissioner Larrick, with the concurrence of Secretary Ribicoff, has conceded our points that the law should not be changed to require affirmative approval and to allow indefinite time for action. At the previous session of these hearings on June 19, 1962, Mr. Springer asked a series of questions about the record of industry cooperation in making sure that new drugs did not go on the market until FDA was satisfied of their safety and why in the light of that record there was any need for requiring affirmative approval and for allowing an indefinite time for action. In response, Commissioner Larrick yielded, stating after conferring with the Secretary:

If you were to add to the 180 days whatever length of time it takes to proceed with this hearing and to conclude it, then we probably would have enough relief. (Transcript, pp. 57-58)

That is the only relief which should be given—180 days for consideration of a new drug application, plus the time thereafter required for any hearing, which should be required to begin within a specified time and to be completed on an expedited basis. The law should not be changed to require affirmative approval.

WITHDRAWAL OF NDA

I turn now to the provisions covering the withdrawal of an effective new drug application by FDA. This is section 104(b) of the bill, which would amend section 505(e) of the Food, Drug, and Cosmetic Act. Of course, a withdrawal order when issued means that the drug in question must be recalled and may no longer be marketed under pain of criminal sanction. At present FDA may take such action only on the basis of new evidence showing the drug to be unsafe and after a hearing. H.R. 11581 would allow the extraordinary procedure of withdrawal if FDA has a "substantial doubt" as to the "safety or efficacy" of the drug on the basis of any evidence—even just the evidence in the NDA file alone. In other words, if FDA merely changes its mind, it may withdraw an NDA. Moreover, such

withdrawal could be accomplished in advance of a hearing if FDA finds that "an imminent hazard to public health" exists. In addition, withdrawal could be ordered because the applicant has failed to comply with any requirements as to records and reports; or because the facilities and controls used for the manufacture, processing, and packing of a new drug are then inadequate to assure and preserve its identity, strength, quality, purity, safety, and efficacy; or because any one of several technical conditions on which the application was approved has been violated.

We do not oppose the idea behind the proposed amendment—that the present standards for permitting FDA to suspend a new drug application may be too rigid and should be relaxed. However, we believe that the amendment goes much too far and that certain modifications are essential as a protection against hasty, ill-advised, and arbitrary administrative action which will be detrimental to the pharmaceutical industry and its ability to serve the public. Our concern centers on the provisions allowing suspension for "substantial doubt," for failure to keep records and so forth, and for immediate suspension without hearing.

1. "Substantial doubt" is a slippery phrase and when it is used in connection with such troublesome concepts as therapeutic "efficacy" and "safety," it becomes absolutely perilous, especially if action can be taken before any hearing. For the reasons given in my discussion of efficacy, and what I am about to say on safety, this power will allow complete censorship and justify essentially dictatorial action on the part of FDA. And we get no comfort from the efforts of Deputy Commissioner Harvey to give substance to the term "substantial doubt," in response to questions by Mr. Rogers at the hearing on last August 6 before the Health and Safety Subcommittee of this committee on H.R. 12437—I refer to pages 32-33 of the transcript of that day.

Since this provision of the bill would expand FDA power over consideration of the safety of new drugs, I would like to discuss therapeutic safety for a moment. As I have previously said, therapeutic "safety," like therapeutic "efficacy," is a relative term which involves opinion and judgment. Although therapeutic "safety" may involve less of the element of subjective opinion and be more demonstrable, it is not an absolute concept. Indeed, it is a rare drug that will not have some toxic effects on some people, and physicians have to take the element of risk, or lack of safety if you will, into account in deciding whether to use a particular drug for a particular patient. Because of this, physicians can and do differ in their opinions of whether a drug is safe for use—whether the situation presented justifies running the risks involved—just as they can and do differ in their opinions of a drug's effectiveness. Penicillin, for instance, is generally regarded as a safe drug, and yet in the 5 years period, 1953 to 1957, a nationwide survey reported 2,517 reactions to this drug and 82 fatalities. In another survey conducted by the World Health Organization of the United Nations, the incidence of reactions to penicillin was found to be 1.5 percent with fatalities occurring in 1 out of 95,000 patients treated. On the other hand, a drug would not generally be considered safe by physicians if it were used for some minor ailment, such as acne or headache, and caused a similar number of reactions and fatalities. In

other words, since the question of therapeutic safety may involve judgment, risk and other variables such as the patient's general health, it can be in many instances a complete matter of opinion on which honest differences can simultaneously exist.

That in most cases therapeutic safety is actually a relative matter and, therefore, a question of opinion is recognized by the agency to which this law will be assigned, FDA. Commissioner Larrick on May 18, 1962, made the following statement to the Antitrust and Monopoly Subcommittee of the House Judiciary Committee in testifying on H.R. 6245 which also seeks to amend the food and drug law:

Mr. LARRICK. As I stated earlier, in response to a question, there is no drug, hardly, which is innocuous, so there is no drug which is safe in an absolute sense.

Mr. LARRICK. So, to determine whether or not the drug is safe within the statutory meaning, we always have to put on the scale on one side the good that the drug will do, the people that it will cure, the lives that it will save, and the suffering that it will prevent.

We put on the other scale what we know about the harm it will do, and if the harm outweighs the good we deny the application—

subjective judgment—

If the good outweighs the harm, we pass the application * * *

Mr. Larrick's concept of this matter is not personal to him. It is the official FDA position. For example, Dr. W. H. Kessenich, Medical Director of FDA, expressed the FDA's role and procedure this way in the January-February 1962 issue of *Clinical Pharmacology and Therapeutics*:

Safety must be considered largely from a relative point of view. When the possible benefit is weighed against the possible harm of new drugs that have reached the market the scale will tip easily in favor of the beneficial effect they have—provided the balance on which they are measured is the sound professional judgment of a well-informed practitioner. (P. 54.)

Let me quote at this point from that part of the report of this committee approving the 1938 amendments to the Food, Drug, and Cosmetic Act which explains the "new drug" provisions:

Section 505(a) requires new drugs to be adequately tested before they are commercialized. In order to insure that the tests made have been complete, the introduction of a new drug into interstate commerce is prohibited unless the manufacturer has submitted full information showing that the drug has been adequately tested and has not been found to be unsafe for use under the conditions prescribed in the labeling. This is not a license provision but is intended merely to prevent the premature marketing of new drugs not properly tested for safety * * *

This provision will not put the Federal Government into the business of developing new drugs, nor will it require the Government to duplicate laboratory and clinical tests made by responsible manufacturers. The provision merely sets up a method for the authoritative review of the manufacturer's tests and will not unreasonably delay the introduction of new drugs in the market. (P. 9.)

This language and the history of this act indicate to me that Congress did not intend FDA to be the final arbiter of medical opinion on matters of therapeutic safety—to decide for physicians what drugs they may use when honest differences of medical opinion exist. We must remember that under present law FDA has tremendous authority over labeling and may and should require full disclosure to the physicians, including disclosure of any differences of opinion that may exist as to risks, side effects, contraindications, and so forth. FDA

should see that physicians are fully informed, not that they may not form their own opinions as to whether it is safe to use a drug in a particular situation in the light of all the circumstances.

However, if Congress now gives to FDA authority to withdraw new drugs from the market because of substantial doubt as to their safety or efficacy, FDA will become the final arbiter of medical opinion on matters of safety and efficacy, the physicians will have their decisions made for them, and industry will be living under a continual threat. Given the fallibility of man, the conflicting opinions which can arise, and the pressures which can be generated, FDA will naturally feel compelled to exercise its sweeping withdrawal power every time its judgment in passing a new drug for the market is subsequently questioned in any degree. The resulting impact on drug manufacture and research and the practice of medicine is a grave thing to contemplate.

Complaints of many different side effects from even the most ordinary product such as a vitamin preparation come to us very frequently. It is very difficult to sift out these complaints and weigh their validity. This is done, however, and most of them turn out to be groundless. With the proposed authority of this bill and the legislative mandate that will follow from its adoption, however, FDA will be put in a position of withdrawing new drugs as soon as any question is raised. One or two incidents of this type with subsequent newspaper publicity can undermine the confidence of the medical profession and the public in good and safe medicine. Once shattered, this confidence is always difficult to reinstate and sometimes impossible. Thus the public will be deprived of good and lifesaving preparations without good cause. In these situations administrative officials will probably adopt the course of least resistance and the course least subject to criticism. That course will be to withdraw first and restore later if subsequent investigations show the error of the initial withdrawal—but by that time irreparable damage to the product and to the public confidence will have been done.

We accordingly urge that the power to suspend because of "substantial doubt" should not be given because it will adversely affect the public health by interfering with drug research and manufacture and the practice of medicine. Let me cite one example in which the power to remove a product from the market because of substantial doubt would probably have been exercised had FDA possessed it. You can judge the consequences. Dr. Harvey W. Wiley, as this committee knows, is generally considered the father of the pure food and drug law of 1906 (it is still popularly called the Wiley Act). He was its first administrator as Chief of the Bureau of Chemistry of the Department of Agriculture. Dr. Wiley himself has published this story and other authors have corroborated it. Dr. Wiley in 1908 conducted a series of tests from which he concluded that benzoate of soda—a common food preservative—and saccharin—as you all know, a universally used artificial sweetener—were injurious to the health of users and specifically requested President Theodore Roosevelt to ban their use in foods and drugs. Of course, no one has ever accused Dr. Wiley of improper motives or of rigged research. His integrity and good faith are beyond dispute. In fact, that is what sharpens the point of the incident. Apparently only because President Roosevelt's own physician had previously prescribed saccharin for him was the Ameri-

involve health, which

matter to look on; and testimony: drug, solute

in the good, and of the

It is rich, lure ogy

the have hey fes-

m-os-

are the the en di-ed

te-ry if id .)

1-n s e e y l

can public spared the enormous loss, inconvenience and wrong that would have followed the banning of these safe and highly useful ingredients. Dr. Wiley has stated that the President had decided to follow his advice on benzoate of soda and reversed it only on learning of Dr. Wiley's position on saccharin. According to Dr. Wiley, President Roosevelt characterized Dr. Wiley's position in these words: "Anybody who says saccharin is injurious to health is an idiot."

We fear that adoption of the "substantial doubt" provisions of H.R. 11581, without change, will make probable a repetition of incidents like this, but without the happy ending that this one had because under H.R. 11581 FDA will not have to ask the President or the Congress—indeed, it may create the unfortunate result without a hearing at all. So we urge that the nebulous concept of substantial doubt be rejected, and submit that the purpose for which it is intended will be fully served by amending the law to provide that a new drug can be taken off the market if new evidence shows that it no longer meets the test for going on the market—that is, if the drug is no longer shown to be safe. This will relieve FDA of the present burden, which it deems too onerous, of proving that a drug is unsafe, and at the same time will protect industry against all the uncertainties which are wrapped up in substantial doubt.

(2) We are also opposed to the provisions for suspension for failure to keep records, to make reports, or to maintain manufacturing standards. Those provisions require the Secretary to suspend if he finds such a failure. He is given no discretion, even though the failure may be minor or inadvertent in nature and have nothing to do with the safety of the new drug. If a matter of safety is involved, suspension can be invoked on that ground. If safety is not involved, other sanctions of the act, such as criminal penalties, seizures, and injunctions, are adequate to enforce the obligations to keep records, to make reports, and to maintain manufacturing standards. The drastic remedy of suspension should not be added.

(3) The power to suspend prior to hearing, as I have reiterated, is drastic indeed. It is contrary to our traditions of due process and it poses fearful consequences for our industry. Once a product is so withdrawn, with all the attendant publicity, it is finished for practical purposes, even if the withdrawal was an honest mistake in judgment which government as well as industry can make. We are accordingly strenuously oppose the grant of this sweeping power of sentence first and verdict after. We think it is unnecessary. The Secretary already has a broad range of sanctions available—criminal proceedings, seizures, injunctions, and public warnings—which are adequate to protect the public.

He also has one very important additional protection. He has the cooperation of our industry when any serious question arises.

Through 24 years we have demonstrated the willingness, the public sense of responsibility, of this industry, and we have cooperated.

The pharmaceutical manufacturers are as concerned as the Government to prevent the marketing of dangerous drugs and we believe that FDA will agree that we have met our responsibilities in that regard.

(4) Finally, the evidence supporting suspension should be new evidence, not available when the application became effective. FDA

should not be permitted merely to change its mind on the basis of unchanged evidence.

To sum up, the objections we have to the broad suspension provisions of section 104(b) of the bill would be met, and the public would be fully protected, if section 505(e) of the act were amended to allow FDA to take new drugs off the market if new evidence shows that such drugs no longer meet the standards for letting them go on the market. That would relieve FDA of the present burden, which it deems too onerous, of proving that a drug is unsafe in order to suspend it—instead, the drug could be suspended if it is no longer shown to be safe. At the same time, such an amendment would not pose the threat to continued progress in drugs and medicine which we see in the drastic provisions of section 104(b) and their possible abuse, however well intentioned any particular action thereunder may be. And, if effectiveness is added to the standard for new drug clearance with the modifications I have urged, suspension would likewise be allowed if there is no longer substantial evidence (not conclusive or preponderant evidence) of effectiveness. That would permit a drug whose effectiveness continues to be supported by substantial evidence to remain available for prescription in the judgment of physicians, even though other evidence may create substantial doubt as to its effectiveness. However, if effectiveness is added as a requirement for new drug clearance, there should also be a grandfather clause exempting previously cleared new drugs from suspension on "effectiveness" grounds. Otherwise, manufacturers who had in good faith introduced a drug on the market before FDA was authorized to consider effectiveness could be penalized by having their investments destroyed even though no question of safety is involved.

CONCLUSION

I close with these thoughts:

Disease, disability, and premature death are man's greatest enemies. They are in every home, rich and poor alike, and the seeds of their destruction lie within each one of us.

Whether you or I live, suffer, or die depends on our physicians and the weapons that are placed in their hands. The pharmaceutical industry is the principal arsenal of these weapons. In large measure, through the research, skill, and know-how that our scientists have patiently developed, we have made more gains in the last half century in the conquest of disease and the prolongation of life than has been achieved in the entire 999 centuries of man's previous existence on earth. And yet our work has just begun. Not a single disease has yet been completely eliminated, and so much remains to be done.

You have heard it expressed in different ways, but to me the basic issue in these hearings is this:

Any legislation in the field of drugs must strike a delicate balance between Government control and freedom to develop and use new products for the conquest of disease.

Whatever safeguards may be needed against substandard practices and manufacturers should be drawn so as not to hobble responsible members of this lifesaving industry with unnecessary redtape, delay, and governmental restrictions. The American people cannot afford

to take a chance on bureaucratic controls which will stifle progress in drug research and in the practice of medicine. That to me, gentlemen, is what these hearings are all about, and that is why I urge the changes in the bill I have discussed.

The CHAIRMAN. Dr. Klumpp, you have given a very detailed analysis of the provisions in this bill from your standpoint, which I am glad to have.

Mr. Dingell?

Mr. DINGELL. Yes, Mr. Chairman.

Briefly, sir, I ask you if you would tell us which sections of the bill you do favor without reservation?

Dr. KLUMPP. Well, Mr. Dingell, there is a great deal in this bill that we do favor with some qualifications and with some amendment. We favor the general purpose of this legislation. We are in accord with it.

The reasons, the arguments that I have given in my presentation as to why certain provisions should not be enacted in their form as they appear in this bill, speak for themselves.

I am not wholly prepared to go through this bill at the present time—I have not marked it up—and tell you which we favor and which we do not.

I hate to shove the burden on my counsel here, but he is in detail more familiar with language and the rest of it.

Mr. DINGELL. The reason I asked that:

Let me say I want to commend you for a very fine statement. I think you have done an excellent job, and your work here in the committee today shows that you have prepared carefully, and I think you have made a very fine statement.

Dr. KLUMPP. Thank you.

Mr. DINGELL. But in fairness I am sure you recognize the Administration has worked very hard to get to this committee a good bill.

Dr. KLUMPP. We recognize that.

Mr. DINGELL. Which, in its opinion, is a good bill.

For example, I note here that you say, speaking on behalf of the industry, that you do not like the idea of "efficacy." You want it changed to "effectiveness."

Then a little later you indicate to the committee that you do not favor "effectiveness," the test of effectiveness, to be applied to new drugs, and then later you say you want the "effectiveness" to be applied to old drugs.

Dr. KLUMPP. Oh, no, no.

We think that the test of effectiveness, Mr. Dingell, should be applied to new drugs. We support that when it is based on substantial evidence of effectiveness.

Mr. DINGELL. I see.

But you do not want it applied to old drugs, drugs which are already on the market?

Mr. CUTLER. Mr. Dingell, drugs already on the market can be taken off the market by action of FDA, if they are worthless drugs.

Mr. DINGELL. If they are worthless?

Mr. CUTLER. If FDA can prove—

Mr. DINGELL. But not according to the same criterion that you would have?

Mr. CUTLER. No, sir.

Mr. DINGELL. With regard to new drugs?

Mr. CUTLER. Yes, they can.

If FDA can prove to a court that a drug already on the market is not effective for the purposes claimed in the labeling, the court under this law is required to withdraw the drug from the market and FDA can start the proceeding by seizing the drug.

Mr. DINGELL. In other words, FDA, to all intents and purposes, must show by the preponderance of the evidence. The function of this bill is to shift the burden of proof. I am sure you agree with that?

Mr. CUTLER. That is very definitely the purpose of this bill with regard to effectiveness, which we oppose, Mr. Dingell.

Mr. DINGELL. So that you oppose the concept of a change of burden of proof with regard to effectiveness?

Mr. CUTLER. That is correct.

Mr. DINGELL. Especially so in the case of old drugs, drugs which are already on the market?

Mr. CUTLER. Both new and old drugs.

Mr. DINGELL. I see.

Now, I want to read something. I checked up on my quote here from the President's Consumer Report, where the following statement was made:

For example, over 20 percent of the new drugs listed since 1956 in the publication New and Non-Official Drugs were found, upon being tested, to be incapable of sustaining one or more of their sponsor's claims regarding their therapeutic effect.

Now, do you think that that is a good situation for the protection of the American public?

Dr. KLEMPF. Mr. Dingell, if there is a drug on the market which does not provide the effectiveness that it claims, the Food and Drug Administration now has the authority to take the drug off the market.

And if there were 20 percent of those drugs, I would be very surprised that the Food and Drug had not acted.

Mr. DINGELL. Just a minute. You are not understanding my question here at all, because I say:

For example, over 20 percent of the new drugs listed since 1956 in the publication New and Non-Official Drugs were found, upon being tested, to be incapable of sustaining one or more of their sponsor's claims regarding their therapeutic effect.

I did not say these were worthless drugs.

Dr. KLEMPF. No, I did not either.

Mr. DINGELL. I just said that some of the claims made as to therapeutic effect were either false or incapable of proof.

Mr. CUTLER. Mr. Dingell, section 502(a) of this act says that:

A drug or device shall be misbranded if its labeling is false or misleading in any particular.

If its claim as to effectiveness is false or misleading, if the Food and Drug Administration can show that it is wrong, the Food and Drug Administration can start out by seizing the drugs in what the lawyers call a libel.

Mr. DINGELL. I am aware of this.

Mr. CUTLER. And on the basis of that, bring an action in the court.

Mr. DINGELL. Why do you think that drugs should be permitted to enter the market, although, according to this very responsible source, where, in over 20 percent of the cases, some of the claims made in regard to these same drugs were found to be incapable of sustaining one or more of their sponsor's claims?

Do you think that a drug should be able to enter the market under these circumstances?

In other words, here is what we are faced with. These drugs come on the market. Then Food and Drug Administration can show these claims are false. Then they can libel, seize them, and so forth, but I am sure you are aware this is a very difficult legal process.

What I want to know is, Why should not a drug which is coming on the market be compelled to bear the same standards that it must bear once it is on the market?

In other words, should not these claims for efficacy or effectiveness be true when the drug comes on the market?

Dr. KLUMPP. Yes, Mr. Dingell.

We think that the standards should be the same for those drugs that are on the market as well as those that are proposed for introduction.

Now, I do not know where you got that quote or what its source was, where it came from.

Mr. DINGELL. I will give you the source right here. It comes from the drug industry antitrust hearings on Friday, May 18, in the Judiciary Committee of the House of Representatives, and the ultimate source is the President's Consumers Report that is quoted there.

Dr. KLUMPP. We agree.

The drugs should be considered for effectiveness before they are introduced on the market, Mr. Dingell, but the question is what the standards should be and how they are to be applied. I have tried to show that with respect to these elements we are in an exceedingly difficult realm.

You are not dealing with matters of exact science or the demonstration of absolutes.

You are dealing with relatives and with opinions.

Mr. DINGELL. I recognize this.

I am both a lawyer and previous to that time I had a degree in chemistry, so I have some familiarity, and, as a matter of fact, I worked on some of these food and drug cases that we are discussing, so I am aware of some of the scientific implications, although not as well aware as you.

But the simple question is: Does it occur to you that it is appropriate that we should say they can come on the market with just "substantial evidence"?

Dr. KLUMPP. I certainly do.

Mr. DINGELL. Whereas in any other situation we have to have a good deal more, in order to prevail in any other kind of legal proceedings you have to have a good deal more, and have to bear a good deal heavier burden of proof?

Mr. CUTLER. Mr. Dingell, may I as a lawyer speak now as a lawyer on this, sir?

Mr. DINGELL. Yes.

Mr. CUTLER. What we are saying in a capsule is that if there is a responsible difference of opinion among responsible clinicians, trained investigators, as to whether or not a drug is effective, the mere existence of a responsible difference of opinion, based on adequate and well-controlled tests, should be sufficient for the FDA to allow the drug on the market.

The FDA's role should be to decide: Is there a responsible difference of opinion; and, if there is, they should let it on the market, even though a numerical majority or a preponderance of evidence, or whatever else you might call it, might still be on the side that the drug is not effective or not proven effective.

That is what we are after.

Mr. DINGELL. Is this not a—

Mr. CUTLER. And that is what the Senate Judiciary Committee agreed on.

Mr. DINGELL. The Judiciary Committee where?

Mr. CUTLER. Of the Senate in S. 3352 and its report on that bill.

And I do not really believe we are in substantial difference with the administration on this point, sir.

Mr. DINGELL. I think there is a great difference between "preponderance of the evidence" and "substantial evidence," you will agree as to that?

Mr. CUTLER. Oh, certainly, but what I mean is that we believe that we and the FDA are close together on what the tests should be, and I think that may become apparent when they testify.

Mr. DINGELL. You also discussed here the matter on page 28 of your statement, you discuss here:

"There is no drug which is safe in an absolute sense."

I am sure you will agree that the statement of Mr. Larrick, which you quoted there, is substantially true; that no drug is absolutely safe, is this not correct?

Dr. KLUMPP. Yes.

Mr. DINGELL. And this being true, essentially Food and Drug, in permitting new drugs on the market, has to, for example, make such objective judgments.

In the case of penicillin, which you cited, penicillin is not absolutely safe, but it is safe enough for the conditions to justify the use, in other words, to justify the risk that must be taken in prescribing this drug, is that not true?

Dr. KLUMPP. It is true, but it is equally true that no two people will come to the same conclusion with respect to all drugs.

That is the problem.

Mr. DINGELL. I recognize this, the Food and Drug did allow penicillin on the market, did they not?

Dr. KLUMPP. Yes, of course, they did, and quite properly so.

Mr. DINGELL. And Food and Drug made the objective or subjective judgment, depending on how you choose to put it, with regard to this, and this was sufficient to admit penicillin, am I correct, to the marketplace?

Dr. KLUMPP. Yes.

Mr. DINGELL. All right.

Now, let us take a little different case.

Are you familiar with MER/29?

Dr. KLUMPP. In a general way, yes.

Mr. DINGELL. MER/29 was marketed principally as an anticholesterol substance, am I correct?

Dr. KLUMPP. Yes, sir.

Mr. DINGELL. And this substance marketed for its anticholesterol properties was suddenly determined to have other effects, am I correct?

It caused skin conditions; it caused hair problems including eyebrows and eyelashes to fall out and change colors; and, over and above this, in rather large quantities it was shown, with some degree of certainty, to have the effect of creating cataracts, am I correct?

Dr. KLUMPP. In some instances, yes.

Mr. DINGELL. Now, is it your view that this is a safe drug to be marketed?

Dr. KLUMPP. It seems to me that the fact that the company voluntarily withdrew MER/29 indicates the company's view that evidence developed subsequent to its marketing no longer allowed that drug to be considered safe.

Mr. DINGELL. I see.

Now, are you in concurrence with this?

Dr. KLUMPP. I do not know enough about the facts, Mr. Dingell.

Mr. DINGELL. All right.

Then let us put this in a different way.

If this drug had not been withdrawn, what would Food and Drug have been able to do to remove it from the market?

Dr. KLUMPP. They could have obtained an injunction, if they saw fit.

Mr. DINGELL. How long would it have taken to obtain an injunction?

Dr. KLUMPP. I am told about 2 days.

Mr. DINGELL. This is perhaps true, but to resolve a case of this sort through the courts involving the food and drug law might have taken 2 to 4 years, am I correct?

Dr. KLUMPP. Seizures, Mr. Dingell, which are another avenue of action and can be exceedingly effective, can be accomplished in a day.

Mr. DINGELL. In a day?

Dr. KLUMPP. In a day.

Mr. CUTLER. Dr. Klumpp's point, Mr. Dingell, is that, while a long litigation went on, if it did, all supplies of the drug can be seized under the present law and withheld from the market.

Furthermore, in your MER/29 case, if the manufacturer had refused under existing law, the Food and Drug Administration could have instituted a proceeding under section 505(e) to define the drug as unsafe and take it off the market.

Mr. DINGELL. You note on page 33 that you were opposed to the provisions for suspension for failure to keep records, to make reports and to maintain manufacturing standards.

You say:

These provisions require the Secretary to suspend if he finds such a failure.

If you were to have—if the requirement were eliminated and it were made permissive upon the Secretary, would this meet your objections to the bill?

Dr. KLUMPP. No, it would not, Mr. Dingell.

Mr. DINGELL. It would not?

Dr. KLUMPP. No.

Mr. DINGELL. In other words, you simply object to the fact that the Secretary can withdraw for failure to adhere to good manufacturing practices and so forth?

Dr. KLUMPP. Yes.

Mr. DINGELL. I find, in substance, that you have very little agreement with the bill, and, basically, you are in substantial disagreement with the bill.

I recognize that this is a perfectly proper and honorable difference of opinion, but I can only see two sections of the bill that you do not object to, one of which is the amphetamine and barbiturate section—the other section to which I note no objection is the section dealing with generic names, and assume that the objection to the generic-name section has been raised by other witnesses on behalf of the Pharmaceutical Association.

Am I correct?

Dr. KLUMPP. Yes, sir.

Mr. DINGELL. So for all intents and purposes here we have involved a situation where the Pharmaceutical Association is opposed, for all intents and purposes, to the whole bill?

Mr. CUTLER. Mr. Dingell, I really respectfully, sir, do not feel that is a fair way to put the matter.

This is a very complicated law, this food and drug law.

Mr. DINGELL. I recognize this.

Mr. CUTLER. There are a series of amendments proposed on some 12 or 14 subjects that take 33 pages.

Mr. DINGELL. I recognize that.

Mr. CUTLER. Mr. Beesley has testified that in principle we agree with a great number of the proposals. We have some changes in language to suggest in a great number of these proposals.

But it is hardly fair to say to us, because we have a few changes in language to suggest in a substantive proposal, that, therefore, we are against the proposal. We are not, sir.

Let us go down the table of contents on page 2 of the bill.

We are in favor of a requirement of adequate controls in manufacture.

Mr. DINGELL. I see, but with regard to that, now, you favor it, but you want this to be advisory?

Mr. CUTLER. No, sir.

Mr. DINGELL. Am I correct?

Mr. CUTLER. No, sir.

We favor a provision in this statute which would make a drug adulterated if it is manufactured in accordance with methods and controls that are not in conformity with good manufacturing practice.

Mr. DINGELL. You differ on this with Food and Drug and the administration. You have reservations on this section.

Mr. CUTLER. No, sir.

We differ with the Food and Drug Administration on whether the Food and Drug Administration should be empowered by regulation to be the final arbiter of what is good manufacturing practice or whether the manufacturer should have an opportunity to show in

court, if he is challenged, that his practice is good manufacturing practice.

That is our only difference.

On section 102 we agree.

We disagree as to the standard of proof. We say if there is a responsible difference of opinion as to the effectiveness of the drug, the FDA should allow the drug on the market and let each doctor decide this difference of medical opinion for himself.

And I could go on through the bill and in almost every case we agree with the principle. We have some changes to suggest in the procedures and standards and burdens of proof.

Mr. DINGELL. Some of your reservations, though, and changes that reflect them are so substantial, in some I am sure you will agree, as to constitute outright opposition to the proposal and substitution of a new proposal.

Mr. CUTLER. And somewhere we have said, frankly, that we do oppose the proposal, but in others I take it that the reason we are here is you are examining the language of this bill, and we are making suggestions about the language of this bill, and I do not think you should say to us that because we are making suggestions to change some words in the bill, we must be against the purpose of the bill.

Mr. DINGELL. I note only that you have endorsed only one section completely and that only by not opposing it.

Mr. CUTLER. I would be very surprised, sir, if this committee has accepted without change more than 25 percent, let us say, of the precise sections offered to it in administration bills.

Your function is to change a bill where you think it is appropriate.

Mr. DINGELL. I am sure this is true.

No further questions, Mr. Chairman.

Thank you very much.

The CHAIRMAN. Mr. Schenck?

Mr. SCHENCK. Mr. Chairman, I was very much interested in Dr. Klumpp's testimony here, and I think he has covered the subject very well.

Where I disagree is a matter of record.

I do not see any reason that the industry should be concerned about keeping proper records.

You certainly have to keep proper records for Internal Revenue.

Dr. KLUMPP. We are very much in agreement with that, Mr. Schenck.

Mr. SCHENCK. It would appear to me that the human side of the picture is even more important.

Dr. KLUMPP. Yes.

Mr. SCHENCK. I have great respect for the pharmaceutical industry and for the very wonderful service and the distinguished service that our dedicated physicians are giving to all of the people of the United States.

I agree wholeheartedly that the health of our Nation and the advance in the manufacture of drugs is the most outstanding in the world.

At the same time, the industry cannot escape the responsibility of the salesmen it hires who visit the doctors, overburdened with heavy schedules of patients, salesmen who are neither pharmacists or scientists or doctors.

Dr. KLUMPP. Most of them are pharmacists.

Mr. SCHENCK. But who really do sell drugs?

Dr. KLUMPP. Most of them are trained pharmacists, Mr. Schenck.

Mr. SCHENCK. Sir?

Dr. KLUMPP. Most of them are trained pharmacists, sir.

Mr. SCHENCK. Well, I have known a number who were not, and that is going back to the salesman, because that has been my life's work, as a salesman.

I would say that you, Dr. Klumpp, are an excellent salesman for your point of view and your company.

Dr. KLUMPP. I could not sell nickels for 5 cents, Mr. Schenck.

Mr. SCHENCK. I would just make the observation that the industry does have a responsibility to hire salesmen who are very conscious of their own responsibilities and who are well informed in this whole field.

Dr. KLUMPP. We make the greatest effort to do that, to hire the very highest type people that we can, and we pay them very well.

May I also add that one of our detail men was the first witness here, Mr. Beesley, who started out as a detail man for our industry, and his company.

Mr. SCHENCK. Mr. Beesley has done a remarkable job.

Dr. KLUMPP. He represents the caliber of the people that we endeavor, and do everything we can, to obtain, and occasionally, and quite often, we succeed.

Mr. SCHENCK. I quite agree with you that your well-expressed confidence in Mr. Beesley is justified but, of course, there are relatively few such opportunities to become a president of a concern as large and as good as the Eli Lilly Co.

Dr. KLUMPP. I agree with that, too.

Mr. SCHENCK. So I would guess that the opportunity for salesmen who aspire to such a position would be quite limited.

The CHAIRMAN. Mr. Younger?

Mr. YOUNGER. I want to thank you for the suggestions that you make in regard to this bill. We want to get out a good bill, and there is no one that I know of who has a corner of all this information, and certainly I for one appreciate the recommendations made by the pharmaceutical industry.

Dr. KLUMPP. Thank you very much, Mr. Younger.

We have a common objective there. We are eager to have a good bill and one which will provide the protection which our 182 million citizens are entitled to have.

Mr. SCHENCK. 186 million, almost 187 million now.

Dr. KLUMPP. You must have seen that clock more recently than I.

The CHAIRMAN. By the time we get this good legislation, maybe we will have 193.

Mr. YOUNGER. The extra ones will be in California.

Dr. KLUMPP. That is right, where my children are.

The CHAIRMAN. Mr. Moulder had to leave, but he did suggest this question, which I also had in mind.

On page 16 of your statement, according to Mr. Moulder, referring to the physician's freedom to prescribe as he sees fit to encourage the development of new products and so forth, he asked me to inquire for him what information or knowledge is given or reported to the

prescribing physician concerning conflicting opinions on the effectiveness or safety or efficacy of a new drug?

Dr. KLUMPP. Mr. Chairman, we go to great lengths to provide the practicing physicians with all the information available concerning the action and use of our products.

We have brochures which are distributed to every physician which tell the whole story, tell both sides of a story, the good as well as the bad.

We believe that every physician should have that, and that, it seems to me, is the most practical way of conveying the full story of the practicing physicians.

The CHAIRMAN. May I then assume from what you have said that the industry will make full disclosure to the physician?

Dr. KLUMPP. Yes, and FDA now passes on our booklets to satisfy itself that we are telling the whole story. That is under the present law.

The CHAIRMAN. I am not talking about FDA for the moment. I am talking about what you tell the doctors, particularly on tests of experimental drugs.

Dr. KLUMPP. Yes.

Mr. Chairman, one of the subsequent witnesses will furnish you and the committee with examples of the kind of information that goes to the practicing physicians.

The CHAIRMAN. Thank you very much, Dr. Klumpp, for your very forthright and fully explanatory statement of your views on this subject matter.

Dr. KLUMPP. Thank you.

I am sorry it was so long.

The CHAIRMAN. Mr. John T. Connor.

I might say for the information of those who are interested that after the presentation of Mr. Connor's statement, the committee will recess for a little while and give everyone an opportunity to relax a little bit and get a bite to eat and we will come back here at 7 to resume hearings.

The Chair is going to hear these witnesses, so that is the information for both the witnesses and everyone else.

Mr. Connor, you may proceed.

STATEMENT OF JOHN T. CONNOR, ON BEHALF OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY LLOYD CUTLER, ESQ.

Mr. CONNOR. Thank you very much.

Mr. Chairman, my name is John T. Connor. I am president of Merck & Co., Inc., Rahway, N.J. I have made available a brief biographical statement which you may wish to incorporate in the record.

As you will see when reading that statement, I am another Federal Government alumnus now working in the pharmaceutical industry.

I shall present the views of the Pharmaceutical Manufacturers Association on these parts of H.R. 11581: Section 101: Requirement of Adequate Controls in Manufacture; Sections 201 and 202: Factory Inspection; and Section 105: Certification of All Antibiotics. In addition, I shall propose a new provision having to do with the registration of prescription drug manufacturers.

DRUG INDUSTRY ACT OF 1962

255

SECTION 101—REQUIREMENT OF ADEQUATE CONTROLS IN MANUFACTURE

Section 101 of the bill provides that any drug—no matter how good it is intrinsically—will be outlawed from interstate commerce if it has been made in inadequate facilities, by improper methods, with inadequate controls, or by the use of unqualified personnel. The purpose of this amendment is to assure that all drug producers meet standards of good manufacturing practice.

Under the amendment, the Food and Drug Administration would issue regulations setting up ground rules for what constitutes a good manufacturing practice, and enforce those ground rules by its traditional procedures of injunction, seizure, and action for criminal penalties.

As background for my comment on this section, Mr. Chairman, let me point out that it takes many things to make drugs that meet the needs of modern medicine. It takes complex chemical factories, scrupulously correct materials and supplies, extremely delicate equipment and facilities, highly trained professional and technical employees, and intricate control systems to guard against error from raw material to finished package. It takes thousands of tests and samplings, and a lot of checking and rechecking. It requires good organization, good communication, and good morale. It requires character and stern discipline in rules, and character in individuals from bottom to top. It requires a good bit of courage, because we are making some of the most complicated compounds that exist, for one of the most intimate, delicate, and sensitive purposes there is. Failures or mistakes are dreadful things—and a respectful fear of them is built into our tradition if we have been doing our work properly for a long time.

Unlike most other products, the care and concern devoted to manufacture of drugs are not visible in our products. Drugs made under the best conditions look like their cheaper versions.

Mr. Chairman, I think I can say that despite public and competitive pressure to cheapen their products, the sound companies in this industry have continued to carry on with their good manufacturing standards, disciplines, control procedures, insistence on top-flight personnel, and other traditions of quality.

When the Commissioner of the Food and Drug Administration testified before the Senate Antitrust and Monopoly Subcommittee in June of 1960, he presented a 21-table summary of the agency's enforcement experience for the period 1950 to 1960. From these tables it can be seen that 28 major firms in that decade supplied 87 percent of the total volume of prescription drugs. An estimated 1,200 firms supplied the remainder. During this time, those major firms were subject to four Food and Drug legal actions based on drug composition. The others, supplying 13 percent of the drugs, were subject to 484 legal actions for the same cause.

Mr. Larrick testified as follows:

* * * The facts are that those manufacturers, large and small, who have adequate scientific personnel and controls are producing pure and safe drugs while those that do not have such controls are likely to violate the Food, Drug, and Cosmetic Act. As a matter of fact, we occasionally encounter a violation by a manufacturer whose controls are beyond reproach, which simply emphasizes the fact that even with the best scientific controls human error will occur. But

It occurs less frequently with those firms who rely on properly trained scientists and with much greater frequency in the case of those firms who rely on improperly trained and unqualified employees who have neither the understanding of modern drug manufacturing nor the appreciation of the serious responsibility that rests on those who offer drugs to sick people.

In view of the importance of scientific control to insure the composition of drugs, this logically raises the question whether we should not propose, to the committee of the Congress with legislative responsibility in this area, new provisions to require the adoption and use of appropriate manufacturing and control procedures by firms producing drugs now subject to the new drug provisions of the law ("Administered Prices," hearings before the Senate Subcommittee on Antitrust and Monopoly, p. 12115).

I would emphasize a point that Mr. Larrick made. Some of our very best and most responsible companies are the smaller ones. Size has nothing to do with the excellence of manufacturing and control standards. The problem for legislators and for officials of executive agencies, and indeed for all of us, is to find ways to set and enforce standards that will bring the performance of all manufacturers closer to the high level of excellence already being set by the better members of the industry.

In our efforts to make more uniform throughout the industry those practices which now characterize the best of the industry, we must have means of dealing with the fringe operators who purvey drugs to the American people. The flow of such drugs has, if anything, increased since Mr. Larrick testified 2 years ago.

A large drug counterfeiting plant, distributing nationally, was uncovered in my own State of New Jersey and prosecuted under State and Federal laws. The owners obtained bulk supplies of important new drugs and formulated and packaged them in containers with labels that simulated those of established, reputable drug firms. I am sure the committee can imagine the manufacturing standards, quality control, and basic sanitation—or lack of it—of such a company.

We are only now beginning to learn the extent to which drugs formulated in this country from raw materials of foreign origin have been placed into the American supply line by people operating in the shadow of the responsible industry, people who have in prior years given the Food and Drug Administration its largest number of enforcement headaches. Within the past year we have discovered that imported drugs are coming here from foreign producers who use technical and scientific data stolen from American firms who first invented the drugs. And unless broad and sound regulatory standards can be established and rigidly enforced, an increasing number of entrepreneurs will probably be attracted into the drug field to exploit the attractiveness of seeming drug bargains.

We thus support, as we publicly announced at the Senate subcommittee hearings last December, an amendment to the Food and Drug Act which gives the FDA the power to enforce proper standards of manufacturing performance across-the-board as to all drug manufacturers.

At the same time that we urge your adoption of this amendment, we wish to present several reservations about its precise language.

1. Our first reservation has to do with who in fact establishes good manufacturing practice. The Food and Drug Administration, which does not manufacture drugs, cannot create manufacturing practice. It can only impose on some manufacturers standards set and met by others. Thus FDA's detailed regulations, in our judgment, cannot

authoritatively state what good manufacturing practice should be, but can only reflect and interpret what good manufacturing practice is. Let me expand on this for a moment.

The standards cannot be extreme, cannot be so unrealistic or unreasonable that they can be met by no one. They cannot, for practical purposes, be so high as to be met by only a few of the best manufacturers. They must not, on the other hand, be so low as to fail to protect the public against weak or shoddy production and control practices. We agree that the standards should, as stated in the amendment, be "good" manufacturing practice. But it simply has to be "good" manufacturing practice as manufacturing experience has established it at the time. And it must also be good practice as manufacturing experience continues to establish it, Mr. Chairman.

Standards of practice are improved with experience. New procedures are discovered, shortcuts found, better ways developed to test and control batches of drugs. In the dozen or so years since Merck started producing cortisone, for example, the number of separate processing steps has been cut from 30 to about half that number, and our control systems are far superior to what they were.

To establish standards by Government fiat over something as dynamic and vital as drug production, testing, and control methodology would be to stifle manufacturing progress and important improvements in control and safety systems.

Thus we say that the Secretary should be empowered to issue regulations on good manufacturing practice that are interpretive of what good practice is, and not determinative of what it is.

We would not object to a provision that would spell out that such regulations will be considered prima facie evidence of what constitutes good manufacturing practice in any enforcement proceeding under that section of the statute. While this would put a defendant manufacturer in the position of carrying the burden of proof, it would still give him the opportunity to show—if true—that his practice is good manufacturing practice despite the agency's interpretation that it is not. Such flexibility will allow minimum standards to reflect the best judgment and practice prevailing in the industry, permit superior standards to be reflected in quality products, and permit all standards to be upgraded with experience.

2. Our second reservation on this section has to do with whether the Food and Drug Administration should have the power to establish and enforce standards of training, experience, and background for all personnel in the multifold operations of a drug manufacturing establishment.

Our feeling is that a Government agency cannot set up meaningful general standards for all those skills and disciplines without doing more harm than good.

It is perfectly true, as Mr. Larrick has said, that firms relying on properly trained and qualified employees are likely to have better compliance records than those which do not. But the selection and use of scientific and technical personnel is a delicate function, involving subjective judgment and long-term, close experience with people.

Should a good analytical chemist, for example, be dismissed from his job because he did not get a degree?

Every company surely has that topflight veteran production chief whose record may not look impressive on paper, but who never makes an operational error. It is rather frightening to contemplate the inevitable arbitrariness of personnel standards set by Government for industry, and the difficulty, hardship, and discrimination likely to attend their application.

We therefore urge that the standard-enforcing authority of the Food and Drug Administration be directed to those measurable things that men and women in our plants make and do—to facilities, buildings, equipment, methods, systems, and procedures—and not to the professional and technical competence of our employees, what they have done, and who they are.

3. Our third reservation on this section has to do with a redundancy.

The purpose of subsection (i) is to establish minimum manufacturing standards to assure that a product's identity, strength, quality, and purity are what they purport to be. We think that is all that such standards can properly assure.

Subsections (ii) and (iii) of the amendment provide that standards of manufacturing practice must assure that a product will not be injurious to health and is properly labeled under the act. Since other sections of the statute deal with whether a product—being what it purports to be—is injurious to health when used in accordance with directions, or is properly labeled under the act, it seems to us that subsections (ii) and (iii) are redundant and create a double layer of enforcement. We urge that these two subsections be deleted.

4. Our fourth and final reservation on section 101 rests on a single word. We would like the word "assure" to be used instead of the word "insure." Our view is based simply on the desire to avoid the possibility of the section's being used to impose on manufacturers an insurer's liability without fault under the common law.

This concludes my comment on section 101. For the convenience of the committee, I should note that S. 1552 as reported out by the Senate Judiciary Committee on July 19, 1962, contains language satisfactory to us for carrying out these recommendations.

SECTIONS 201 AND 202—FACTORY INSPECTION

May I turn your attention now to section 201. This section would amend the factory inspection authority of the Food and Drug Administration to include everything in a drug-producing or drug-storing establishment (including records, processes, controls, and facilities) having a bearing on violations or potential violations of the act.

We also support, and have publicly supported since last December, this broadening of inspection powers over drug manufacturers as an appropriate requisite to enforcement of the new section establishing minimum standards of manufacturing practice.

We have two reservations about the language proposed in section 201.

1. The first can best be stated as a question.

Should the Food and Drug Administration, through its inspectors, be authorized to go through all the records and files of a manufacturer whether or not they are relevant to enforcement of the act?

We believe the words of the amendment before us would permit him to do this if he insisted. The only restraint in the amendment

on chief
r makes
the in-
ment for
ly to at-

of the
e things
s, build-
t to the
at they

ndancy.
ifactor-
quality,
all that

ndards
t be in-
e other
what it
ce with
at sub-
yer of

single
of the
oid the
ers an

ence of
by the
e satis-

would
g Ad-
g-stor-
facili-
he act.
ember,
as an
ishing

ection

ctors,
ufac-
?
ermit
lment

is that the records and files have a bearing on a violation or a potential violation of the act. An inspector could say of almost any record that it might have a bearing on a potential violation of the act. He could say, even about financial records, pricing records, personnel records, and fundamental research records, that he could not know whether or not they had a bearing on a potential violation until he had seen them.

This raises a constitutional question, Mr. Chairman.

The guarantee against unreasonable search and seizure has been held to mean that Government agencies should not invade and search a citizen's private premises without probable cause to believe that a crime has been or is being committed. We do not maintain that argument against the proper needs of the food and drug enforcement agency. But we do maintain that the power of inspection should not be so broadly worded as to authorize unlimited search into irrelevancies. Such unlimited search is unfair and detrimental to us as manufacturers, and from the public standpoint opens the amendment unnecessarily to constitutional attack in future enforcement situations.

We suggest that the language should clearly limit inspectors to matters that have a real and substantial bearing on enforcement of the Federal Food, Drug, and Cosmetic Act. We ask that the phrase "material bearing" be used, and that the catchall phrase "or potential violation" be deleted.

We further suggest that there be specific exclusion of types of confidential records that would not properly concern the Food and Drug Administration in its legitimate enforcement activities—records such as financial data, sales data (other than shipment data), pricing data, personnel data, and research data (other than clinical records of the type that must be furnished to the Food and Drug Administration under the new drug provisions of the act).

2. Our second reservation on section 201 has to do with the confidentiality of complaint files. The inspection powers will, of course, extend to complaint files. Such files normally contain a great deal of helpful correspondence from doctors and other professionally trained people, as well as the general public. It is essential, of course, that all such correspondence continue to flow freely without fear of the disclosure of professional confidences. And while we agree that the Food and Drug Administration should have access to reports from professional medical correspondents, we feel such reports should be made available only to physicians on the FDA's staff.

We thus request that provision be made for the Secretary to issue regulations that place this safeguard around the complaint file inspection. At the same time, we believe provision should be made to permit physicians in the affected company to examine similar information received from professional sources by the Food and Drug Administration itself.

Section 4(a) of S. 1552, as reported on July 19, 1962, contains language which is generally satisfactory from our point of view concerning these qualifications we have on section 201 of the instant bill, but some additional language would be needed which we will be glad to suggest.

We have one reservation on section 202 of the bill which relates to protecting the confidentiality of information learned during a fac-

tory inspection. These expanded factory inspection powers will put inspectors into the midst of the most confidential aspects of production, processing, and control operations, and will enable them to learn scientific and technical data that are invaluable competitive assets. While so far as we know it has never happened, any disclosure of such assets to competitors by inspectors should be very carefully guarded against. The beneficiaries of revealed data are always saved the cost and given the advantage of the innovator's scientific and technical work; and the manufacturer who has done the innovative work is forced to compete in the marketplace—at an obviously unfair disadvantage—against those who have capitalized on his own research and technical development.

We therefore support section 202, but ask that it be further strengthened by permitting disclosures only when "required" by law, not when "authorized" by law.

SECTION 105—CERTIFICATION OF ALL ANTIBIOTICS

We have supported the principles of sections 101, 201, and 202 of this bill, Mr. Chairman, but must strongly oppose section 105, which extends to all antibiotics the batch-by-batch certification which now applies only to five specified antibiotics.

In order to understand our position on this matter, it is necessary to go back to the original 1945 amendment that placed this special control on penicillin.

Penicillin was developed during World War II. It was a wholly new kind of drug material produced by a micro-organism grown in fermentation media. Under critical conditions of material supply, the American drug industry hurriedly developed and put into operation factory fermentation processes for penicillin—one of its outstanding contributions during the war. But even while these facilities were being rushed, penicillin was desperately needed for both military and civilian populations. The decision was made to get it into use despite the absence of uniform manufacturing methods, tests, and controls.

To ensure uniformity, it was decided that there should be a central agency to test each batch of every manufacturer's product. The War Production Board first had the responsibility for this function. When WPB went out of existence, the Congress transferred the responsibility to the Food and Drug Administration by an amendment to the Federal Food, Drug and Cosmetic Act. The words of the amendment made clear that the function was intended to be temporary.

Streptomycin came along 2 years later, and the statute was amended to include it. The statute was further amended in 1949 to include three new antibiotics— aureomycin, chloramphenicol, and bacitracin. Mr. Oscar Ewing, then Federal Security Administrator, supported this amendment before the Congress, and added:

It is probable that as improved techniques in manufacture and better methods of testing are developed, the need for pretesting and certification of aureomycin, chloramphenicol, and bacitracin may no longer exist. That probability with respect to penicillin and streptomycin was recognized in section 507(c), which directs the Administrator to promulgate regulations exempting the drug from certification requirements when that procedure is not necessary to insure safety and efficacy of use. This provision would apply equally to aureomycin, chloramphenicol, and bacitracin if the recommended amendment is adopted.

The situation is quite different today. Antibiotics can be produced and controlled with as high an assurance of uniformity and quality as other commercially produced and much more complex drugs. We are no longer dealing with pioneer techniques of production and control. Consistently reliable methods have been developed for testing purity and potency. There are more than 20 other antibiotics now on the market which have gone through the regular new drug procedure and are not batch certified. They have an excellent record of safety and usefulness, and the Food and Drug Administration's own record of drug recalls during the last 4 years shows that they have presented no serious difficulty in manufacture or control.

In the 13 years since Mr. Ewing explained to the Congress the temporary character of the batch-testing controls and predicted administrative end to them at the appropriate time, the Antibiotic Division of the Food and Drug Administration has grown larger and larger. It has not substantially relinquished control as to any of the five antibiotics, in the sense intended by the original amendment. It has instead expanded the original control. The agency has extended batch control to other antibiotics when they are combined with batch-tested antibiotics. It has superimposed the controls onto other products containing antibiotics, even when these products are controlled by other sections of the statute.

As you know, Mr. Chairman, Mr. Roberts and other members of the Health and Safety Subcommittee of this committee have wrestled in recent weeks with the complex problem posed by multiple controls over animal feedstuffs. As they know, an animal feed may have to be cleared under three different sections of the act—food additives, new drugs, and antibiotics batch testing. The sections, administered by three different regulatory branches of FDA have different yardsticks for approval. An animal feedstuff may get through one branch, but not another. This complex and confusing triplication of regulation has raised difficult problems for the Food and Drug Administration, the drug and animal feed industries, and the livestock producers. To resolve these problems our association and the Animal Health Institute have proposed new legislation to deal separately with drugs for animal use.

The problems and the proposed legislative solution are fully discussed in the statements filed for our association and the Animal Health Institute on August 7 in the hearings of the subcommittee on H.R. 12437, and I simply want to state at this time that extension of batch certification to all antibiotics will further complicate an already difficult problem.

Now, what is the end result of this outmoded Government double-checking on the individual batch production of five well-established antibiotics?

In the fiscal year 1960—according to the Controller General's report to Congress dated September 1961—the FDA rejected one-eighth of 1 percent of all batches submitted to it by the manufacturers for testing. In some cases, rejections are based on failure to meet standards that have nothing to do with safety or potency. Some manufacturers speed certification by submitting batches before they have the final results of their own tests. It is certain that a number of FDA-rejected lots would have been rejected by the manufacturers anyway, on

the basis of their own tests. And it is a good guess that the remaining deficient batches would have been stopped by the tighter application of the manufacturer's own controls, which he would have exercised had he not had the crutch of a Government doublecheck.

This steadily growing branch of the agency used up about 150 man-years of technical talent in the batch certification of antibiotics last year. By almost everyone's admission, Mr. Chairman, the FDA badly needs, and we feel should have and properly use, additional scientific and technical manpower. That manpower is scarce enough as it is—everywhere. Placing 20 additional antibiotics under the certification system will simply make an obsolete function bigger and will use up additional talent that could be put to work on the enforcement of a statute that will be significantly stronger after this bill is passed.

Good judgment, in our opinion, dictates that the agency should use its manpower where it will do the most good—to carry out proper factory inspections, to enforce other essential provisions of the law, and to achieve adequate manufacturing and control standards among all producers of all drugs.

In summary, Mr. Chairman, we oppose section 105 on the grounds that batch certification is no longer needed; that it is wasteful of time and energy and scarce manpower; that batch certification of antibiotics, either some of them or all of them, weakens the development of strong, self-reliant manufacturer control systems, and that responsibility for safety and quality of antibiotics can be well safeguarded by the FDA, without duplicate testing, under existing authority and through the additional authority that would be provided under other provisions of H.R. 11581.

REGISTRATION OF DRUG MANUFACTURERS (NEW PROVISION)

Now that I have covered three provisions of this bill that we feel will strengthen the act, and one that we oppose, let me advance a new provision that we think should be in the bill. A proposal that would require every drug manufacturer in this country, whether he operates in interstate or intrastate commerce, to register with the Food and Drug Administration every one of his establishments that produce or process drugs. Under our proposal, failure to register would be, in itself, a violation of the act.

A provision such as this would bring into the open every individual or organization that embarks on the serious and responsible task of making drugs for the people of this country. Knowing who they are and where they are, the Food and Drug Administration could inspect and take any appropriate action needed to clean up or close down illegal operations by criminal action, injunction, or product seizure.

To assure no oversight, we think it should be mandatory that every registered establishment be inspected by the Food and Drug Administration at least once every 2 years.

Foreign producers who send their raw materials or finished products into this country should be subjected to no less stringent controls than domestic manufacturers, and we believe they, too, should be required to register.

For the assistance of the committee I submit, with the request it be inserted in the record, a draft of an appropriate amendment to carry

out these registration proposals. Similarly, I submit a draft of an amendment to carry out Mr. Beesley's recommendation that the counterfeiting provisions of the act be tightened. This is a necessary corollary of our registration proposal and our support for the principles of strengthened inspection and manufacturing controls. The drug counterfeiter is a menace to all and the law should contain provisions for dealing severely with him.

CONCLUSION

No law, Mr. Chairman, can guarantee infallibility or assure against mishap or deliberate violation. The best protection will always be the manufacturer's integrity and driving concern for his reputation and survival.

And no legislation can supply the incentive to build quality into a product. It must remain the desire for good reputation, the need to be trusted by physicians and patients, and the competitive urge to excel, that supply the fuel for outstanding performance.

The laws should serve to encourage the best of these motivations, to build discipline and a sense of responsibility, to foster self-reliance and initiative. The laws should place a floor under industry performance for the public safety; they should not permit industry standards to be lowered for the sake of marginal performers.

We believe that the sections of H.R. 11581 I have here supported will do these things.

We believe they will greatly strengthen the act where it should be strengthened, and will set the stage for the type of performance and the constant improvement of performance that the American public is entitled to from those who manufacture prescription drugs, and we urge your enactment of them with the changes I have discussed.

(The amendments referred to follow:)

FORM OF AMENDMENT TO STRENGTHEN THE COUNTERFEITING PROVISIONS OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, PROPOSED BY THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

SEC. — Section 301 of the Federal Food, Drug, and Cosmetic Act is hereby amended to add a new paragraph (a) as follows:

"(a) (1) Placing or causing to be placed upon any drug or upon the container of any drug transported, received, or held for transportation in interstate commerce, with intent to defraud, the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing; or (2) selling, dispensing, disposing of or causing to be sold, dispensed, or disposed of, or concealing or keeping in possession, control, or custody, with intent to sell, dispense, or dispose of, any drug or any container of any drug transported, received, or held for transportation in interstate commerce, with knowledge that the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing has been placed thereon in a manner prohibited by subparagraph (1) hereof; or (3) making, selling, disposing of or causing to be made, sold, or disposed of or keeping in possession, control, or custody, or concealing, with intent to defraud, any punch, die, plate, stone, or other thing designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any drug or container thereof, transported, received, or held for transportation in interstate commerce."

FORM OF AMENDMENT TO PROVIDE FOR REGISTRATION OF DRUG MANUFACTURERS,
PROPOSED BY THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Section 3 of S. 1552 as reported to the Senate on July 19, 1962, contains generally acceptable provisions for registration of domestic drug manufacturers. To provide for registration of foreign manufacturers and to make necessary clarifying changes, such section 3 should be further changed as follows (all page and line references are to S. 1552 as reported on July 19, 1962):

On page 24, at line 19, insert after the words "owns or operates" the words "in any State."

On page 24, at line 22, after the words "in accordance with" insert the words "the foregoing subsections of."

On page 24, at line 24, after the words "owns or operates" insert the words "in any State."

On page 25, at line 9, strike the word "This" and insert in lieu thereof "The foregoing subsections of this."

On page 26, following line 14, add the following:

"(i) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs shall be permitted to register under this section pursuant to regulations promulgated by the Secretary. Such regulations shall include provisions for registration of any such establishment upon condition that:

"(1) adequate and effective means are available to enable the Secretary to determine from time to time whether the methods, facilities, and controls used in such establishment fulfill the requirements of section 501 (a) (2) (B);

"(2) the registrant permits the inspection of such establishment from time to time in accordance with section 704 of the Act;

"(3) the registrant pays such fees as are determined by the Secretary to be necessary to provide and maintain adequate inspection of such establishment;

"(4) the registrant files with the Secretary a designation in writing of the name and post office address in the District of Columbia of a person residing or having a place of business in the District of Columbia upon whom process issued by or under the authority of any court having jurisdiction of the subject matter may be served in any proceeding at law or equity brought against such registrant, and upon whom service of all notices and process and all orders, decisions, and requirements of the Secretary may be made for and on behalf of said registrant."

The CHAIRMAN. Mr. Connor, thank you very much for your statement.

Mr. CONNOR. Thank you, Mr. Chairman.

The CHAIRMAN. We are glad to have your suggestions and recommendations which deserve careful consideration. Obviously the committee will consider the merits of the proposals.

Mr. Dingell.

Mr. DINGELL. Thank you, Mr. Chairman.

I commend you for a very excellent statement, sir.

Mr. CONNOR. Thank you, Mr. Dingell.

Mr. DINGELL. I note here in red ink a statement made not too long back by Mr. Goodrich, who is Assistant General Counsel of the Food and Drug Administration, wherein he says as follows about factory inspection:

All too often inspectors are treated to a guided tour through the establishment. They are refused access to formula files, complaint files, shipping records, and a great deal more information that is absolutely essential for them to see, in order to determine whether products are being produced in compliance with the law. Every working day food, drug, or cosmetic manufacturers refuse to give our inspectors access to information needed to safeguard the public. These refusals are not restricted to the fly-by-night operator, but extend to some of the very largest manufacturers in the country.

He goes on and he says:

The list of refusals is indeed a long one. It covers all types of business. It covers all kinds of requested information, and it all arises from the uncertain conditions that prevail under existing law.

Then he goes on to say as follows:

We found some firms with a fixed policy against inspection were applying for effective new drug applications, certification of antibiotics, insulin, and coal-tar colors, exemption from certification food additive regulations and hazardous substance labeling exemptions. They were presenting data to us to support these requests asking us to rely on it, but at the same time denying our inspectors the right to inspect to determine the accuracy of the data.

You have endorsed strengthened factory inspections. You have of course suggested some modifications in it. Specifically, you suggest, as I note, that the language should clearly limit inspectors to matters that have a real and substantial bearing of importance to the Federal Food, Drug, and Cosmetics Act. You ask that the phrase "material bearing" be used. That is on page 10.

First of all, I am sure your counsel, seated next to you, can tell us—have you ever heard that word used in connection with statute before, "material bearing"?

That is not a work of art.

Mr. CUTLER. The word "material" appears in this statute, I believe, several times.

Mr. DINGELL. I said "material bearing." Have you ever heard that as a work of art?

Mr. CUTLER. Mr. Dingell, I have never seen the phrase "having a bearing" before in a statute. I agree with that.

Mr. CONNOR. We are just suggesting that if the word "bearing" is used as it is in this bill that it be modified by the word "material."

Mr. DINGELL. I see. Now, your principal concern is protection of trade secrets in this regard; am I correct? Protection also of the doctor-patient relationship and the relationship that your company has with doctors and with patients who are subject to clinical investigations; am I correct?

Mr. CONNOR. Mr. Dingell, you have three or four questions all rolled up in one. May I first take the question having to do with trade secrets?

With respect to new drugs that are subject to the new drug application procedure, I think it is safe to say that we have no trade secrets from the Food and Drug Administration, because we are now required and do in fact submit to the FDA as part of our new drug application detailed information about our production and control procedures. So with respect to all the drugs subject to the new drug procedure, they have that information.

Now, with respect to trade secrets for the production of old drugs, we are agreeing with the Food and Drug Administration suggestion that their inspectors be given broader authority than they now have. I think it is quite clear that if the Congress decides to give this broader authority, the FDA will have access to what we would call trade secrets with respect even to old drugs.

We are not objecting to that, but we think there are some of our records that would be subject to the language of the bill before this committee that do not properly come under the scrutiny of the Food and Drug inspector. Those financial records having to do with

production costs and profits in many cases become available to the Bureau of Internal Revenue in connection with the audit of our income tax returns, and this is proper. But we do not see that those matters having to do with that highly important competitive information necessarily have to be made available to the Food and Drug Administration for the exercise of their jurisdiction. So we are opposed to that.

The third part of your question had to do with the confidentiality of case clinical reports submitted to us by clinicians who are experimenting with our drugs or who are actually using the drugs after they have received an effective new-drug application.

We think that the material submitted by physicians to our physicians concerning the specific effect of the drugs on their patients does contain confidential information subject to the doctor-patient relationship.

We are agreeing with the proposal in this bill that information of that kind should be made available to the Food and Drug Administration, but we are suggesting that it should not go to everyone in the FDA. In order to maintain the confidential nature of the reports and to encourage clinicians to continue sending in reports, they should go just to medical personnel where they will be handled in accordance with the traditional requirements of the medical profession.

Mr. DINGELL. I wonder if this is really necessary when we have a situation where Food and Drug—if we require Food and Drug to maintain the confidentiality of this information, I wonder if we have to limit it to physicians.

Mr. CONNOR. We think it is important and we would refer you to some representatives of medical associations who might have some views to express on this.

Mr. DINGELL. Is there anything in the canons of medical ethics that requires that this information be preserved to physicians only?

Mr. CONNOR. Oh, absolutely. You heard Dr. Scheele and Dr. Klumpp testify on the importance of this.

Mr. DINGELL. What I am concerned about is, let's say that Food and Drug has a man who is a pharmacologist, not a doctor of medicine or a particularly qualified specialist, in another field. He is the only man who can do this work. How can we say, then, that he is not qualified to look at this or should not look at this if he looks at it under adequate safeguards to preserve the confidentiality of the information?

Mr. CONNOR. In a situation such as you describe, there perhaps is good reason for him to see it, and in accordance with medical traditions he probably would be able to see it.

What we are doing here is raising a point which we think needs to be covered.

Certainly all employees of the FDA should not have access to this kind of information and we think, therefore, that there should be some kind of safeguarding words used in the statute.

Mr. DINGELL. What if it were just limited then to qualified investigators in the Food and Drug who had clearance to maintain the confidentiality, and so forth?

Mr. CONNOR. Perhaps that is the best way of explaining it, but I think this is something that should be given some more thought and worked out with counsel.

Mr. DINGELL. I am sympathetic, but I think this is a better way than the rather inflexible way that you have.

Now, the next question I wanted to ask you, on page 9 you raised a constitutional question here with regard to unreasonable search and seizure.

Counsel perhaps remembers this a good deal better than I do, but I do not think you want this to stand in the record as you have it, and the reason is this: You are familiar with fire inspections, health inspections, and things of that sort that have gone on in the field of public health and safety for generations. These have never been challenged on a constitutional ground, am I correct?

Mr. CUTLER. No, sir. They have been challenged and the most recent decisions of the Supreme Court were 5 to 4 on this issue. It is a very close and hotly contested issue.

Mr. DINGELL. Excepting, though, that these are generally held by students of the law not to be instances where the protection against unreasonable search and seizure apply, at least insofar as access to the premises.

Mr. CUTLER. I am afraid I cannot agree with that, Mr. Dingell. Of the eight present members of the Supreme Court who sat on the *Frank* case, and there was another case after *Frank*, they split 4 to 4 on this precise issue.

Mr. DINGELL. What was the holding in the case?

Mr. CUTLER. The holding of the case was that an ordinance of the city of Baltimore which permitted the commissioner of health to enter any home when he had cause to suspect that a nuisance existed in the house was a constitutional statute, 5 to 4.

Mr. DINGELL. What did the lower court hold?

Mr. CUTLER. In that case?

Mr. DINGELL. Did the lower court hold that it was constitutional?

Mr. CUTLER. I believe the lower court did hold it constitutional, yes.

Mr. DINGELL. And the Supreme Court upheld it?

Mr. CUTLER. By a vote of 5 to 4, and of eight present members who sat in that case, they split 4 to 4.

Mr. DINGELL. You as an attorney are aware of stare decisis?

Mr. CUTLER. Not in the Supreme Court, Mr. Dingell.

May I point out that the statute in this case was a probable cause statute? It started out:

Whenever the commissioner of health shall have cause to suspect that a nuisance exists.

This statute has nothing like that. The inspector may have no cause to suspect any violation whatsoever, but under this statute he is allowed to come in to see if he can find one.

We do not even object to that as long as there are some reasonable limitations on the scope of the search.

Mr. DINGELL. On the scope of the search. I have no objection to reasonable limitations on the scope of the search, but I do not want you to have us have constitutional questions raised in the record where really I do not think they properly belong.

Now, you have not shown me that this section is unconstitutional by this language. As a matter of fact, you have shown me that the most recent decision is that again the Supreme Court has upheld the traditional constitutional interpretation of statutes of this kind.

Mr. CUTLER. Where the statute stated that if the commissioner had probable cause to suspect a violation of law, this statute does not so state.

It says in effect whether or not he has any cause to suspect, he may go in and search, to see if he can find anything.

Mr. DINGELL. This is true. This is also true of many of the local statutes involving wiring of houses or construction statutes; building inspectors, for example, enter premises regularly without having to have probable cause at all. They just enter the premises.

Mr. CUTLER. Mr. Dingell, I really do not see the point in debating this when such strong-minded liberal lawyers as Chief Justice Warren, Justice Douglas, Justice Black, and Justice Brennan firmly believe that it is unconstitutional. It is at least a substantial question.

Mr. DINGELL. The Supreme Court has upheld the constitutionality of this for years.

The CHAIRMAN. The Chair thinks we cannot settle the constitutionality question.

Mr. DINGELL. I just want to have the record correct, Mr. Chairman. I realize the hour is late.

The CHAIRMAN. Any witness has the right to give his opinions and express whatever legal opinions he may have and I might say that the Constitution gives any person the right to express his beliefs.

Mr. DINGELL. I wholeheartedly believe in that, Mr. Chairman, but I wanted the record to be correct.

I have no further questions, Mr. Chairman.

The CHAIRMAN. Thank you very much, Mr. Connor.

The committee will recess until 7 o'clock.

(Whereupon, at 5:50 p.m., the committee recessed, to reconvene at 7 p. m., the same day.)

EVENING SESSION

The CHAIRMAN. Mr. George R. Cain. Mr. Cain is president of the Abbott Laboratories of North Chicago, Ill.

Mr. Cain, we are very glad to have you with us and we will be glad to have your presentation.

STATEMENT OF GEORGE R. CAIN, CHAIRMAN OF THE BOARD AND PRESIDENT OF ABBOTT LABORATORIES, ON BEHALF OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY LLOYD CUTLER, ESQ.

Mr. CAIN. Thank you, Mr. Chairman. My name is George R. Cain. I am chairman of the board and president of Abbott Laboratories, of North Chicago, Ill. My career with Abbott started in 1940. I have been president since 1958 and became board chairman and president in April of this year.

I am a member of the board of directors of the Pharmaceutical Manufacturers Association and have served other organizations in the health field.

Today I am speaking on behalf of the Pharmaceutical Manufacturers Association, of which Abbott Laboratories is a member. I shall deal with two subjects covered by H.R. 11581.