Mr. GORDON. Mr. Stetler, pursuing the problem of content rather than format, the article, "The Anonymous Drug That Hospitalized a Patient," which is part of the advertisement is based on a letter which was sent to the Canadian Medical Journal on January 12, 1963, on tolbutamide. The chairman referred to it a while ago.

The article in the PMA ad does not include the fact that the generic product used was outside the limits set by the Food and Drug regulations of Canada as the chairman stated. Don't you think that was a very important piece of information that should have been included?

Mr. STETLER. No, I do not.

Mr. GORDON. In other words, you are comparing a brand name drug with a generic named drug that was on the market illegally?

Mr. STETLER. Well, I suppose all of them that after the fact are determined not to meet standards are on the market illegally. But they are on the market to be used to fill prescriptions that are written generically at that time. That is the point that is being made here. It is very easy after the fact to say it is an illegal drug—it does not meet the standards. But who knows that when the prescription is presented and it is on the shelf of the drugstore, and it is used—this is basically one of our points. That merely an indication on a label that it allegedly meets USP or NF standards is not the beginning and the end of the story.

Mr. GORDON. But we are dealing with the problem of equivalency, or at least clinical effectiveness of drugs that meet USP standards—not drugs that do not.

Mr. STETLER. I suppose the person that got this, and the pharmacist that dispensed this assumed it met USP standards, or it would not have been on the market to be available to fill that prescription.

Senator HATFIELD. Mr. Chairman, I would like to interrupt here. Mr. Gordon brings up something I have found over the hearings to be difficult to comprehend and a lot of discussion but little fact.

Is there in your opinion any kind of scientific data which shows therapeutic equivalency between generic and brand names, or a differential?

Mr. STETLER. It is not a matter of opinion of mine, Senator. We have had concrete, specific, scientific documented evidence that was presented to the committee on Monday of this week, which we are prepared to present today——

Senator HATFIELD. You have it with you?

Mr. STETLER. We have it.

Senator HATFIELD. Could we have it?

Mr. STETLER. This is from Parke, Davis. Dr. Lueck is here prepared to discuss it if he is permitted to.

Senator HATFIELD. Mr. Chairman——

Senator NELSON. When did we receive that testimony?

Mr. STETLER. Monday of this week—the first chance we had to give it to you. But on the 6th of this month, when we presented my statement and Dr. Lueck's statement we said "We have preliminary information and we will have more, and we will get it to you as soon as we can." That was delivered on Monday of this week, 3 or 4 days ago, in full detail, with all the charts to document the material in the statement, and Dr. Lueck is here prepared to talk about it today.

Senator NELSON. I have not had a chance to read that. It is difficult enough to read the material that arrives 10 days in advance.

Mr. STETLER. This is a comparison of four brand and generic versions of Chloramphenicol that shows very dramatically the differences that exist therapeutically between these different versions of this drug.

Senator HATFIELD. Mr. Chairman, to follow up my question, is this the document that you are talking about that has been handed me—"Supplement to the statement of Dr. Leslie M. Lueck?"

Mr. STETLER. Correct.

Senator HATFIELD. Will this be presented today in the testimony for the record?

Mr. STETLER. He is prepared to do it.

Senator HATFIELD. I think it is important to have this type of thing in the record, because I feel we have had a lot of discussion—most of it has been opinion. And I have not read this, because this is the first time I have seen this. But if this is scientific evidence, Mr. Chairman, I think it ought to be a part of our record—whether you read it or not.

Mr. STETLER. That is our wish.

Senator HATFIELD. May we make it then—accept it as that? Because I have not had a chance to read it. But I think if it is what they claim it to be, it ought to be part of our record.

Senator NELSON. I have not had a chance to read it, because it only came in on Monday, and not 10 days ago. So I do not know what is in it.

Senator HATFIELD. May I move to accept it as part of the record?

Senator NELSON. Well, I would rather wait until Dr. Lueck testified.

Senator HATFIELD. Are you going to read this in your testimony, Mr. Stetler?

Mr. STETLER. He is. But he is No. 5 at bat here. At the rate I am going, I am not going to be through today.

Senator HATFIELD. Mr. Chairman—let me say, Mr. Stetler, the chairman has—we have pursued these hearings by interruptions, because we have felt it is important to clarify points being made by the witness. But I think it is also the policy of this committee, according to my understanding, that when a witness has not been able to give all of the statements that he has prepared, the committee receives that and incorporates that in the record as if he had given it. Because of time restrictions that we have, it is not always possible to hear all these statements in full. But the chairman has always been very fair in accepting all the written material prepared for this committee, and making it a part of the record as if it had been given. Is that correct?

Senator NELSON. My policy has been that if the witness who appears before the committee has submitted his statement in adequate time for me to look at it, and then there is not enough time for him to cover all of it, we have printed the complete testimony in the record of that day's proceedings. I have reserved the right not to put it in if there are some important questions that ought to be asked of the witness. I do not know enough about this statement because it did not come in 10 days in advance.

Senator HATFIELD. Mr. Chairman, then may I ask if it is not possible—to me this is the guts of what we have been discussing for a long time—to get the witness on the stand today, for the full in-

corporation of this material in our record. Or, may I request that the witness be called back next week, or some future time when we can get this into the record?

Senator NELSON. There is no question about that.

When I looked at the mass of material that had been submitted, the supplementary documents, and the size of the statements, I told the staff that there was no doubt in my mind that we would never finish this in 1 day. And to be fair to the PMA, as I always have been, we will have them back for several more days if it is necessary—as many days as is necessary to cover all the details of the problems that have been raised. You asked for 3 days, and I have given you 3 days. I am sure we won't finish it in 3. I will be willing to give you 3 more or 5 more, whatever is necessary.

Mr. STETLER. Dr. Lueck happens to be from Detroit. He is here today. If we could get to him, I would appreciate it.

Senator HATFIELD. Mr. Chairman, what I would like to clarify for the record—if this is what you claim it to be, then in the 3 days that you have before this committee, may I depend upon the fact that you will get this material before this committee in some form so it can be part of the record, Mr. Stetler?

Mr. STETLER. It is before the committee as far as we are concerned. We will be glad to present it any time we have the opportunity.

Senator HATFIELD. The point is that I want to see this as part of the record of the committee. If it necessitates your returning again and giving some of your time up for Dr. Lueck——

Mr. STETLER. We would be glad to do that.

Senator NELSON. All right. Thank you.

Go ahead, Mr. Stetler.

Why don't you proceed, and at any place you want to summarize or skip, where it is just elaboration, or a point that it is not necessary to go into detail, since the full statement will be printed you may do so and if I have a question at that stage, I will interrupt you at that time.[2]

Mr. STETLER. Thank you, Mr. Chairman.

I would like to introduce the gentlemen that are with me—a little late, but I guess I can do that.

Mr. Lloyd N. Cutler, our special legal counsel, Dr. A. E. Slesser, who is the associate director of quality control for Smith Klein & French Laboratories, and Dr. Robert Quinnell, who is on the staff, a physician from the PMA.

I want say, Senator, despite what has gone ahead of this, I do appreciate the opportunity to come before the committee, and to answer some of the charges made by previous witnesses in the hearings, and to describe how this industry does its job, and, of course, we think it does it well, and how it serves the public health.

My statement and the statement of the other witnesses that are scheduled to follow me, not only today, but on November 29, and the third day in December, which we have been promised—it has not been assigned yet—are going to address themselves to the principal

[2] See complete prepared statement of Mr. Stetler, p. 1414, infra.

questions that have been raised here, as well as to the other issues which we believe merit the committee's consideration.[3]

Senator NELSON. Let me interrupt just to say that our problem with the third day is that it appears that Congress may be running into December. And if we are—which I think we will—then we will be at the tail end of a heavy session, and going from 10 o'clock in the morning straight on through the day. And I cannot very well handle a hearing under those circumstances because some of the most important bills will be before us.

Mr. STETLER. I appreciate that. I think if we just can get across that we have really gotten a lot of people prepared, and there are studies in depth that have been done, that we would like the opportunity to get into the hearing, and whether that is in December or January—just so we have that opportunity.

Senator NELSON. You will have the opportunity if it takes 5 days of hearings or 10 or whatever length of time it takes, to cover all the material on all the issues, so that you won't feel that the industry has been discriminated against.

Mr. STETLER. As far as today is concerned, as you know, as you have mentioned, in addition to the lengthier prepared statements, we have submitted for inclusion in the record some of the studies—and I am not now referring to the supplemental statement that was just discussed—but material that was submitted as of the 6th of November. We would like to have that made a part of the record of today's hearings.

Senator NELSON. I have not had a chance to go through all those. I will look at them and see. I do not know how necessary you feel they are.

Mr. STETLER. We do think they are necessary, sir, and we would like to have them part of the record.

Senator NELSON. If they are a useful part of the record, I will put them in. I have not studied those. I don't know what is in them.

Mr. STETLER. There is a lot of material that we have gone to a lot of trouble and expense to prepare. And I hope you will see fit to put it in the record.

Senator NELSON. I will put it in. I have not had a chance to go through it all. But we will put it in the record.[4]

Mr. STETLER. They were submitted on the 6th. That is part of attachments to our statements today.

Senator NELSON. All right, proceed.

Mr. STETLER. The PMA witnesses who follow me today and later will comment in greater detail on some of the points I am going to touch on briefly in my statement. We will deal with the issues of prescribing and dispensing drugs by their generic names, and will discuss drug prices and profits. We will deal with research trends and expenditures. We will discuss the high-risk characteristics of the pharmaceutical industry and its need to attract capital for growth and for continued health progress. We will also discuss the vital aspects of produc-

[3] The statements of Dr. Leslie M. Lueck, Dr. A. E. Slesser, Dr. Leonard A. Scheele, Dr. Hart E. Van Riper, and Leland W. Blazey, originally scheduled for appearance with Mr. Stetler, appear in hearing date, Wednesday, Nov. 29, 1967, Competitive Problems in the Drug Industry, pt. 5.

[4] Material retained in files of committee's record of the hearings.

tion and engineering techniques and quality control in the manufacture of drugs, and the difference that may exist among drug products containing the very same active ingredient, but which come from different manufacturing sources. We will set forth the unique importance of the industry's promotional efforts in the delivery of product information to physicians. It is not an exaggeration to say that much of the misunderstanding that exists with respect to the drug industry arises from the failure to distinguish between these different types of manufacturers that are now in this business. The company which has the complex and extensive facilities and the highly trained personnel necessary to discover and develop drugs which someone else has not already marketed maintains cost burdens which are reflected in its prices. The noninnovator does not support such effort and therefore does not incur the expense in time and dollars necessary to make comparable vital contributions to the heal of mankind.

Senator NELSON. You have 136 members of your association?

Mr. STETLER. That is correct.

Senator NELSON. Do I remember correctly from your testimony that your members manufacture 95 percent of the prescription drugs sold in this country?

Mr. STETLER. That is right.

Senator NELSON. Do any of your companies manufacture nonprescription drugs?

Mr. STETLER. Several of our companies do. I might say that as far as the PMA is concerned, we represent them only with respect to their prescription drug business. They are represented by other associations in those other activities.

Senator NELSON. You have 136 members?

Mr. STETLER. That is correct.

Senator NELSON. And how many of those members would you call innovators, and how many are not?

Mr. STETLER. I would say that the vast majority attempt to be innovators. In other words, they do research. They do it with varying degrees of success. But one of the requirements at the present time for admission into our association is that the applicant be significantly engaged in research. This varies obviously with the size of the firm.

Senator NELSON. And you do in some of your supplemental material list the new drugs, as I recall it?

Mr. STETLER. Yes.

Senator NELSON. For the past how many years?

Mr. STETLER. This is since 1940 to 1966—the last 27 years.

Senator NELSON. You list some 800?

Mr. STETLER. 823 I believe was the number.

Senator NELSON. I cannot recall from my glancing at your material. Are they listed by year?

Mr. STETLER. No; they are not listed by year.

Senator NELSON. Would it be too difficult to identify them by year so that we have some picture of the development of innovative drugs?

Mr. STETLER. I am fairly confident that is available. I am not going into the detail of listing. But I will check back to see if that cannot be supplied for the record.

Senator NELSON. Somebody else will discuss those drugs?

Mr. STETLER. Our following witnesses are going to discuss the testing that has been done, the quality control, the research and development, the medical aspects of manufacturing, and production and engineering.

The discovery of a new potentially useful product moreover is merely the beginning. It must then be developed, another long and costly procedure which often requires more pople, more processes and more time than the original discovery. This stage requires years of animal and clinical testing, and the submission of a New Drug Application, plus exhaustive supporting data to the Food and Drug Administration.

Because the innovator discovers new compounds and health-saving uses for them that have never before existed, he must be particularly sensitive to, and capable of, assuring purity, potency, and safety through the uncompromising high quality of his product. Quality control and quality manufacture are the sine quo non of the research-oriented pharmaceutical industry. These precise disciplines are inextricably linked with the operation of the innovator firm.

Briefly, they consist of indispensable specifications and tests for each ingredient in the formula, proper design and formulation of the product, multiple inspections and test during processing and packaging, final product checks, and the preparation of detailed and meticulous records to show the complete manufacturing and control history of each batch, and to enable the manufacturer to trace his products after shipment. Quality firms are well organized to recall with precision from all commercial channels any particular lot of a suspected drug product at any time, or to provide emergency advice as to where a particular drug product can be obtained when needed.

Beyond the production process, the drug product, in all its forms and dosages, must be available when it is needed, where it is needed. Through his system of distribution points, the innovator reaches the entire Nation.

Furthermore, through the same system, he can cover an emergency within hours in virtually any village, city or county in the United States. No matter what the market situation, his product—in its full line—is there whenever and wherever the physician needs it.

Senator, on page 6, where we describe the PMA, I could skip that. I would like to start over on the top of page 8.

The pharmaceutical industry as we know it today is very young—less than 30 years old. Within these three decades, we have seen the emergence of a variety of new drugs that have all but revolutionized the practice of medicine—sulfonamides and antibiotics, cardiovascular preparations and antidepressants, vitamins, hormones, and tranquilizers—an impressive array of drug products that have virtually wiped out some killing diseases, have shortened the length of the average stay in hospitals, have reduced the space requirements of mental institutions, and have been a boon to doctors everywhere in the practice of their calling.

From 1940 to 1966, an amazing total of 823 new single chemical entity drugs were introduced as prescription drugs in the United States. That is the listing that was attached as a supplement that you referred to a moment ago.

It does, Senator, in the front of that break them down by year, as to number.

Senator NELSON. I had forgotten that.

Mr. STETLER. At this time, I would like to submit this document, and you have it, for the record, this listing which was prepared by Paul de Haen who is an authority on the listing of the drugs, and has done it for many years.[5]

I think this compilation is significant in your reconsideration of this great industry for it shows that the United States originated 502 of the 823 new weapons against disease and suffering which have been placed in the physician's armamentarium in the last 27 years.

Senator NELSON. May I interrupt for a moment?

You mentioned 823 new weapons against disease. Were they all brand new entities that treated some disease in a different way, or were they drugs that went on the market although there was already a drug available to treat the disease?

Mr. STETLER. Well, I am sure they varied. They are single chemical entities. Some of them replace a drug on the market for the reason probably that it was a more effective product for that particular disease. But it does not include the list of combinations or mixtures. They are really the new single entities, innovative type of drugs.

Senator NELSON. Is there any claim by the industry that in each one of these 823 cases the new chemical entity was a better and more effective drug to treat a particular condition than the ones already in existence?

Mr. STETLER. No; that is not the claim. The point is merely that each drug is effective for the claims made.

As you know, under the Food and Drug Act, that agency does not look at relative effectiveness. It looks at safety and effectiveness. So that there obviously are drugs on the market that—all or several of which treat a particular disease.

Senator NELSON. We have had some testimony that some of the drugs that come on to the market are simply drugs that treat a condition for which there is another drug already marketed that is just as good, or better, than the new drug.

What I am wondering is, do you break this 823 down in such a way as to indicate for the record how many of them are new drugs to treat a condition in a new way as contrasted with a new drug which treats a condition in the same way that other drugs in existence already do?

Mr. STETLER. Senator, that would be impossible, because of the variety in medical opinion, as to the relative effectiveness of drugs that attack the same disease entity. I am sure you would get one opinion from certain physicians, and you would get varying opinions from others. So this is not really susceptible of that kind of breakdown or documentation.

Senator NELSON. You are aware that there are distinguished people in the field of pharmacology who do state, and some have testified, others will later, I assume, that a considerable amount of research is done simply to find molecular manipulations of other drugs. These modifications, which do the same thing as the original drugs can get their own trade names, when in fact they are not necessary, and do not

[5] Material retained in files of committee's record of the hearings.

do anything other drugs do not do. You are aware of that assertion, are you not?

Mr. STETLER. Very definitely. And actually Dr. Sheele, who is here to testify today, when he talks about research, wants to deal in some little detail with molecular modification, and to show the other side of this situation. He will mention some of the very fine products and cures that have resulted from this research which I assure you is not fallacious or flimsy.

Senator NELSON. We have had testimony, as you know, that there have been fruitful results from what is sometimes called molecular manipulation and modification. On the other hand, we have had testimony that there is a considerable amount of research which is really aiming at getting another combination of molecules to develop a drug which is not more effective than a drug that is already on the market. But the new version can be identified with a brand name, and then promoted.

Mr. STETLER. Of course, the mere existence of multiple drugs on the market that have a similar effect is not necessarily bad. I suppose if we were to outlaw that, we would eliminate a lot of very healthy competition. So that there is an economic and a medical aspect to this question, both of which are complex.

Senator NELSON. I have not suggested that it be outlawed. But I think there ought to be some attempt to understand this.

Mr. STETLER. I really think that the statement that Dr. Scheele has submitted, which we will comment on later will help to clarify that.

Of the U.S. discoveries, the laboratories of American manufacturers were responsible for 87 percent. The others came from university, nonprofit, or Government sources.

The issue of generic prescribing and dispensing—and that certainly has been one of the major issues discussed—a great deal has been said during these hearings about prescribing by the generic name of the drug. I would like the record to be perfectly clear that the prescription drug industry and the PMA do not oppose the physicians' freedom to prescribe in this way. We believe a physician should be entirely free to prescribe as he wishes, whether by a manufacturer's brand name, by the generic name with the manufacturer identified, or by the generic name alone.

Senator NELSON. I do not think we have had any witness before us who has testified that the physician should be deprived of his right to prescribe by trade name?

Mr. STETLER. Well, there has been legislation introduced which—at least with respect to governmental programs, like medicare—would involve compulsory generic prescribing or compulsory substitution if a doctor prescribed by brand name. Obviously, that legislation has not been before this committee. But there has been a close tie-in in some of the discussion by people who have advocated that, and some of the theories I think lap over. There also has been a misunderstanding that our association is strictly brand oriented, and that we are advocates of a compulsory or exclusive brand prescription posture for doctors. And that is really the point I wanted to make here—that we recognize all three are completely legitimate depending on the circumstances and the doctor's wish.

Senator NELSON. To the best of my memory, we have not had any witness who said that doctors should be allowed to prescribe only by generic name. We have had some distinguished pharmacologists and doctors who have said that it is much better medical practice to prescribe by generic name, and then if the doctor wishes, to name the brand he wants—whether it is prednisone, Schering, or prednisone, Lilly, or predisone, Wolins, or predisone something else. It is a much better way to practice medicine. But our witneses did not testify that the doctor ought to be deprived of his right to name the company where the generic name drug is manufactured.

Mr. STETLER. That is my recollection.

In a true generic prescription, the physician delegates to a pharmacist or nurse the selection of the manufacturing source for the product prescribed.

Senator NELSON. The suggestion that generic prescribing delegates to the nurse is new to me.

Mr. STETLER. In some situations, in some areas, the nurses have some authority that would extend into the prescription drug field. This is obviously not to the degree with nurses as it is with pharmacists. The predominant situation would be that delegation of authority goes to the pharmacist.

Senator NELSON. I have never heard of this kind of responsibility being given to a nurse. That is why I raised the question. Are you referring perhaps to a situation in which a nurse may be practicing in a hospital which has a formulary?

Mr. STETLER. No, I am not trying to make a big point of this. I am not thinking of a nurse in the situation, where the hospital has a formulary. That would normally be the decision of the hospital pharmacist.

Senator NELSON. You agree that whenever a hospital establishes a formulary, you do deprive, for all practical purposes, the doctor's right to prescribe entirely as he sees fit.

Now, in all formulary situations that I am aware of, the formulary committee and the hospital administration says, "Well, if the doctor really wants to prescribe this brand name, he can come to us, and he may be authorized to do so." But as a matter of practice, what you have done is agreed by an evaluation of the drugs through the formulary committee that this will be the formulary for the hospital, and maybe 99 percent or more of the prescriptions written by the doctors are written according to that formulary, and it is only the rare exception, when a doctor says "I want to prescribe this brand name." Isn't that correct?

Mr. STETLER. That is true.

Of course, with respect to a formulary—the word covers a large area. There are all types of formularies, even at the hospital level.

I think the important thing to remember in connection with the formulary is that most of them operate at the local or the hospital level, and the decision is as to the drugs included on the formulary is made by a therapeutics committee, probably consisting of the doctors who practice on that staff, and the administrator, and the hospital pharmacist, that you have got a pretty good formulary in terms of the practices of the men that are going to be governed by it.

But the one thing you mentioned which is important is that escape valve that permits the doctor to go outside of the formulary if he decides to do so. I think that is the ultimate saving feature.

Senator NELSON. I take it you agree that the formulary system, if it is a good formulary, is a sound method of establishing the drugs to be prescribed in a hospital; do you not?

Mr. STETLER. We have not opposed it. I think the formulary system has been effective in many of the larger hospitals, particularly where they have people with particular competence that can serve on these therapeutic committees, it has been used as sort of an inventory control in some situations to reduce the cost to the hospital.

Now, that is not necessarily bad, if it is tied in with the sound medical decisions or drug decisions that go into the ultimate listing of the drug products. But we have not taken a position in opposition to hospital or local formularies.

Senator NELSON. What is your view with regard to the adoption of hospital formularies by practicing physicians or by smaller hospitals? In other words, you have a hospital in New York or Los Angeles that has a large number of patients, and all the specialties of medicine practicing there. The formulary is developed by the specialists in all aspects of medicine, along with the pharmacists, and then published for that hospital.

What is your view of a smaller hospital without those facilities adopting this formulary, or of a private practicing physician adopting a formulary to use in his own practice?

Mr. STETLER. I think the test really is, and the one that would govern our reaction to your question—if the doctor decides it for himself, that is, if it results from his independent professional decision, it is agreeable. As far as the decision by even a small hospital is concerned, if it really represents the wishes of the doctors that are going to be governed by it, there is no objection to it. If it is something that is foisted on them by the administration, or somebody that cannot speak for the medical judgment within that hospital, then it is probably wrong.

Senator NELSON. Well, would you agree or disagree that it is a very sound and beneficial approach to use a formulary system and make it available from distinguished hospitals, and to encourage doctors to use a formulary that has been developed by the great variety of special expertise that a hospital has?

Mr. STETLER. I think that depends on the local situation. If, in the opinion of the doctors that are governed by it, it does not impede their practice, or thwart their individual decisions with respect to drug therapy, then it is a fine, valid procedure. If it impinges on any of those things, then it is probably not good.

That means it is going to be difficult to transplant a formulary that happens to work at one particular hospital to every other hospital situation around the country.

Senator NELSON. I wasn't suggesting the question compulsion. I was simply suggesting that because there are 7,000 different drugs and 21,000 brands of these 7,000 drugs, it is really hardly possible for a practicing physician to be aware of the best selection to be made unless he is in a very narrow specialty, and only uses a handful of drugs.

My question is whether it would be a good educational device, good

for the practice of medicine, and good for the patient. Should not the use of the formulary system be encouraged—not compelled—but encouraged? Would you not solve a lot of problems if the physicians practicing in New York City or Chicago or any place else had available to them a formulary developed by a distinguished group of clinical specialists in all aspects of medicine, so that they could use such a formulary in their daily practice? And, would it not be beneficial to the patient?

Mr. STETLER. Just commenting on that, I really think the fallacy that exists is the impression that a doctor, any doctor in practice any place ever gets close to 7,000 drugs.

Senator NELSON. I have not suggested that.

Mr. STETLER. No—I am just commenting on that. Because the need to solve all these problems for a doctor in terms of how many drugs he must be conversant with is not as big as some would indicate. I have a hunch that most doctors in their practice probably routinely use no more than 25 or 50 drugs.

I think it would be a good exercise for some hospitals to just keep track of all the prescriptions written by their medical staff in a year, and see how many drug products are involved.

I think you could devise a formulary after that that would not be very restrictive, and would probably accommodate the great bulk of the needs or the prescribing habits of the doctors that operate on that staff. And it would not approach anything like 7,000 products, even for a hospital.

I am not in disagreement. I am not saying formularies are bad. I think when they are devised and administered, taking into consideration the needs, the wishes of the doctors, and it can be done without really leaning on them—then I think it can serve a good purpose for all—for the hospital, and for the doctor, and for the public.

Senator NELSON. One of the problems, as you are aware—your association and the industry people raise it very frequently—is the reliability of drugs, the problem that perhaps some of the generic drugs do not meet USP standards.

Since a private practicing physician does not have the facilities to do the testing, and cannot always have the consultation of distinguished specialists, there may very well be a tendency for him to stick to a drug priced far higher than it ought to be, when in the hospital formulary they are using the same drug at a fraction of the cost. And from a patient's viewpoint, in terms of cost, the doctor is charging this patient much more than the patient ought to be charged. The doctor may not be aware of the alternative drugs, or he may be concerned about prescribing one that he does not know, whereas the hospital may be using generic or trade-name drugs that are much cheaper.

This is one part of the question I am getting at.

Mr. STETLER. I am going to get into that in a little bit.

There is no question in our minds—there are valid and serious differences between drug products, and just because they have the same generic name, you cannot equate that with therapeutic effectiveness. That is a little bit of a side issue. But it is certainly germane to the point.

I would also say I am sure there are individual and I hope rare situations where a price disparity might be handled by a knowledge-

able formulary committee to the advantage of the patient and the doctor. But nobody should get so enthusiastic about price that they override the medical judgments of a doctor because he happens to practice in a hospital that has a formulary.

I do not think you are suggesting that. And that is all I am trying to say. That is the element that ultimately has to be preserved.

Senator NELSON. This dispute about therapeutic equivalency and clinical effectiveness, and so forth, keeps being raised all the time. The reason I raise it here is, if we had a formulary, I doubt if there would be very many doctors, if any, in the United States who would prescribe a prednisone that cost $17.90 to the pharmacist, which would be about $27.28 to the consumer, depending on the fee, when an equivalent drug is available at $2, or $1, or even at as little as 75 cents. This is what bothers me.

The Medical Letter, on the basis of chemical tests and opinions of a distinguished group of authorities consulted around the United States, flatly asserted that the 22 prednisones they tested are equivalent.

Really it would be a shocker to me—and more of a shocker to some poor person who is on social security—if he found that he pays $25 or $26 for a hundred prednisone tablets when therapeutically effective tablets are available according to the Medical Letter, at $2 a hundred. This is what shocks me.

Now, if there were a formulary—I doubt whether there is a physician in America who would be using Meticorten at $17.90, when they can get Merck's at $2.20.

Mr. STETLER. A comment on that, Senator.

As you know, from previous testimony that was presented, the feeling does exist, and I share it, that doctors should be permitted to make the decision on the drug. But—I am sure this is not an appealing statistic to one of our members, Schering—but, nevertheless, their share of the market on prednisone has gone from a hundred percent down to 5, so absent the formulary—they apparently have decided on their own to either write for a generic product or for another brand. So the free forces of our economy, and the knowledge of doctors about not just medicine, but economics, have in a large extent taken care of the prednisone differential.

As far as the Medical Letter is concerned, they have not said that based on their testing, they have found therapeutic equivalency between the products they looked at.

One other thing. There are probably 75 or a hundred manufacturers of prednisone, and if a doctor were to write generically, neither he nor the patient would know whether they are getting one of the products from the 21 who they found chemical equivalency for, or the other 50 that nobody has bothered to look at all.

But the Medical Letter does not talk in terms of therapeutic equivalency.

Senator NELSON. What they do is just to reach a flat conclusion, which is just as good.

"The great price spread—purchased from different pharmaceutical companies suggested the desirability of prescribing by generic name, and specifying that the prescription be filled with low-priced prednisone tablets." They just flatly reach the conclusion that they are equivalent.

Mr. STETLER. They have reached a very broad conclusion, if they have made it based on the testing they did.

Senator NELSON. I suppose what is proper to say about it is that if there is any evidence they are wrong about it, the evidence ought to be presented.

Mr. STETLER. Well, that is what we are prepared to do.

Senator NELSON. But if you have a formulary, you would not be paying $17.90. I am not picking on any particular company. I think I can find a case like this in almost every company manufacturing trade names.

Mr. STETLER. I doubt that.

But in any event, as I say, in 95 percent of the cases it has been taken care of, because they only have 5 percent of the market.

Senator NELSON. There is another company charging $17.88.

Mr. STETLER. They are not charging $17.88. You remember when Schering testified the average price they reported to the committee was considerably less than that. There is a disparity, however.

Senator NELSON. We also referred to the Red Book and used the Red Book figure. When Schering testified they said that subsequent to the last publication they had reduced the price. Well, it doesn't matter. It is off a dollar or two.

We took this from the Medical Letter, and the Medical Letter was June 2, 1967.

Mr. STETLER. Are you interested in some comment on that particular thing?

Senator NELSON. We would be glad to have it. I was thinking of prednisone where the manufacturer said the price we list is not the price charged to the pharmacist. They said there was another Red Book coming out.

Mr. STETLER. I wondered if you wanted any discussion of any length on the study done by the Medical Letter on prednisone.

Senator NELSON. Yes; go ahead.

Mr. STETLER. Could I ask Dr. Quinnell to comment on that?

Senator NELSON. The time is now 12:20. Why don't we hold that question and resume with it after lunch.

Senator JAVITS. Mr. Chairman, I would like to ask a couple of questions before lunch, if we could lay prednisone aside momentarily.

May I ask you this, Mr. Stetler.

Would you agree that what the problem here is, is that there is some kind of a cabalistic mystery about what a doctor writes in a prescription. Hence, it is not as though the patient went down to a department store and shopped competitively with a supermarket or the drugstore, a large drugstore, where he might buy notions and other things that he knows about. But if Dr. A says—this particular kind of a product—he is scared to death to take any other.

The question that I would like to ask you is this:

Isn't it really the duty of the industry to put competition on a basis on which it exists in most other elements of American business—where the consumer can buy any brand of product that he wishes to? He doesn't have to buy percale sheets, other than Burlington, if he doesn't want to. But he can, because he knows that percale sheets are percale sheets, and they are made with a certain kind of denier, and a

certain kind of weave, and a certain kind of cotton, and the rest is up to him.

Now, what is your comment on that?

We talk about formularies and compendiums and so on. But isn't that really the essence of the thing? That is what this is all about?

Mr. STETLER. Senator, if we were—if we could—and I make the point right at the beginning we cannot—if we could be sure that all of the drug products that are on the market were safe, effective, and if they bear the same generic name, that they are equivalent therapeutically, then a doctor could with freedom and ease and safety write generically and permit the prescription to be filled by any drug the pharmacist carried.

That is not a fact. That assumption cannot be made today in this country. And I doubt, frankly, given the varying credentials of manufacturers and the way they do their job, that it will ever be made validly.

But I do not disagree with your basic premise, and that is that the people that make the decision as to what drug they are going to finally purchase, whether it is the patient or whether it is the doctor as the agent for the patient, has to know more about the prices that exist for the products that he is going to prescribe.

He has to make that decision first on the basis of known therapeutic effectiveness and a quality source.

But assuming there are multiples that fill that requirement, he should know something about price, and he should help the patient save money.

We say that in our statement, and we are sincere about that view.

Senator JAVITS. Dr. Goddard—and I am obliged to the chairman for this, and the minority counsel, Mr. Grossman—testified as follows on page 768 of the record.

This was in answer to a question by Senator Scott.

Senator Scott asked:

> At this time your agency cannot assure physicians that the chemical equivalent drugs now on the market are therapeutically equivalent. But is it not a fact that you are working toward that end, that you are seeking to be able to do that?
>
> Dr. GODDARD. Yes, sir. I do not think anyone can provide absolute assurance that the therapeutic equivalency exists for every drug in the marketplace. But by the same token I have not seen any good evidence from any firm, large or small, that their drug is superior to anybody else's. I hear the statement made time and again. I have challenged representatives from firms who have made this statement to show me the evidence that its drugs are superior. Generally now we are talking, you understand, from the pre-1962 drugs where effectiveness did not have to be proven.

Now, do you have any comment?

Mr. STETLER. I have a very specific comment on that. I cannot recall when Dr. Goddard made that statement. But some of the discussion that has gone here a little earlier today——

Senator JAVITS. The 10th of August.

Mr. STETLER. We have stated that we have today, and the material has been given to the Food and Drug Administration, that on a very significant product, chloramphenicol, these tests have been made, FDA has had them, the preliminary results, for several weeks, they now have all the results, and so does this committee.

Now, we are prepared to discuss it. But it was decided earlier today that the committee has not had a chance to review it. But whenever

the committee is ready for it, we are prepared to discuss it in great detail.

Senator JAVITS. Dr. Goddard testified to the same thing on November 9—practically the same words.

Mr. STETLER. He has had this material in his hands before November 9.

Senator JAVITS. This is all lost in the whole forest of the fact that you submitted highly complex data on one product among many, and he has got it, and everything is hung up in long discussions.

I was a lawyer long enough to know how this can be done, and business can go on as usual for decades. Some cases are still pending that I had before World War II—not in this field, but in others.

What I would like to ask you is this:

Is there any plan to be affirmative and constructive that you can bring in, if we give you time to do it, which would try to make a better competitive situation than—and I think the word "we" is not inappropriate—certainly I think so—exists today?

What about an industry plan which will give the public a better break so the public can have more weight in the decision than in my judgment—I won't join anybody else with me—it has today?

I am all for your innovations, and I am all for profits. I am very straight about that. I don't want to thwart you in that. We don't expect you to give the stuff away. But I think that the competitive result of letting the buyer make the decision on some concrete base which either the Government or the industry will establish will right the competitive situation, and you will not have these extremes, which seem ridiculous to me, too, of one outfit selling prednisone at $2 and another outfit at $17.88. I cannot believe that competitive advantage is warranted.

I am just a reasonable fellow buying it at the window and paying for it.

So I would like to ask you that—to answer it now or answer it later. But I think the industry ought to think through the deep complaint here. And I will tell you one thing. Something is going to happen. There is just too much evidence on this to let it stand as it is.

Now the question:

Isn't it better if the industry can come in with a recommendation as to what is the best thing to do to right a serious competitive situation? And I think a serious competitive situation exists. It is very unfair to some that the public cannot tell between the fellow that charges $2 and the fellow that charges $17.88, just because the doctor writes cabalistic symptoms on a prescription.

Mr. STETLER. Well, I will comment on that briefly. Obviously, that is a big order. The point about how the doctor prescribes and the fact that it may seem complicated, is justified because of the fact that regardless of what Dr. Goddard said just a week ago, these variations do exist, and a doctor cannot safely write his prescriptions generically.

Now, that does not get to your economic question, I agree. But you have to start there. There is a serious problem there, and it cannot be solved.

The economic question cannot be solved just by generic prescribing. We are not at that stage yet. Whether we will get there, I don't know.

But absent that—I think that we should, and we are willing to try and devise a system. But when we talk about the economics of drugs—we cannot start or stop at manufacturers' prices. We have to be prepared to talk about it up and down the line, because ultimately we are talking about the price paid by the patient.

So we have to examine the elements of this whole distribution system. The pharmacist, the wholesaler, and manufacturer.

Now, to the extent there is inadequate price information available to anybody that makes that decision up and down the line, we think he should get more information. We think he should have more information about manufacturers' prices, and we think the public and the doctors should have more information about retain prices.

When he gets this, he is going to be able to make a more intelligent decision.

Now, how this is done, I don't know. Getting this information around and making it available is not a simple proposition. But we definitely would like to be a party to the discussion of how that could be done most effectively.

Senator JAVITS. I don't think I quite got my point across to you, from your answer. My point isn't that I want to take surveillance over the distribution costs, advertising cost, research cost, and so forth.

I want it to be a matter of private business decision.

But what I say is, Why can't a fellow who goes into a drugstore, or a doctor who prescribes, the minute he says prednisone, then the patient knows and the doctor knows that he cannot possibly get a product from the pharmacist that does not meet certain minimum standards set by the FDA or by you people——

Senator NELSON. Senator, he can.

Senator JAVITS. Just a second—which qualifies for prednisone.

Now, if the doctor says, "Look, there are lots of prednisone. They all qualify technically. I don't like most of them. I like this one. I want you to have this one."

The patient would probably do it.

But, nevertheless, having that concrete base that anything marked "prednisone" is illegal unless it meets certain minimal standards, the competitive situation will bring down these inordinate disparities in price.

The question I asked you is, Who do you want to do that—do you want the industry to do it or the Government to do it, and if you want the industry to do it, what kind of a plan have you got?

Mr. STETLER. Obviously, we want the industry to do it. But could I just say that the premise that you state with respect to prednisone is not right. You cannot say today that the hundred sources of prednisone on the market are all in compliance with Government standards.

Senator JAVITS. Let me interrupt you. I am not saying it today. I am asking you, How do I get to the point where I can say it?

Mr. STETLER. I suppose we get to that point when we can say that all manufacturers of drugs at least meet some kind of standard as to expertise of their employees, adequacy of their facilities, know-how, and some consistent way to assure that on a day-to-day basis they utilize the facilities and the people they have in the proper way.

Now, we don't have that today.

I realize an effort is made through the FDA and the Food and Drug Act to attain this. But it doesn't exist today. And this is not critical of the Food and Drug Administration.

Senator JAVITS. I am sorry, sir. You and I have one point that we don't see eye to eye. All I want to know is that the end product meets a certain standard when tested. I don't care how he made it. If he has a better way to make a mousetrap, bless him. If his employees work 8 hours instead of 8½, that's his business. Performance is the only thing I care about. I don't care about all the other things you talked about—except I ask you, How do you get to the point where if a person goes in and buys a particular item that is designated by a particular name—not a trade name, but a generic name—that he knows at least it meets such and such minimum performance standards? That I think is the real issue.

Mr. STETLER. I thought I was being responsive to that. Maybe I am not. I am interested in performance, too. But you don't get performance in the drug industry unless you have the other ingredients.

Senator JAVITS. That is not our business or the consumer's or the Government's business.

Mr. STETLER. It may be the Government's business in this way. In our present Food and Drug Act, we anticipate that the FDA can do a continual surveillance on whoever is in the drug manufacturing business.

Now, we don't look initially at the credentials of people that are in the drug business, and given the number and variety of people that manufacture drugs, we burden the FDA with an impossible situation, in my opinion. At least to that extent, maybe we ought to look again at what the Government might do properly in terms of the credentials, first of all, of the people that manufacture drugs. That will get down to the end process, the end product.

Senator JAVITS. All right.

I think we have made our respective points of view clear. I don't think they are necessarily parallel yet.

I would like to ask just one other question.

You have talked about a formulary. We have been up and down that track.

What about this compendium?

Now, are the industry and Goddard together on getting this out? He says it will take 18 months and you people think it will take 2 years.

Well, that's not too much difference.

Are you people and Goddard together in getting that out, and if not, what's holding it up?

Mr. STETLER. May I have a moment to discuss this. This has a little history to it.

This discussion of a compendium has gone on now for two and a half years. It was initiated at that time by the Food and Drug Administration when they asked representatives of the PMA and the American Medical Association to consider the possibility of eliminating the package insert that is now a regulatory requirement with respect to drugs and substituting a compendium.

Those discussions broke off. They did not get very far along because Mr. Larrick, who was then Commissioner, indicated that such a com-

pendium would have to be in existence for some time before he would entertain the idea of discontinuing the package inserts.

More recently, the Drug Research Board of the National Academy of Sciences has had for the last year or 18 months a series of meetings with interested parties. That is not just the FDA, and it is not just the PMA. It includes the American Medical Association, the American Pharmaceutical Association, the American Society of Hospital Pharmacists.

Those conferences have been held to answer five or six specific questions. Is an additional compendium necessary—and mind you, there are compendia now on the market and available. If it is necessary, what should its format be? Should it be published by private sources or by the Government? What is its estimated cost, and how should it be financed?

Now, despite the fact that Dr. Goddard sincerely believes that all these questions have been answered to everybody's satisfaction, they have not to the satisfaction of most of the parties involved and they have not been to ours.

We have a serious question as to whether or not existing compendia, such as the U.S. Pharmacopeia, the National Formulary, New Drugs, put out by AMA, or the Physicians' Desk Reference, possibly could be revised to make acceptable document for the physician.

I have been personally at every meeting that has bene held by the Drug Research Board on this question. I know the nature of the discussions.

I have yet to hear what the doctors think about this proposed compendium.

I happen to believe, in view of my past employment, that doctors are not in agreemnt with this compendium as now proposed. And I think, since we are talking about a tool for physicians, the best thing we could do is ask the doctor—What do you need or what do you want in the way of a compendium?

They are not, despite what was said last week, in agreement that this compendium should be initiated.

Frankly, if we are going to be asked to pay the bill, we think we should have the answer to such things as, What is the format of this book going to be; are all drugs going to be listed; are they going to be listed generically; is there going to be a classification for a group of therapeutics; how are they going to be handled? Will all dosage forms be accommodated or not?

Now, I know that the objection to the PDR is that it is a document paid for by the industry. In other words, these are allegedly ads put in this book.

Senator NELSON. They are ads; aren't they?

Mr. STETLER. They are paid for. But they are labeling—that is why these "Dear Doctor" letters have gone out. They have got to comply with FDA regulations.

Senator NELSON. Just to have it clear—they don't go in the PDR unless they are paid for.

Mr. STETLER. That's right. I am not denying that.

Senator NELSON. So it is a paid ad.

Mr. STETLER. If PDR is vulnerable for that reason, would any compendium be suspect if industry paid for it?

I am wondering if possibly the material in PDR could be made acceptable if in every instance it had to be FDA-approved language.

Senator NELSON. You are aware, of course, of Dr. Goddard's proposal which he has discussed casually a few times—once before this committee—that he would like to see the publication of a compendium financed by industry. And if you have a compendium, he would waive the requirement of the package insert which costs $5 million a year; and then that $5 million would be spent by the industry on the compendium.

His further comment was that he would like to see it done by PDR, because every doctor is familiar with it. The compendium should list all the drugs by their generic name, use, side effects, the contraindications, and then list the companies that manufacture the drug. All of this would be done with FDA approval.

This, I think, is a rough statement of his position.

And if publishing it and keeping it up to date regularly would cost $5 million, as Dr. Goddard estimates, the industry would break even on the cost.

Mr. STETLER. Both of those figures, of course, are pure guesses.

Senator NELSON. Correct. I said "if he is correct, they would break even on the cost."

Mr. STETLER. Obviously, one point I think we should be interested in, and you, too, as a sponsor of a bill—What would the doctors want in the way of information on drugs? I think that is the main point—one concerning which we would like to hear more discussed.

Now, I don't think whether it is $1 million, $2 million, or $5 million we would be interested in paying for a book if it is going to be a futile exercise and not of use to the doctor.

Senator NELSON. You say you want to know if the doctor is interested in such a compendium. These discussions started with Mr. Larrick two and a half years ago. Haven't you been able to find out in the last two and a half years what doctors might want?

Mr. STETLER. I happen to think that the doctors don't want this compendium. I realize you heard testimony last Thursday to the contrary. But let's hear from the doctors. I think they do not want this compendium. If they don't, I don't see why we should put up $5 million to pay for a useless book.

Senator JAVITS. What about the millions of consumers that pay the bill?

Mr. STETLER. This book would not be for the consumer.

Senator JAVITS. Wouldn't it help the consumer in the sense that you have a group of doctors advancing through medicare and many other ways in which the Government pays doctors—which would have to use this book, and the way it should be used, on a competitive level?

In other words, if you don't prepare it at all, this thing will never get off the ground. I am considering, as you have heard, to join the Chair in a piece of legislation. Then we will have some hearings and find out what this is really all about.

Mr. STETLER. I happen to think that's exactly what you should do. I think there should be a bill introduced and I think there should be hearings, and everybody should be allowed——

Senator JAVITS. Good. And if the doctors have an objection, they should state it, and especially, why.

Mr. STETLER. I think there should be hearings.

Senator JAVITS. I think that's extremely helpful. And probably any proposal on this subject would come to the Labor and Public Welfare Committee—thus giving us a chance to get at it.

Senator NELSON. The point the Senator makes is a very good one from a consumer's standpoint. I am not frozen into any position as to what I think ought to be in a compendium. But one item that might be in there—I think the Senator would be interested—is the price of each drug listed, and, of course, FDA must be equipped with the personnel to properly inspect plants and assure quality control. If you did that, when a doctor opened up the compendium and found 22 prednisones, or 50 or 75 reserpines listed or something else, he would know that FDA has quality-control checks, that all drugs meet USP standards, and that FDA has given them all a stamp of approval. I think the doctor would be pretty likely, unless he had specific clinical experience that somehow would persuade him otherwise—to look at that compendium, see the FDA approval, have confidence in the quality-control program that is being supervised, and prescribe the drug that is most economical for the patient.

I suppose that the industry would object violently to that, because they like to get into the marketplace and advertise, and even after the patent runs out have so imprinted the name of the drug in the doctor's mind that he is going to prescribe it even though there are equivalents on the market. I don't blame the companies for that, but that, in fact, does happen.

Mr. STETLER. Senator, you know from our statement that we have made the point, and I make it very sincerely, that I think more price information should be made available to the doctor and to the public.

I know you have written to a lot of people and a lot of companies to ask about their views on a compendium, so that a bill could be perfected. But on this issue of price—and I want to tell you I am not opposed to price information being distributed. But consider for a minute whether price is a proper ingredient of a compendium.

Are we talking about manufacturers and retail prices in the compendium? If the former, would the prices of the hundreds of manufacturers that are in this business be shown? If it is retail—I don't know how we could keep up in a compendium with the day-to-day, store-to-store differences in price or how it would be shown and kept up to date.

Senator NELSON. As I say, I don't have a rigid position on that, because I don't know. It is worth considering. And, as you are well aware, under the present law no prescription drug can go onto the market in America and comply with the law unless it complies with USP standards.

You shake your head?

Mr. CUTLER. I am shaking my head, sir, because while it is a violation of law for drugs to go on the market under those circumstances, the FDA is in no position to assure that it does not happen. It can and it does happen.

For example, the FDA today has no inspection or registration procedure for foreign plants—a very difficult problem, of course. But they don't. They don't have any idea whether those drugs entering this country do meet these standards, except on a spot check basis.

Senator NELSON. You should have been nodding your head. You are saying exactly what I said.

Mr. CUTLER. It is a violation of law.

Senator NELSON. I said under the law a prescription drug may not go onto the market in this country unless it meets USP standards. And if it doesn't, it is in violation of the law.

Mr. CUTLER. That's correct.

Senator NELSON. You just repeated what I was saying.

Mr. CUTLER. We are quibbling, sir.

Senator NELSON. I am not quibbling, you are.

Mr. CUTLER. It can get onto the market even though it violates the law.

Senator NELSON. Under the law a prescription may not go onto the market in America unless it complies with USP standards. If it doesn't, it is in violation of the law.

Do you agree with that?

Mr. CUTLER. I agree with that; yes, sir.

Senator NELSON. That's exactly what I said.

So there are some problems. One of them is whether or not there is adequate plant inspection. The Chair is well aware of that. We have had many witnesses long before you came here on this exact point. The question is to be sure that the inspection is adequate to assure that only high quality drugs are on the market. Everybody wants that. If the manufacturer cannot meet the standards or won't or is not equipped to, I am the first one to say we ought to close his business. One of your major members had his business closed up by the Government 3 years ago.

Mr. STETLER. Senator, that plant was closed voluntarily by Squibb, not by the Government.

Senator NELSON. It was after a very tough report by the Government.

Mr. STETLER. But it was not closed by the Government.

Senator NELSON. In any event, if drugs meet USP standards, and you have had adequate inspection, then you are all set. I think you probably need some support from PMA that will increase the inspection capacity of the FDA. Do you support a big expansion of their inspection program?

Mr. STETLER. We have supported their request for appropriations for additional inspectors, and think they should be given more of the tools to do that job.

Senator NELSON. Good, I commend you for it. I think that is part of the problem.

Mr. STETLER. Me, too.

Senator JAVITS. I hope you will understand my point. I want to see a compendium or call it what you will where the whole list of availability is there. But when the name "prednisone" appears on a product, whatever else appears, how much advertising they do—it is all private enterprise. When the name "prednisone" appears on a product, that it is a criminal offense if it does not meet a minimum standard, so that the patient knows when he takes a tablet marked "prednisone" somebody is guilty of a crime if it does not at least meet a minimum prednisone standard. I think if you did that, the marketplace would take care of not all the rest but most of the rest.

Mr. CUTLER. May I say one thing on that?

I don't know of a product—you spoke earlier of your vast business experience, which you certainly have, and your legal experience. But I don't know of a single product, no matter how many Government standards there are, as to which the buyer of that product, be he a giant corporation or an individual, does not make a judgment in the market based both on quality and price. There are differences in quality among products that meet some minimum Government standards, be it steel, automobiles, bourbon whisky, anything you mention. The problem we face—and it is a real problem—you have your finger on it—and that is the judgment for a drug as to quality really cannot be made by the patient—it must be made by the doctor.

At the same time the doctor is not spending the money. So the doctor may be more indifferent to price than he should be. But that is our dilemma.

Senator JAVITS. Well, that is not my dilemma. My dilemma, as a Senator, is to get the Government to lay down a standard for prednisone.

You can claim X is better than Y. But I say if a patient knows that anything he takes, that his doctor prescribes, or however he gets it—if it says prednisone, he is getting a basic minimal product that the U.S. Government says satisfies a basic minimal standard for prednisone. That is in my judgment the reason for the competitive base. And I think it is the same reason you have the FDA—because this is a business in which the individual cannot himself judge that the minimal standard is met. And I think—for myself, I think if that happens, then you would be well abreast of dealing with this and still leaving a very large field for private enterprise.

Mr. CUTLER. On that we fully agree.

Senator NELSON. I might say, that there is a Government standard, and it is not a minimum, it is a maximum. The drugs have to meet the USP standards. The drug industry, pharmacologists, physicians, and so forth, consult and establish highest standard possible for every drug and it is a criminal offense to violate the standard.

So if there is a problem, the problem is on surveillance of the marketplace.

Senator JAVITS. And setting it down somewhere where the consumer can see it. That is why we are talking about this compendium. That is what I am talking about.

Senator NELSON. We will recess at this time and resume at 2 o'clock.

(Whereupon, at 1 p.m., the hearing was recessed until 2 p.m., the same day.)

AFTERNOON SESSION

Senator NELSON. We will resume the hearings.

STATEMENT OF C. JOSEPH STETLER ET AL.—Resumed

Senator NELSON. Mr. Stetler, were you on page 10?

Mr. STETLER. Yes.

Senator NELSON. As I said, if there is any place where you want to summarize or skip, you go ahead and do it. Since you did prepare a summary, you are a better judge of what you might want to skip.

Mr. STETLER. What I have done on my copy is bracket out paragraphs. I am going to be skipping through. If you want me to answer a question just refer to the page——

Senator NELSON. If you do, just let me know. I may have some questions.

Mr. STETLER. Should I proceed, Mr. Chairman?

Senator NELSON. Go ahead.

Mr. STETLER. We also believe that, in prescribing, doctors should supplement their medical judgments and decisions regarding drug quality and effectiveness with considerations of cost to the patient. If the doctor believes that two manufacturers market drug products of substantially identical therapeutic effectiveness and quality, he should, of course, prescribe the less expensive one for his patient.

I would like to say a further word on the subject of prescribing by using the generic name of the drug. While we favor the right of the doctor to prescribe as he wishes, we emphatically disagree with the assumptions and statements advanced by certain earlier witnesses before your subcommittee that generic and therapeutic equivalency go hand in hand.

Senator NELSON. What do you mean by that?

Mr. STETLER. You can have equivalency in terms of equal content of the drug, and you may have chemical equivalency, but that is not the whole problem. You have to determine whether or not the drugs act the same way in the patient, and that is how we refer to therapeutic equivalency.

Senator NELSON. All right.

Mr. STETLER. As has been pointed out in papers by a number of leading physicians and pharmacologists in the previous testimony before this subcommittee, the term "generic equivalent" refers only to the name of a drug product and does not necessarily connote its safety or therapeutic effectiveness. Although two drug products may contain, or are supposed to contain, the same amount of the same active ingredient, this provides no assurance that both products will produce the same clinical effect in any particular patient.

Senator NELSON. Are you going to give some examples where two drugs did in fact meet USP standards and they were not therapeutically equivalent?

Mr. STETLER. Yes, sir. That is the thing we talked about this morning, and the thing I really am alluding to in this next paragraph. Two of our witnesses scheduled for today—Dr. Slesser, who is supposed to follow me, has an extensive indication of published data in this regard—and then Dr. Lueck who has submitted the supplemental statement, has the results of some very specific testing on the product Chloramphenacol. Between those two presentations I think we will have provided you with a considerable amount of evidence in that field.

Senator NELSON. My memory is that Dr. Miller, Director of the USP, took the position that there are only about a dozen examples of drugs which meet USP standards and are not equivalent.

Mr. STETLER. Dr. Goddard made that statement in his testimony—yes, sir.

Senator NELSON. In testimony before this subcommittee, Dr. Miller stated:

The important point, however, is that not more than a dozen drugs have presented problems with respect to physiological availability. Thus to damn the entire Pharmacopeia of some 2,000 drugs for the failure of a mere handful is unscientific in the extreme.

As I understand his statement it is that drugs that meet USP standards are equivalent, and that, to his knowledge, there are only a dozen proven cases of two drugs meeting USP standards and having different therapeutic results.

Mr. STETLER. I think you are entitled to that conclusion from what was said. But I think really what he said is that—he estimates—12 drugs where there is proof of lack of equivalence. But the burden has always been shifted to the proof of lack of equivalence. Nobody has come up with proof of equivalency. This is a very spurious assumption that is made because USP has standards. Whether or not they exist, whether or not they are followed, and what they mean in the final analysis in terms of therapeutic effectiveness is still a question.

Now, he talks about 12. I think Dr. Goddard and FDA are currently testing about 50 products. We have some others here that we will talk about when we get around to it.

But the important thing which cannot be forgotten is that there is not absolute proof of effectiveness for the 3,000 products. There is lack of proof of therapeutic equivalence for many or most of those products. It is a question of where the burden of proof lies in this matter.

Senator NELSON. But I would suggest that if Dr. Miller is right, that there are about 12 proven cases—not just testimonials—proven cases, that the burden would rest, it would seem to me, in my approach to the matter, on those who say that this is not the exception that tests the rule.

Now, if it is the other way around, that the burden is on USP to prove that if they meet USP standards they are therapeutically equivalent, the doubt that is cast is cast equally upon all brand names and all generic names.

So what you have done is eliminated the whole argument. There is no use in pressing the point at all, because since you do not have any evidence to the contrary, there is no basis for selecting one drug over another, brand name or otherwise, since there is no positive proof that they are equivalent—you would end up just a guess anyway.

Mr. CUTLER. If I could just say one thing, Senator. A new drug under the food and drug law—and most of the ones we are talking about I think are new drugs—must be proven to the satisfaction of the FDA to be safe and effective. You cannot have your New Drug Application approved if you offer evidence that there is no proof that it is unsafe or ineffective. You cannot get by with a double negative. You must prove the positive. And many of the drugs that you are speaking of, particularly those developed by the innovative manufacturers, have survived that test.

Under the 1962 law—they have been proven to the satisfaction of the FDA to be safe and effective.

Senator NELSON. Yes. I do not quarrel with that. So if you take any of the drugs to which the 1962 statute applies, and the compounds on the market manufactured and produced by 20 companies meet USP standards, they are considered to be safe and effective.

Mr. CUTLER. But only one submitted proof it was safe and effective. The other 19 did not. And the FDA did not find proof that the other 19 were safe and effective.

Senator NELSON. Are you talking about the case where a New Drug Application is approved and the company licenses 19 other companies to manufacture it?

Mr. CUTLER. No, sir.

Mr. STETLER. That could be one situation. But whether you have a licensing arrangement or not, the ones that come later with an identical or similar product, are not necessarily required to have proof of clinical effectiveness of their products. You cannot assume just because the first one who processed the NDA has proven up all these things, that everyone who follows has the same capabilities or that their drugs have.

One other thing on USP. We have talked about 7,000 drugs today. You know, USP only includes 600 drugs. So there is a question of coverage—even if you make the assumption, which is not valid, that because USP standards are identified, that you have the therapeutic equivalency.

Mr. GORDON. Dr. Modell says that if the drugs have the same chemical components, and they do meet USP standards, then the assumption has to be made that they are clinically effective.

I do not want to get the two terms mixed up—"effective" and "clinically equivalent."

Mr. STETLER. There is a good deal of difference between clinical equivalency and therapeutic equivalency. Dr. Modell may have said that the assumption can be made. The assumption does not have to be made and really should not be made, in our opinion.

Mr. GORDON. Dr. Garb says you cannot practice medicine unless you make the assumption that when a doctor prescribes something here or in California, or this year, or 20 years from now, that drug is the same—otherwise you cannot practice medicine.

Mr. STETLER. I think the doctors that prescribe generically probably make that assumption. But you realize that in 95 percent of the cases the doctor either prescribes by brand name or indicates the source. So he has not made that assumption. He practices medicine in 95 percent of the cases not making that assumption.

This is a statement in USP:

> The term physiological availability connotes an attribute of dosage form of a drug that constitutes a measure of the extent to which the active ingredient is taken up by the body in a useful form. Progress has been slow in developing methods to measure physiological availability that would be suitable for USP use. Consequently, however desirable it is to give assurance or complete availability to every patient requiring the USP article, the problem of providing objective standards and methods remains in the exploratory stage at this time.

The NF has the same paragraph.

I do not mean to say that Dr. Miller has made a misstatement. And we have no quarrel with the USP or NF. It is just that while it is an easy transition to make from USP standards to therapeutic equivalency, it is a faulty one, and one which we think should not be made.

Senator NELSON. Correct me if I am wrong about this.

If a New Drug Application is approved, its approval is based upon the testing that has been done by the applicant, in compliance with the

law, on animals and humans, and substantial experimentation to demonstrate that they have gone through all the steps to prove the safety and efficacy of the drug.

Then the New Drug Application is approved.

Am I correct thus far?

Mr. STETLER. Senator, you are absolutely right on the first New Drug Application. But somebody else can come along later, file another New Drug Application for the same drug, and on the second, third, or fourth time around, a New Drug Application can be approved with less than all of the data you have described. Animal toxicology, animal testing, clinical investigation to the same extent may not be required the second time or third time around.

The first one has met all these requirements. The latter ones may or may not have, and probably have not.

Senator NELSON. If I recall the law correctly, this matter is in the discretion of FDA. In other words, X may be granted a New Drug Application after he submits all the extensive tests. Then this drug is in the marketplace and extensively used by the clinicians, and they have not developed any contraindications or bad side effects, and find that it is effective and valuable. Thus, you have developed a whole body of medical knowledge about the drug.

At the stage that the FDA is satisfied that the tests that were submitted in fact prove that a drug is effective and valuable they have the discretion to say, "A, B, C may now market this drug without further clinical proof of safety and efficacy provided that their product meets the chemical standard."

Is that correct?

Mr. STETLER. That is correct. And as a matter of fact, the example that we are going to talk to you about, that Dr. Lueck is going to talk about, is a specific situation where for the first brand of Chloramphenacol, Chloromycetin, a New Drug Application, or the comparable form for an antibiotic, was processed by Parke, Davis. Later, the three other products that are discussed in this comparative testing were approved by FDA. But the FDA did not require clinical investigation. Now, this was a discretionary matter, and they said "No." Now, as we look at these products on the market available from the drugstore, we find that in performance they lack the ncessary ability to get into the bloodstream and to perform effectively. With an antibiotic of this type, that is a very serious proposition. But it did represent an exercise of discretion.

But our case will show that unless you do require clinical proof from every manufacturer, you have a problem, or at least a potential problem, with that drug.

Senator NELSON. Well, this gets at the question I am interested in.

The New Drug Application is approved after extensive investigation and testing. And nobody else can go to the market with that drug, except the one who got the New Drug Application.

However, the firm whose application was approved can, under the law, turn around and license other manufacturers; can he not?

Mr. STETLER. No, sir. His only authority to license is with respect to his patent rights.

Senator NELSON. He cannot license the new drug?

Mr. STETLER. No, sir.

Senator NELSON. To be manufactured by anybody else?

Mr. STETLER. No, sir.

Senator NELSON. This is contrary to the testimony we had.

Mr. STETLER. Normally, if it is still a new drug, the second manufacturer will be required to go through the NDA procedure at Food and Drug. But a drug can become an old drug, either by being declared so by the FDA, or by becoming generally recognized as safe and effective. When that happens, another manufacturer can produce it, without going through the new drug procedure.

Senator NELSON. We will check the testimony. I think Dr. Goddard said when a New Drug Application is granted, the company that is granted the New Drug Application may then license X, Y, Z to manufacture the same drug forthwith.

Mr. STETLER. I think that is incorrect.

Mr. CUTLER. The first company, Mr. Chairman, could provide its clinical data to the second company it licenses, and FDA then in its discretion might decide to approve the second company's application based on that data. That is a possibility.

Mr. STETLER. No, but that is different. They still have to go through the FDA procedure. FDA makes that decision, not the company.

Senator NELSON. As I recall, Dr. Goddard said that if X gets the New Drug Application approved, and supplies his data on experiments to companies 1 through 10, they can then manufacture the same drug and put it on the market without doing the experiments that were required for the drug that received the original approval, is that correct?

Mr. STETLER. They can do that. But still it is within the discretion of the Food and Drug Administration whether they want to approve that application or whether they want to let that manufacturer put that product on the market.

A company that has a New Drug Application processed does not make that decision for the Food and Drug Administration. If they want to give their data, that is all right. But even if they give it, the FDA is going to look very carefully at the capabilities of the new manufacturer, as they should. I could get a lot of data, but it would not qualify me to manufacture drugs. So unless I have the capabilities to duplicate all of the protocols of this first manufacture, and can demonstrate that I can do that, I have no right to be in the drug business. And the FDA has to check that.

Senator NELSON. You are putting in the reservation that the right to license has to have the approval of the FDA.

Mr. STETLER. This is not a licensure procedure. The company does not license an NDA.

Senator NELSON. What do you call it?

Mr. STETLER. They license if they have a patent for the drug.

Senator NELSON. I have been using the term license as it relates to a patent. The patent holder may make an agreement to permit other companies to manufacture this new drug?

Mr. STETLER. Not without the authority of the Food and Drug Administration, sir.

Senator NELSON. Well, I am not talking about that.

Mr. STETLER. If they want to, if they have a New Drug Application approved, and if they want to pass over to some manufacturer all of the testing and research and clinical work they have done, and in-

vite them to go to FDA, they can do it. This is not going to be a very prevalent practice in the industry.

Senator NELSON. I believe Dr. Goddard testified that they could do this. I will have to check the record.

The question I raised with the FDA was that a company with a New Drug Application approval can authorize 20 other companies to manufacture the drug, with the approval, as you say, of FDA. None of them need to be any of the known brand name companies. And yet the best known brand name companies who have not received a license from the one who received approval cannot go on to the market with it, even if he duplicated it from analysis as perfectly as it could be done, even if you could take his tablet and mix it up with all the rest and never tell the difference.

Mr. STETLER. I really think on this point, we are proceeding on a wrong premise. I would suggest we check that testimony.

Senator NELSON. I will read that testimony again.

I had a long colloquy with Dr. Goddard on this exact point. I will read it and bring it up at a later date.

Mr. GROSSMAN. I would like to ask a question, Mr. Stetler.

With regard to the equivalency question again—we had testimony from Dr. Goddard last week that "The drugs are therapeutically equivalent until proven otherwise." And I specifically asked him whether this was an assumption or what we could call it. And when I asked him if the purpose of the present FDA study into equivalency then is to corroborate the position he now holds as to equivalency, his answer was "Yes."

In other words, he is conducting the study to corroborate a position that the FDA I assume now holds?

Mr. STETLER. This is an assumption he has stated. If you look back where this has been discussed by Dr. Goddard from time to time, I think he has said rather specifically that the FDA is in no position to guarantee equivalency between drug products.

He has said "I personally believe that when products are chemically equivalent, usually you can assume they are therapeutically equivalent, * * * to prove whether we are right or wrong, I am in the process," he says, "of conducting a test on X products." I understand that testing is being done at Georgetown University, and it will be helpful. But there is no valid assumption on that at the moment. As a matter of fact, our position is diametrically opposed to that assumption.

Mr. GROSSMAN. Have you been consulted at all with regard to this study?

Mr. STETLER. No. Well, there may be people in the industry that have discussed it from time to time. But the protocols for the study and the way it is being handled and the selection of the drugs being tested is pretty much a project between FDA and Georgetown University.

Mr. GROSSMAN. The problem I see here is that we are going to have an endless series of these studies. You will do a study and prove there is an example where they are not therapeutically equivalent. Dr. Goddard will do a study that proves they are. And we are going to go on for years and years. What is the end of all this?

Mr. STETLER. Although it would be a nice, handy, easy thing, to be able to say "We have proven equivalency" the facts of the matter are that nobody will ever be able to make that statement as long as there

are so many well- poor- and medium-qualified people making drugs. Because you have to be able to say therapeutically equivalent today, tomorrow, and next week—because they do not always do the same job every day.

Now, we did not make this problem, and we are not trying to complicate it. It just evolves from the nature of the situation that exists.

Mr. GROSSMAN. Can I assume then you would feel that the USP standards, the standards they now have, are not adequate?

Mr. STETLER. USP standards—in other words, the USP does a fine job as far as they have gone. They recognize as we recognize, that there probably should be other standards developed, and they are now being developed with the cooperation of the manufacturers.

What we say on USP standards is not intended at all to be critical of that book, and it is not. But USP is not the whole answer.

There are other standards, and they are being revised now. When those are in the book, USP standards will mean more than they mean now. Whether they will ever answer completely the problem, I cannot say.

Mr. GROSSMAN. We can probably say, then, as soon as Dr. Goddard's study is completed, we will be in no better position than we are now.

Mr. STETLER. Well, we will be in a better position as to what he finds on those 12 or 50 products. But I don't think, after he studies the 12 or 50, that he can say across the board all products bearing the same generic name are equivalent—no; he cannot say that.

Mr. GROSSMAN. Thank you.

Senator NELSON. All right. Go ahead.

Mr. STETLER. On that point—if you would like—I would read just one statement here. This is from Dr. Feldmann, of the National Formulary.

This brings up a closely related matter that is a national limitation of the compendia. Many people in pharmacy have the mistaken notion that if a product meets all the specific tests and requirements detailed for the article in the USP or NF monograph, then that particular product has to be perfectly satisfactory. While I wish this were true, I am sorry to say that it is not, and the nature of the problem is such that we can never hope to develop compendium monographs which will give complete assurance of any product's complete and absolute suitability.

Mr. GROSSMAN. Could I ask you one last question.

With regard to the USP, I understand their tests are essentially physical; is that correct?

Dr. SLESSER. Yes.

Mr. GROSSMAN. Could you then recommend their tests be extended to biological areas, and to animal testings like that?

Dr. SLESSER. Mr. Grossman, according to Dr. Miller a committee has been appointed for this very purpose, and they are exploring this particular matter, and hopefully some time in the future they may come up with tests which will come much closer to doing what you have indicated here than the present compendia are able to do.

Senator NELSON. In establishing the USP standards, it is not purely a chemical matter, really, is it? That is, the consultants involved in setting standards include not only the industry but also the expert physicians who have used this drug around the country. So there is a cumulative clinical knowledge about this compound and its effect that

goes into the final decisions as to what the chemical tests should be. Is that not correct?

Mr. STETLER. There is no question that the people that work on the compendia are well-qualified people, and the standards that are there are well done. Our quarrel is only with what you can assume, having those standards, and recognizing they are good standards.

Senator NELSON. I guess we have been through that before. The point is, it applies to any drug, whether it is trade name or any other. Go ahead.

Mr. STETLER. Bottom of page 11. On this subject, there appears to be a rather common, mistaken belief that the Federal drug laws somehow guarantee a uniform high level of quality in all drug products which reach and are dispensed from the shelves of a pharmacy. This is not so and, as a practical matter, can never be so.

Although Food and Drug Administration personnel do a conscientious job, it is impossible for them to inspect every manufacturer and distributor often enough to insure that every drug product meets every bare minimum quality standards.

Maximum quality and reliability can only be built in by the manufacturer. Even antibiotic drug products, every batch of which FDA tests before shipment, have turned up with variations in quality and potency.

Mr. GORDON. Mr. Stetler, your testimony suggests that simple reliance upon a product meeting official compendia tests and specifications is not sufficient.

Mr. STETLER. Correct.

Mr. GORDON. You also suggest because of this situation the physician or pharmacist should rely upon the reputation of the particular manufacturers. Is that correct?

Mr. STETLER. Correct.

Mr. GORDON. Apparently you feel that some firms are not performing adequately insofar as their quality control, good manufacturing practices, and so on are concerned with the result that they do not produce reliable drugs.

Is that a correct interpretation of your statement?

Mr. STETLER. For some manufacturers; yes.

Mr. GORDON. Will you name some of these firms?

Mr. STETLER. Will I name some?

Mr. GORDON. Yes.

Mr. STETLER. No.

Mr. GORDON. If you have such knowledge, it should be made part of this record.

Mr. STETLER. I think it is obvious to you that this statement is not meant as an indictment of any firms. What I am saying is that there are varying capabilities in drug manufacturers. Some produce consistently poor drugs. Some do it sometime. My purpose is not to identify them, it is not my job, and I do not propose to do it.

Mr. GORDON. If you won't disclose this information, and if the information is not generally made available, how, then, is the physician who writes a prescription out in some small isolated town to know this? Certainly we cannot expect a busy general practitioner to be familiar with all of the qualifications of personnel, or adequacy of facilities and

procedure utilized by various manufacturers hundreds or even thousands of miles away from him.

Obviously, such a physician or a pharmacist, must rely upon objective standards to evaluate the quality of the drugs he prescribes and dispenses. We have heard a great deal of propaganda about a manufacturer's reputation, and yet just about a month ago the witnesses from Squibb & Co. freely admitted before the subcommittee that their Brooklyn facilities had been in atrocious condition only a short time ago.

Would you comment on that, sir?

Mr. STETLER. Yes. What you say makes my point.

I am ready to agree with you that doctors are in no position to prescribe generically and take their chances with the product of any of these manufacturers, some who are not, or some who are poorly qualified to produce. So given the inability of anybody, including the Federal Government, to guarantee, certify, or approve the products that are on the market, the physician's best and the patient's best safeguard is in the doctor being free to prescribe the quality products that he knows to be quality products, to use as his source of products, manufacturers that have consistently done a good job for him with his patients, in his private practice. On your other point—I have not said, and I make the point again, that just because a company is a member of the PMA they are automatically perfect. Our companies make mistakes, and they will make some more. But given their capabilities and their attention to quality and their expertise in personnel, the chances of them making mistakes are much less, and they do a consistently better job, obviously, than a manufacturer that is not similarly qualified.

Mr. GORDON. He has a better chance, but he is not sure of that, either; right?

Mr. STETLER. I said nobody is sure. Nobody can every day produce a perfect product, even with all the expertise and capability. Mistakes happen.

Mr. GORDON. So much of your statement and testimony leaves me with the impression that you are attempting to say that if a physician prescribes a drug by its generic name he is not certain the patient will end up getting a good product—whereas if he prescribes by brand name, he will be sure.

Mr. STETLER. No; I have not said that. As a matter of fact, I have already read that paragraph and said very specifically—I think a doctor should be free to prescribe generically, generically with a manufacturer identified, or by brand—anything he decides is fine. But he probably has based it on a good professional decision.

Mr. GORDON. Well, I have here some information to show that many brand-name products have had changes in their formulas, while the official generic names mentioned have not been changed. And in looking at these changes we find that they represent changes not only in flavor, solvent, and excipient, but actually in the therapeutic or active ingredients. When a drug product has been changed to the extent that an active ingredient is either added or deleted from that preparation, this means the patient is getting a substantially different product from the case of the previous formulation.

Mr. STETLER. You realize when this happens, this all has to be processed through the FDA with a supplemental New Drug Application. So it is not something a manufacturer just decides to do on his own. He has to prove up again by clinical testing what happened, and then it is approved.

Mr. GORDON. That is not entirely true, either, sir. I have here some information we secured from the Food and Drug Administration, where a drug called Lomotil, which is sold by G. D. Searle & Co., had a very important ingredient added, atropine sulfate, after the FDA had accepted the original drug without it.

I ask that this information be put in the record at this point.

Senator NELSON. So ordered.

(The information referred to follows:)

SUMMARY FOR NDA 12-462

LOMOTIL

(G. D. Searle & Co., Chicago, Ill., AF 13-505)

This review was initiated because of the reports of two fatalities in children due to overdose of Lomotil Tablets. Lomotil is put out both in the tablet form and the liquid form. Each of these doses that is one tablet or 1 teaspoonful of the liquid contains 2.5 mg. of diphenoxylate and .025 mg. of atropine sulfate. The drug is promoted for producing hypomotility of the gastro-intestinal tract primarily of course, in cases of diarrhea and dysintery.

According to the PDR of 1964, the recommended adult dose is two tablets, 3–4 times daily and for children 3–6 months of age 3 mg. daily and for children 4–12 years of age 8 mg. daily. The doses for ages in between these ranges must be interpolated. According to the labeling atropine sulfate is added to discourage deliberate overdosage but I cannot understand why this is so. Atropine sulfate is not notorious for being an emetic.

The first case reported was a 22-month-old child who received 26 tablets which contained 0.65 mg. of atropine sulfate and 65 mg. of diphenoxylate hydrochloride. The usual dose of atropine is 0.01 mg./kg./24 hours. Assuming this child weighed 11 kg. the usual daily dose would be .11 mg. He actually received 6 times this recommended dose of atropine or average dose of atropine.

The second child weighed 35 pounds (16 kg.) and received approximately 15 tablets which contained 0.375 mg. of atropine and 37.5 of diphenoxylate chloride. The usual dose of atropine to a child this size would be 0.16 hours. Therefore each of these children got an excessive dose of atropine as well.

The weight of a normal child at 3 months of age can vary from 9.8 lbs. to 16.4 lbs. depending on sex. At 6 months of age the range is from 12.7 lbs. to 20.8 lbs. At 8 years of age from 45.3 lbs. to 79.4 lbs. and at 12 years of age from 94.5 to 179 lbs. Taking the smallest size child at 3 months and the smallest at 8 years the recommended dose of atropine in this labeling would not be excessive.

With this background data on the ingredients and labeling of the drug and the two fatalities from overdose, I will now review the single volume of the NDA to determine the adequacy of the data to substantiate the safety and efficacy of this drug in all age groups. This will be reviewed in chronological order starting at the rear of the NDA with the original submission and proceeding forward to the most recent data.

Before starting this review I might point out that the original submission was on May 31, 1960 and it was found incomplete on July 29, 1960. It was subsequently made conditionaly effective on August 30, 1960 and fully effective on September 15, 1960. Subsequence of this there were several supplements.

The first paragraph is subdivided into 7 different parts. Section I appears to be a general summary of the data included in the other sections referring to diphenoxylate hydrochloride (R–1132). The descriptive formula of diphenoxylate hydrochloride (R–1132) is 2,2-diphenyl-4-(4-carbethoxy-4-phenyl-1-piperidene) butyronitrale hydrochloride. The toxicity data is briefly reviewed an it is obvious these data were obtained only from work done on this chemical entity which did

not include atropine at the time. In other words, the toxicity data were not obtained from the drug as it is marketed in a combination of atropine sulfate and diphenoxylate hydrochloride. It is obtained only on the diphenoxylate hydrochloride.

Under the heading Clinical Evaluation it points out that 31 clinicians have submitted observations on 521 patients. When I review these in detail it will be seen that very few individual case histories were submitted and these were glossly inadequate. It will also be seen that most of the data were submitted in the form of tabulations which gave us absolutely no information of any significance about the clinical course of these patients.

Under the heading Types of Diarrhea and Response to R–1132 it recounts how the drug was used in all types of diarrheas, specific and nonspecific.

Under age range it refers to the drug as being given to patients as young as 3 months of age and that 89 of the patients ranged in age from 3 months to 14 years. The oldest patient in this series was 80 years of age. Again, as I will point out later, the data on children is grossly inadequate and incomplete.

Under the heading discussion of clinicians report in referring to the work of Dr. David Cayer was pointed out that some patients had nausea, itching of the skin and skin rashes. There were two episodes of hepatic coma which occured in one patient with advanced cirrhosis during medication and recovery occured in each instance when the drug was stopped. This of course, suggest that the drug is toxic to the liver. It also indicates clearly that the clinical trials were performed with only one ingredient of the drug as it is now on the market.

The work of E. C. Texter, Jr., also indicated that patients had nausea, drowsiness and light headedness.

Dr. H. C. Moeller noted that his patients developed nausea, vomiting and numbness of the extremities all of which disappeared when the medication was stopped. A Dr. W. H. Bacharach noted that in addition to two patients who complained of nausea, one patient developed a progressive anorexia.

One of the clinical investigators was a Dr. A. J. Modlin, a pediatrician from Laurel, Maryland who submitted patient record forms on 27 patients, 14 of whom were 3 to 21 months of age and 13 were in the age range from 2 to 9 years. It is interesting that the company did not submit these individual case histories of Dr. Modlins' but merely listed them in the tabulation. It is also interesting that Dr. Modlin was a close friend and neighbor of Dr. Bennett A. Robin who just today, May 4, 1964 pleaded nolo contendere to charges of falsifying data that came into the Food and Drug Administration. Certainly the least we can do is demand that we be furnished these individual case histories on the 27 patients of Dr. Modlin.

A Dr. C. H. Brown who treated 50 patients described an episode of hypotension in 1 patient while undergoing anesthesia who had received the drug up to the time of the operation. The patient had also received an anime oxidase inhibitor and it was believed that this drug rather than the drug under discussion percipated to hypotension. A Dr. Frank McGlone had a patient who developed ataxia confusion and hallucination when also receiving a barbiturate.

A Dr. Hugo Moeller had a patient who had a similar response so the statement is made that it might seem desirable to include in the Physicians Reference Manual on Lomotil a statement to the effect that the preparation should be administered with caution to patients taking barbiturates concomitantly.

A Dr. David Cayer had a patient who developed two episodes of hepatic coma in a patient with cirrhosis of the liver.

Under the heading Discussion of Addiction Liability it was concluded that the product R–1132 possesses abuse liability. This seemed definitely less than that of morphine and greater than that of d-propoxyphene. It seemed about comparable with codeine in several respects. Some of these patients experience insomnia.

It seems that the atropine sulfate was added not exert any clinical effect but to make it much more difficult if not impossible to extract the drug R–1132 for purposes of abuse. However, it seems obvious that this mixture of atropine sulfate and the dyphenoxylate hydrochloride which is the R–1132 is an entirely different drug from the R–1132 alone. Under the heading Other Studies not in the United States, it quotes the Janssen Laboratories, Belgium, as providing a summary of observations made on 830 patients by 89 clinicians and these included 122 children ranging in age from 1 month to 12 years. It is stated that the results of these observations were in general the same as those obtained

in the United States with perhaps a somewhat lower incidence of side effects.

Section 2 is a paper from the Journal Medicinal and Pharmaceutical Chemistry Vol. 1, No. 4 of 1959 by Paul A. J. Janssen and others concerning the pharmacological properties of R–1132 and related compounds. There was no clinical material included.

Section 3 was a confidential brochure of the Searle Company concerning the pharmacological and toxicological data on R–1132. This section also had to do with 14 day oral toxicity studies in rats.

Section 4 was a report from the Woodard Research Corporation to the Searle Company on the Chronic Oral Toxicity of R–1132.

Section 5 was entitled a Summary of Case Reports of 521 patients to whom Lomotil was administered by 31 clinicians. *This does not make clear whether the Lomotil included the atropine or not.* Furthermore this was merely a tabulation which listed the investigator by number, the number of patients he saw, the age range, the diagnosis, the clinical result, side effects, dosage, and milligrams per day and duration. I presume that is duration of treatment. It is noted that investigator number 5 had 30 patients but only 16 record forms were submitted. Investigator number 6 had 39 patients but only 22 record forms were submitted. It is noted that investigator number 18 had 28 patients of which 14 supposedly ranged from 3 to 21 months of age and 13 ranged from 2–9 years of age. This was probably Dr. Modlin because his location is listed as Laurel, Md. Investigator number 28 had 25 children. Investigator number 29 had 18 children.

The final sheet is a summary of side effects which included nausea, drowsiness or sedation, dizziness, vomiting, skin eruption, restlessness, itching, cramps, headache, swelling of gums, numbness of extremeties, blurring of vision, euphoria, depression, malaise and abdominal distention.

Section number 6 contained some covering letters which were mainly testimonial and a few individual case histories. There were 43 individual case histories which were grossly inadequate as far as details were concerned. Most of them are not legible and in general they add very little to the new drug application.

In this whole original submission there is no explanation of the physiological effect of this drug on the human being except for the gastrointestinal tract where it is supposed to produce hypomobility. Neither are we told anything about its absorption, its metabolism or its excretion.

The receipt of the NDA was noted by a letter dated June 7, 1960. A FDA memorandum dated July 18, 1960 from the Division of Pharmacology to Dr. Madigan in the New Drug Branch who was handling the NDA, which stated "The animal toxicity data are sufficient and satisfactory to suggest safety of *Lomotil* at the recommended dose levels (up to 20 mg. daily for adults and lesser amounts for children); however, because of the limited clinical studies in children less than 3 months old the dose level recommendations for children under 3 months of age should be deleted from the labeling. I recommend that this NDA 12–462 for Lomotil be made effective upon compliance with the labeling changes suggested above."

This was signed by Kent J. Davis and initialed by V. J. Vos.

On July 22, 1960 a letter was written by the firm to Dr. Madigan and Dr. J. William Crosson of the firm stated "In accordance with our telephone discussion on this date, we wrote delete from the labeling reference to administration of Lomotil to children under 3 months of age."

Comment

After reviewing this original submission it is very obvious to me that there was inadequate data on children of all ages under 12 years of age. In the 43 individual case histories there was only 1 child 8 years of age. Furthermore, all of the animal toxicity data were obtained on animals from the diphenoxylate hydrochloride alone which did not include atropine sulfate as the finished formula drug on the market included.

In a letter dated July 29, 1960 Dr. Madigan found the NDA incomplete on 1) manufacturing controls 2) on the basis that the application proposes to make the literature furnishing information for the professional use of this drug available to physicians solely on request.

In a letter dated September 13, 1960 from the firm to Dr. Madigan, this was a covering letter for the final printed labeling. Dr. Madigan acknowledged this in a letter dated September 29, 1960 and stated that the NDA was now effective.

The next item of any significance was a letter from the firm dated September 18, 1963 to Dr. Madigan to report the occurrence of a fatality with Lomotil. This

was a two year old child who had ingested approximately 15 Lomotil Tablets of 2.5 mg. each. Dr. Madigan replied to this on October 15, 1963. He requested a copy of the autopsy report on the child. This was submitted with a covering letter dated November 1, 1963. This was acknowledged on February 28, 1964.

In a letter dated December 26, 1963 the firm reported the occurrence of a fatality with Lomotil following the ingestion of 26 tablets of 2.5 mg. or a total of 65 mg. of Lomotil, by 22 month old child. Substantiating data was included.

This was acknowledged by FDA on February 28, 1964. Additionally data was sent in on February 24, 1964. This was acknowledged on March 3, 1964 and additionally data was requested. The firm replied in a letter dated April 6, 1964 stating that the data requested had been furnished. This completes the new drug application.

Although *both of these children died as the result of ingesting a marked overdose of the drug* and not from a recommended dose, nevertheless, review of the new drug application finds it deficient in data to substantiate the safety or efficacy of the drug. All of the animal data were obtained with the one ingredient and without atropine. Apparently all of the clinical studies were done on the same ingredient. The atropine sulfate seems to have been added after all of the studies were done.

In the whole NDA there are only 43 individual case reports of which only one is a child. The remainder of the clinical data is represented by a tabulation in which not even the name of the clinical investigator is listed. It is indicated that more individual case reports were furnished to the firm than were submitted to FDA. At least 1 clinical investigator who did work with children is a man whom I suspect because of his association with Dr. Bennett A. Robins and the general quality of the work I have seen elsewhere from him.

Since the data now in the NDA do not substantiate the safety and efficacy of this drug particularly in children there is no choice but to state that from the strictly medical point of view this drug should not be on the market. My recommendation is that the New drug application be suspended and the drug removed from the market until data are submitted which substantiate safety and efficacy.

JOHN O. NESTOR, M.D.

SUMMARY OF NDA 12-462 VOL. 2

LOMOTIL

(G. D. Searle & Co., AF 13-505)

At the time I reviewed Vol. 1 it was my understanding that it contained all the data pertaining to this new drug. Dr. Ellenhorn has since sent me Vol. 2 with a note to the effect that there may also be another volume.

To begin with, it might be well to state that in the entire NDA I could only find evidence that 84 children were given the drug. I could not find evidence that a single pregnant woman had received the drug.

In general the clinical data consisted mainly of medical testimonials which were obviously uncontrolled studies. Laboratory work was practically nonexistent, that is, such things as stool cultures. In many cases there was concurrent therapy with other drugs such as steroids, sulfonamides, tranquilizers, etc. In many cases it was difficult or impossible to read and interpret the individual case histories which were lacking in significant detail. For instance, in many cases there was no record of the age, sex, name, or weight of the individual.

Side effects consisted of nausea, vomiting, sedation, restlessness, dizziness, vertigo, weakness, dry mouth, ataxia, confusion, hallucinations, angioneurotic edema, giant urticaria, swelling of the gums, malaise, flatulence, and bloating.

Although this NDA pertains only to tablets it appears that many of the children were given the drug in a different dosage form, that is a liquid form

A Dr. Charles N. Brown of the Cleveland Clinic who was one of the investigators mentions a confidential brochure which I have not seen in the NDA. The last item number 38 is a report from the research laboratories of Dr. C. Janssen of October 1, 1959 which is stamped confidential, and refers to the use of R1132 in 830 cases. R1132 is the code assigned to this drug Lemotil which is also known by the generic name of diphenoxylate.

The human pharmacology and investigation of the addictedness of the drug is in section 36 and was worked out at the Public Health Addiction Research

Center in Lexington, Kentucky by H. F. Fraser and H. Isbell. This was quite a thorough work and naturally I can only summarize the high points. It seems that diphenoxylate is a congenar of meperidine and it produces euphoria in somewhat the same fashion as morphine and codeine. It is about ½ as potent as morphine and 1 and a half times as potent as codeine. The main difference from the codeine effect was the time of effect the codeine took from one to two hours, and R1132 which is the diphenoxylate took from four to six hours. R1132 is an effective suppressor of abstinence from morphine. It induces constipation similar to that of the opiates such as morphine and codeine. It also depresses the respiratory rate, is addicting, constricts the pupils, produces euphoria, and when administered in large doses orally and intravenously in subject to abuse liability. It has no advantage over codeine in physical dependence. Addiction to it is similar to that of morphine and codeine.

The final clinical study was done by a group of three men from the Department of Internal Medicine at the University of Louvaine in Belgium. The clinical pharmacology was included in section number 37 and in section number 38 there is a tabulation of 830 cases. This is strictly a tabulation giving the case numbers, sex, age, weight, daily dose, duration of treatment, the doctor who treated, side effects, results, and diagnosis. No mention is made of laboratory work and there are no individual case histories. In this particular study there were supposedly 51 children of which 23 were cases of acute diarrhea, and 28 cases of chronic diarrhea.

This drug does have a constipating effect but also it is like opiates in that it can produce addiction. There are fewer than 100 children in the two volumes of the MDA reviewed to this point, and there are no pregnant women. Except for the excellent study in human pharmacology done by Fraser and Isbell in a relatively small number of the total number of patients, the clinical data is testimonial in character and does not represent well controlled studies. Laboratory data is practically nonexistent.

Since to this point I have not run across any labeling in this volume, I must conclude that the small amount of labeling in volume 1 constitutes the total at the present time.

The additional clinical data submitted in this volume 2, despite its inadequacies, do seem to indicate that the drug can produce constipation and control diarrhea. The data also indicate that it produces a significant number of adverse toxic effects. Certainly the data do not substantiate the safety and efficacy of this drug for use in children under 12 years of age and in pregnant women.

Until the additional volume of the MDA is found I will be unable to draw any final conclusions.

I had previously pointed out that it had not been used at all in pregnant women during the investigative stage as far as the MDA showed, and that there were very few individual case histories pertaining to its use in children although there was one long tabulation of children from a study done in Belgium. However, this was merely a tabulation and did not contain any significant details of the medical history and laboratory work. There were a total of only 40 very brief completely inadequate individual case histories submitted in children. 21 of these were for children under the age of 2 years 14 for the ages between 2 years and 6 years, and five between the ages of 6 years and 12 years. The sum total of all of the children mentioned in this MDA whether it applies to the 40 individual case histories or to the tabulations amounted to a total of 235. Obviously, this was grossly inadequate to substantiate the safety and efficacy of the use of this narcotic drug in infants and children. Obviously also there was no demonstration whatever of the safety or efficacy of this in regard to the fetus of a pregnant woman.

Since the best study in the NDA was the study performed by Dr.'s Fraser and Isbell of the National Institute of Mental Health Addiction Research Center in Lexington, Kentucky I will review that work in more detail. The title was, "The Human Pharmacology and Addictedness of Diphenoxylate or R1132."

These authors pointed out that this drug is a congener of meperidine which is Demarol. They stated that it had a pronounced constipating and antidiarrheal effect in man and many species of animals. Small doses of 2.5 to 5.0 mgs. daily with a maximum dose of 30 mgs. are effective for this purpose. Because of the potential use of the drug for this purpose they decided to study this human addiction liability. They performed a series of very careful studies and came up with the following information.

As a eupheriant or a euphorogenic agent 60 mgs. of R1132 is more effective than 30 mgs. of morphine or 90 mgs. of codiene. It is roughly ½ as potent as morphine and 1 and one half times as potent as codeine in this respect. The peak effect with codeine was in one to two hours and with R1132 was in four to six hours, however, the effect lasted much longer with R1132.

R1132 proved to be an effective suppressor of abstinance from morphine. It was more effective than codeine in this respect. Long-term studies in persons who were not addicted and who received the drug for an average of 57 days produced sleepiness, depressed respiratory rate, and produced abstinance effects.

A short double-blind direct addication test of 18 days duration showed that patients developed constriction of the pupils, considerable sedation, constipation, and pruritus plus nausea. Compared to morphine and codeine it had more sedative effect than epiete effects. The intensity of the abstinance syndrone was only slightly less severe than from codeine withdrawal but significantly less severe than from morphine withdrawal.

The continuous administration of R1132 was associated with a low incidence or morphine-like subjective effects but with definite morphine-like changes in behavior and was associated with a moderate degree of physical dependence.

The incidence of nonnarcotic symptoms was far greater from R1132 than from codeine. It was concluded that when R1132 was administered on a temporary "Euphoregenic" schedule the patients liking for the drug was comparable to that of codeine. Since the doses of morphine, codeine, and R1132 used in these euphorogenic studies were from 3 to 16 times those which would be used clinically for controlling diarrhea it was apparent that addiction to any of these drugs is not likely to occur if given orally under strict medical supervision for the purpose.

Comment

This careful study clearly outlines that this drug is a narcotic with addicting potential and ability. There is no doubt that it can stop diarrhea and produce constipation, but it also can produce opiate-like effects. With this in mind I will review the presently approved labeling for the drug as well as recent advertising promotional material in medical journals.

The final printed labeling for this drug was submitted on September 15, 1960 and was acknowledged as effective by Dr. Madigan in a letter dated September 29, 1960. I will now review this labeling to see how well it correlates with the data in the two volumes of the NDA just reviewed.

The physicians brochure number 81 and the package insert seem to be identical and therefore the comment made about the statements in the brochure would apply to the package insert also. Immediately it becomes apparent again that the drug Lemotil, as promoted, is a combination of diphenoxylate hydrochloride with atropine sulfate where as all of the investigational studies both on man and animals and all of the clinical work was done on only diphenoxylate hydrochloride. In the investgational stage this was in the form of 5 mg. tablets, whereas for final use it's in the form of 2.5 mg. tablets. Also, it is well to point out that when given to the children in many cases it was given in a liquid form which was not part of the NDA. It is stated in the brochure that the subtherepeutic amount of atropine sulfate included in Lemotil is to discourage deliberate overdose. Each 2.5 mg. tablet contains .025 mgs. or 1/2400 of a grain of atropine sulfate. Since the labeling permits up to eight tablets a day this would be a total of 1/300 of a grain of atropine sulfate in 24 hours which is certainly within the therapeutic range. Atropine is not noted for being a good emetic and therefore it is difficult for me to understand how this would produce or would discourage deliberate overdose. In fact, deliberate overdose might produce atropine toxicity in addition to narcotic toxicity.

On page 3 of the brochure is the following paragraph, "Diarrhea has also been treated classically by the Administration of Narcotics such as camphorated tincture of opium, but such agents are frequently ever constipating, and they have a recognized addicting potential.

Comment

This paragraph is obviously misleading because it implies that this is not a narcotic and it implies that it is markedly different from camphorated tincture of opium which is paragoric. It also implies that this drug, Lomotil it not recognized as having an addicting potential, when, in fact the opposite is true. As a matter of fact this is the excuse given for adding atropine to Lomotil. Starting on page

3 is the following quote, "The pharmacology studies in many of the clinical investigations reported herein were conducted with the single chemical substance described under chemistry. To this substance has been added a subtherapeutic amount of atropine sulfate to discourage deliberate overdose."

Comment

Since up to eight tablets a day are permitted this would include a dose of 1/300 of a grain of atropine sulfate which is within the therapeutic range. Therefore this statement is misleading and incorrect.

I am in the process of reviewing the brochure and the insert.

On page 7 of the brochure under the heading "Children" the following quote: "adequate daily dosage of Lomotil for children is determined by the child's age and is given in the following table":

	Milligrams
"3 to 6 months	3
6 to 12 months	4
1 to 2 years	5
2 to 5 years	6
5 to 8 years	8
8 to 12 years	10."

Comment

As I previously pointed out, the data to substantiate safety and efficacy in infants and children is extremely inadequate and incomplete. The drug was administered in a liquid form instead of in the tablet form as indicated here. There were only 40 individual case histories submitted for children and these were grossly inadequate and incomplete as far as clinical data and laboratory data were concerned. These detailed dosages were not worked out in the NDA.

On page 8 the following quote: "Side effects incidental to Lomotil administration are relatively uncommon."

Comment

This statement is certainly untrue, for instance 10 out of 25 children in one series had side effects. The authors write "Their incidence, in 501 patients as reported by 28 United States investigators, is shown in the accompanying table."

Comment

Actually this table plus the caption unler it indicates that in this 501 patients there were 104 side effects which represent an incidence of over 20%. Furthermore, the side effects were listed in such a way as not to indicate completely the nature. For instance, there were 6 cases of skin eruption noted but it did not state that in this group there was one case of giant urticaria and one case of angioneurotic edema. There was one case of euphoria noted in the footnotes which indicates very clearly the opiatelike effect of this drug.

On page 9 the following quote: "Because of the structural similarity of Lomotil and drugs with a definite addiction potential, Lomotil should be administered with considerable caution to patients who are also receiving such addicting drugs."

Comment

In view of the data in the NDA which demonstrates definitely that Lomotil is a narcotic and has a definite addiction potential, this statement is very misleading. It implies that Lomotil does not have an addiction potential which it obviously does. It imples that Lomotil only has a structural similarity to these other drugs and yet the firm's own data demonstrates that it has a very similar action to codeine and morphine. It differs from these mainly in degree.

In the next paragraph on the same page 9 the following quote: "Finally, competent studies indicate a possible dependency when Lomotil is given in high dosage."

Comment

In view of the previously quoted paragraph referring to addiction, then this reference to dependency is misleading. Furthermore, these competent studies did not indicate a possible dependency when Lomotil is given in high doses, they indicated a definite dependency or addiction. At the bottom of page 9 the authors quote McHardy as stating "I frankly feel that we have satisfactorily disproved the possibility of addiction to R1132."

Of course, the excellent study done at the Lexington Center has proved that this drug is addicting when given in the high dose for even a relatively short period of time. Obviously, Dr. McHardy had not proved that there was no possibility of addiction to R1132. If he had, why is the firm adding atropine sulfate to the drug to prevent it being used for overdose and addiction.

On page 10 the statement under the heading "Chemistry", "Lomotil consists of this substance to which a sub-therapeutic amount of atropine sulfate is added deliberately to discourage overdosage."

Comment

As I stated before, "I don't understand how atropine sulfate is going to discourage overdosage, and I don't agree that it is a sub-therapeutic amount of atropine sulfate when under the recommended dose you can get 1/300 of a grain in one 24 hour period."

On page 11 under the heading "Addicting Liability" the following quote: "Lomotil prevented withdrawal symptoms when it was administered to monkeys addicted to morphine. Thus, the drug can be said to have addicting liability."

Comment

It seems unusual that they would cite the monkey studies and not the human studies in the NOA which clearly indicated that the drug could be addicting in humans.

Also, page 11 the following quote: "When measured on a milligram-per-milligram basis, the addicting liability of Lomotil was approximately equal or slightly less than that of meperidine. However, meperidine is used clinically as an analgesic in doses of 100 or 150 milligrams three or four times daily while Lomotil is effective in adults as an anti-diarrheal agent in oral doses of 5 milligrams three times daily."

Comment

I do not recall seeing this work with meperidine in the NDA. I do recall seeing the work done comparing it with codeine and morphine illustrating that 60 milligrams of this drug has the effect of producing the equivalent euphoria of about 30 milligrams of morphine or 90 milligrams of codeine. It was considered one half as potent as morphine and one and one half times as potent as codeine in this respect. The final quote in this paragraph on addicting liability is "This low dosage of Lomotil carries little or no risk of addiction as clinical evaluation has not revealed any evidence of dependency."

Comment

This statement is patently untrue because Fraser and Isbell in their study at Lexington showed that this drug could produce addiction in humans. Obviously this entire paragraph is very misleading and should be revised completely.

On page 12 under the heading "Mydriatic Activity" with regard to a study in mice, the following: "Doses of 10, 20, 40 and 80 milligrams per kilogram of body weight failed to produce significant mydriasis."

Comment

However, the human studies done by Fraser and Isbell demonstrated definite mydriasis in humans when used.

On page 12 under the heading "Human Pharmacology" the following quote: "In these studies it was observed that Lomotil was capable of preventing withdrawal symptoms in known narcotic addicts. Because of this observation Lomotil must be legally classified as a narcotic, although there is little or no evidence in clinical use of any tendency for it to cause either dependency or analgesia."

Comment

Again the studies done at Lexington by Fraser and Isbell prove that this is a narcotic, that it produces euphoria in humans, that it produces mydriasis, that it produces nausea, that it produces constipation. Furthermore, it also produces euphoria and is more potent in this respect than codeine.

Obviously, then, this statement could serve to mislead the practicing physician and should be completely rewritten.

On page 12 under the heading "Addiction Potential" the authors referred to the study done by Fraser and Isbell and on page 13 under the same heading they write; "As a result of their studies they conclude, in general, that the abuse liability is less than that of morphine and more comparable to codeine."

Comment

This is proof of the criticism I expressed over the previous paragraphs. I therefore conclude this summary with the statement that the presently approved labeling is grossly inadequate and would serve to mislead the practicing physician. I might add that the advertisement for Lomotil which appeared in the July, 1964 issue of the Virginia Medical Monthly on page 23 could also serve to mislead. This advertisement promotes both tablet and liquid and nowhere in these two volumes of the NDA did I see any data or anything in the approved labeling that would substantiate the use of the liquid.

JOHN O. NESTOR, M.D.

REFERRALS AND RECOMMENDATIONS

ISSUANCE DATE MAY 25, 1964

To: Division of Toxicological Evaluation,

Please review Dr. Nestor's & Dr. Moling's comments. Do you have further comments? Thank you.

M. J. ELLENHORN.
NDSnB.

M.J.E. My summary states my view and points in detail but I will list some briefly below:

1. The promotional material in PDR is labeling and the source of the material is the firm. My understanding is the firm submits the material in exactly the form it is to be printed.
2. The animal studies were performed only on one ingredient and not on the final product as marketed.
3. The clinical data are grossly inadequate in all age groups but especially in children.
4. The investigators were not fully and adequately identified. Many individual case reports were not submitted. There were only 43 in the whole NDA.
5. Finally, two children died as the result of ingesting this drug.
6. In my opinion the data to substantiate safety and efficacy are grossly deficient and the drug should come off the market.

J. O. NESTOR, M.D.
July 8, 1964.

REFERRALS AND RECOMMENDATIONS

ISSUANCE DATE MAY 18, 1964

To: J. H. Moling.

Do you have any comments on this summary (of Dr. Nestor) or the NDA?

M. J. ELLENHORN.

M. J. Ellenhorn: Have reviewed Dr. Nestor's summary and major portions of NDA 12-462. Dr. Nestor notes the factual deficiencies in the clinical work in this NDA as usual. The toxicity studies apparently were on the diphenarylate Hcl only but the drug is marketed with a small atropine content, possibly to prevent overdosage. This obviously was not effective in the two deaths reported. D.P. would perhaps like to comment further on the toxicity studies in this light. The case histories are tabulated rather than being submitted in original form but it would appear that the pediatric experience was wanting as Dr. Nestor suggests. Hepatic toxicity is alluded to in the labeling but the hazard of such is not thoroughly explored in the clinical data submitted. These data and deficiencies should be satisfied or the labeling modified to exclude the younger age groups. The NDA is effective as it exists but efficacy may be questioned in Oct. if not safety.

J. H. MOLING, M.D.

MEMORANDUM

JULY 8, 1964.

To: Joseph F. Sadusk, Jr., M.D., Medical Director, Bureau of Medicine.
Through: Ralph G. Smith, M.D., Director/DND.
From: Mathew J. Ellenhorn, M.D., Chief, New Drug Surveillance Branch.
Subject: NDA 12-462 Lomotil safety and efficacy. Recommendations for action on new drug application.

(G. D. Searle & Co., Chicago, Ill., AF 13-505)

I have reviewed this subject including the comments and memoranda submitted by Dr. John O. Nestor and Dr. John H. Moling, pediatricians in the New Drug Surveillance Branch, and Dr. Kent J. Davis, pharmacologist, Division of Toxicological Evaluation.

Certainly the two deaths in children are unfortunate occurrences but must be considered as strictly a problem of overdosage.

The fundamental basis for action in this NDA as stated by Drs. Nestor and Moling and as reflected in the new drug application are the paucity of clinical reports which form the basis for substantiating safety in this drug. We, of course, may consider action with regard to efficacy at the appropriate time. However, at this time and with the inadequate data present in the NDA both from a pharmacological (absence of studies on the full preparation) and clinical viewpoint (minimal studies performed), it would now seem advisable to consider issuance of a letter to the firm requesting immediate submission of detailed data on the cases originally submitted with the NDA and any further data that they have to substantiate safety.

If such data is not forthcoming after a reasonably short period of time, then it would appear indicated to initiate action for withdrawal of this new drug application.

MEMORANDUM

MAY 16, 1966.

To: Commissioner of Food and Drugs.
From: Robert J. Robinson, M.D., Acting Director.
Subject: IND 1454, Lomotil Pharmacologic Effects.

(G. D. Searle & Co., Chicago, Ill. (AF 13-505))

G. D. Searle & Co., sponsor of the subject IND, notified the Food and Drug Administration of discontinuance of clinical investigation of their product in a communication dated November 9, 1965. This notification followed requests for additional information in a letter dated October 22, 1965, from Frances O. Kelsey, M.D., Chief of IDB. These requests were found to be necessary after review of the submission and parts of NDA 12-462, to which we were referred, failed to support the studies outlined.

"Lomotil" is a product presently on the American market which contains in each tablet or 5 cc: Diphenoxylate hydrochloride 2.5 mg. Atropine sulfate 0.025 mg.

Diphenoxylate is chemically related to meperidine (Demerol). Reference was made to the dosage recommendation and to the animal data contained in the approved NDA (#12-462) as supporting information for the exemption. Data obtained from the NDA revealed the following facts:

1. There was no recommended dose for infants under the age of 3 months.
2. The toxicity studies in animals were done with diphenoxylate alone. There was no evidence that studies in very young animals had been done.
3. Atropine was added to the formula after all studies (animal and human) had been completed. This, apparently, was to qualify the drug as an exempt narcotic.

The IDB Medical Officer, Everlee G. Franks, M.D., recommended suspension of studies in infants under the age of 3 months pending completion and evaluation of acute, subacute and chronic toxicity studies in animals using Diphenoxylate

and atropine in the proportions present in the product. These studies were also to include acute toxicity studies in animals under 24 hours old.

The need for these studies was further emphasized by the fact that older children have died or become seriously ill following the recommended dosage of the drug. The clinical picture of toxicity closely resembles atropine poisoning which suggests synergism of diphenoxylate and atropine.

IND A 2849 is for Lomotil with Neomycin and is sponsored by the same company. It is still active and studies include patients of all ages.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
June 6, 1966.

MEMORANDUM

To: Ralph G. Smith, M.D., Director, Division of New Drugs.
From: Frances O. Kelsey, M.D., Chief, Investigational Drug Branch.
Subject: IND 1454.

Note that the recommendation we submitted to the Office of the Commissioner has been returned and the point has been raised "why should this letter issue."

Our concern is that this drug appears to have considerable toxic potentiality when used in young children. The company has withdrawn the application, but of course at any time they could resume clinical testing by just notifying us.

We should like to impose upon them the condition that they must await positive assent from us before resuming such testing. We would not, of course, approve of resuming human testing unless the requested animal work had been submitted.

In the past it has not been possible for a letter of this type to issue at the Branch level. For this reason, we drew up the letter for the Commissioner's signature.

JUNE 12, 1964.

To: Division of New Drugs, Surveillance Branch, attention Dr. Ellenhorn.
From: Dr. Kent J. Davis, Division of Toxicological Evaluation.
Subject: NDA 12-462. Lomotil Safety and Dr. Nestor's May 1964 Review, G. D. Searle & Company Chicago, Illinois AF Number: 13-505.

Following generally the order of Dr. Nestor's review we can add the following:

(1) The PDR apparently rounded off dosages since the company's literature gives more specific and detailed instructions for younger age groups. I don't know how much influence FDA has on the PDR editorial policy and expect that the company is still less influential so I don't know whether FDA can make the PDR expand their recommendations to conform with package inserts.

(2) The 22-month old child which died took approximately 52 times the recommended single dose. Atropine intake was only approximately double the recommended therapeutic dose and was probably not influential in the outcome with this patient.

(3) The second child took approximately thirty times the recommended dose. The atropine dose in this case would hardly be considered excessive.

(4) We agree that addition of atropine sulphate to R-1132 would make the combination a new and different drug from R-1132. The addition of atropine in these proposed amounts would not be considered a serious alteration in formulation, however, and additional safety data required by this change would be minimal.

(5) There is considerable information included in the NDA on the absorption metabolism and/or excretion of the drug from the standpoint of safety. Toxicity data are the screen for absorption since most of the toxicity can be attributed to the portion of the drug absorbed rather than to local effect. Toxicity tests also screen against the most toxic fraction in the amounts present whether it is parent compound or some metabolite. Recovery and repeated dose studies give information as to the metabolism and/or excretion of the active and/or toxic principle of the drug. In addition the animal toxicity studies have the advantage that the animals taking the drug evaluate the significance of the toxicity, while reviews of pages of tables of chemical formulas of possible metabolites and serum or tissue levels only give something for the people not involved in the test to speculate on.

Explanation of the physiological effects is lacking on many drugs including aspirin.

(6) While the incidence of reported side effects is somewhat higher than we would like, it should be noted that patients reporting side effects also had diarrhea. The diarrhea existing prior to taking the drug can hardly be considered a side effect attributable to the drug, and it is questionable whether the more common side effects reported—nausea, sedation, dizziness, and vomiting—should be entirely attributed to the drug. Certainly I did not consider the side affects predominantly attributable to the drug at the time the drug was originally reviewed, nor do I do so at this time.

(7) I considered the animal safety data sufficient and satisfactory when reviewed in 1960. I see no reason for requesting any additional animal studies now. Unless there are additional data being withheld, safety is apparent from clinical experience to date. We still would not recommend the drug for very young children.

(8) It was my understanding that atropine was added primarily to make the drug less attractive to addicts. This would not have anything to do with preventing a single over dose. Some synergistic effects against diarrhea might also accrue from the atropine addition.

(9) Clinical safety and efficacy evaluations should be readily apparent after a review of the company's production and complaint records. Acceptability and repeat sales should be good indicators. since few customers are likely to continue to use a drug which either sickens them or which doesn't help their diarrhea.

(10) While the deaths of the two children are unfortunate, few drugs are "safe" when the recommended doses are exceeded by factors of thirty and fifty-two times.

(11) Most of these differences appear to be matters of professional opinion. Dr. Madigan considered the data adequate when he had to make a decision on the NDA in 1960. Dr. Nestor considers the data inadequate when reviewing it in 1964. While the NDA has deficiencies under the present standards of review, it was not considered unusual at the time it was received.

(12) We see no reason for questioning the status of this NDA 12-462 at this time unless there are additional factors involved which we are not now aware of.

KENT J. DAVIS, D.V.M.

MEMORANDUM

JUNE 18, 1966.

To: Director, Minneapolis District.
From: Fred S. Halverson, Inspector.
Subject: Adverse Drug Reaction Investigation—DPO/DRM Memo of Phone Call, June 14, 1966.

In response to the above listed memo, I visited Dr. Charles Jarvis at Childrens Hospital on June 14, 1966. Dr. Jarvis is the pathologist for Childrens Hospital.

On February 25, 1966, at 2:45 p.m., Dr. Jarvis performed an autopsy on Terrance J. Ehrich, a three-year-old white male, who had expired on February 25, 1966, at 10:10 a.m. at Children's Hospital.

Dr. Jarvis listed Diphenoxylate (Lomotil) toxicity under the "Diagnoses" section of the autopsy report. (See exhibit #1, which is the autopsy report of this case.) Dr. Jarvis stated that he attempted to obtain Lomotil toxicity data from the G. D. Searle Company, and he was not satisfied with the information they were able to provide. Exhibit # 2 is a copy of a letter of reply to a phone call made by Dr. Jarvis to the G. D. Searle Company. Dr. Jarvis had sent blood samples from the deceased to G. D. Searle for chemical analysis; and he filled out the adverse drug reaction form referred to in the letter and returned it together with a copy of the autopsy report. Exhibit #3 is a copy of a letter acknowledging a telephone call from Dr. Jarvis; a copy of a memo concerning the determination of Lomotil in the serum sample which is referred to in this letter was not available from Dr. Jarvis. He stated that he had sent this memo together with the letter which he had written to Dr. Goddard, Commissioner of the Food and Drug Administration. Dr. Jarvis feels that the child died as a direct result of an overdosage of Lomotil. He feels that the overdosage resulted from the child getting too much Lomotil, that the drug is apparently not excreted, and is accumulated to toxic levels. Dr. Jarvis gave the opinion that any pediatric medica-

tion should be capable of a double or triple dose without any toxic reaction because of the possibility of this happening to the measuring of the dose by the mothers. Dr. Jarvis felt that the information provided by the G. D. Searle Company was wholly inadequate, and his feelings are expressed in the letter which he sent to Dr. Goddard, dated May 19, 1966, which is quoted below:

"The G. D. Searle Company apparently knows little or nothing about their product Lomotil (Diphenoxylate HCA with/Atropine). On February 25 I performed an autopsy on a three-year-old boy who (I believe) died as a direct result of Lomotil overdosage. Enclosed is a copy of a report from the Searle Company which appears to say that the postmortem serum samples submitted to them for assay had a Diphenoxylate level as high as their high standard. However, in personal conversation with Dr. McGovern of their Division of Clinical Research, I gather that they do not know what an overdose is, or how it reacts on the living organism.

"I find this state of affairs somewhat appalling, so I am referring the matter to you. If you wish, I will send a copy of the autopsy."

The sequence of events with respect to this case are as follows:

The patient was examined at a Minneapolis Naval Air Station, Outpatient Clinic on 10/20/65, 1/22/66, 1/29/66, and 1/30/66. (The father was a member of the Navy at this time.) The patient was seen for respiratory problems. (See exhibit #6, which is a copy of "Doctor's Progress Notes" from the Naval Air Station.) The "Doctor's Progress Notes" indicate that in the course of the visit to the facility, Penicillin and an expectorant were prescribed. Note that the entry dated 1/30/66 indicates an Rx of referral to a private M.D. for hospital admission.

On 1/30/66 at 4:05 p.m., the patient was admitted to Bethesda Lutheran Hospital, St. Paul, Minnesota; again, with a diagnosis of respiratory distress. (See exhibit #7 for the complete chart of this hospital admission.) The attending physician was Dr. S. Loken, St. Paul, Minnesota. Again the patient was given Penicillin and also Decadron, Chloromycetin, and on 2/3 and 4, Lomotil was given. (The progress and treatment record dated 2/3/66 indicates a "loose stool," and this was when the Lomotil was first prescribed. The patient was discharged on 2/6/66. On 6/15/66, I talked with Dr. Loken at his office. Dr. Loken stated that the patient was suffering from upper respiratory trouble with difficulty in breathing, and that he was rather acutely ill for what his temperature and other vital things would indicate. He stated that he was rather alarmed and called in Dr. Jack Hilgen, an ear, nose, and throat specialist. (See exhibit #7 for notes of Dr. Loken and Dr. Hilgen and others.) Dr. Loken stated that the patient was listless and had difficulty in breathing over and above what would be expected from his temperature.

On 6/14/66, I talked with the parents of the deceased, Mr. and Mrs. Richard Ehrich at their home at Route 1, Hugo, Minnesota. (The address of 445 Sherburne, St. Paul, Minnesota, on the hospital forms is not correct since the family has recently moved.) According to the mother, the patient was receiving Penicillin for his throat, and on approximately February 19, a prescription for Lomotil was obtained from Dr. Loken for diarrhea. According to the mother, the Lomotil was given at the rate of 1 teaspoon four times each day. On 2/24/66, the child could not be awakened and was again taken to Bethesda Lutheran Hospital, St. Paul, Minnesota. The provisional diagnosis, discharge summary, etc., may be seen on the chart for this second admission to Bethesda Hospital, which is exhibit #8. The child was admitted in a comatose state as indicated. Dr. Martha Strickland, pedatrician at Childrens Hospital at St. Paul, Minnesota, was brought in as a consultant. The child was transferred to Childrens Hospital on the same day.

The patient was admitted to Childrens Hospital on 2/24/66 at 6:45 p.m. and expired on 2/25/66 at 10:00 a.m. The sequence of events and the notes on this episode may be seen on the chart for this admission to Childrens Hospital, which is exhibit #9. Many of the entries are by Dr. Strickland and some by Dr. Bloom, who was a pediatric resident at that time. On 6/20/66 I talked with Dr. Strickland at Childrens Hospital, St. Paul, Minnesota. Dr. Strickland stated that she first saw the patient at Bethesda Hospital when he was brought in comatose on 2/24/66. The patient had pinpoint pupils and other indications which caused her to think first of an overdose of some opiate. The patient at his best downhill course did not appear to have the classic encephalitis symptoms. According to Dr. Strickland, the patient had very low blood pressure (impossible to get a blood pressure reading initially) and low renal function, neither condition being

normal in pneumonia, although the patient had aspiration pneumonia on admission. Dr. Strickland stated that similar aspiration pneumonia cases have not been fatal.

When I talked to Dr. Jarvis, he told me of two other cases where Lomotil toxicity was suspected in the death of children of the same approximate age as Terrance Ehrich. Therefore, in connection with this investigation I also obtained information on these two additional cases. The first of these is the case of Lisa Hoffman of Coon Rapids, Minnesota, who expired on 5/16/66 from an overdose of Lomitil. In connection with this case, I talked with Dr. Ronald Bloom at University of Minnesota Hospitals, Minneapolis, Minnesota. According to Dr. Bloom, he is familiar with the case, but the attending physician was Dr. Gregory Culley, who saw the patient on admission and stayed on the case until the patient expired. (Dr. Bloom also worked with Dr. Strickland on the Ehrich case.) Dr. Culley was not available for an interview at this time. The hospital chart for this case contains a sequence of events and notes on the case by Dr. Culley and is exhibit #10. The patient apparently ingested 25 milligram Hydrodiruil and Lomotil tablets. According to Dr. Bloom he was interested in this case because of his association with the Ehrich case. Serum from the Lisa Hoffman case was submitted to G. D. Searle Company, and the letter of reply is exhibit #11. According to Dr. Bloom, the figures given with respect to the blood level are absurd, taking into account the blood volume of a child of this size. Dr. Bloom stated that T. G. Hiebert, Ph. D., M.D., the Director, Division of Medical Intelligence at G. D. Searle Company, visited the hospital but could not provide them with any definitive information with respect to what constitutes a therapeutic or toxic blood level of Lomotil. Also, the Searle people allegedly could not provide any information with respect to Lomotil toxicity. Dr. Bloom also pointed out that after 18 hours (see exhibit #11) a drug is still absorbed. However, no meaning can be attached to the blood level figures since, according to Dr. Bloom, the Searle people could not indicate what these figures meant with respect to Lomotil toxicity. The background information referred to in the exhibit #11 letter is a binder of information entitled "Lomotil Background Information" which was sent to Dr. Bloom by the G. D. Searle Company. Dr. Bloom pointed out that the only study he could find in this where the Lomotil was the only variable is the Study No. 5, which is circled on the contents page. Parts of this background information are in French. An autopsy was performed on the deceased in this case, but the report was not available at this time. The report is being sent to me by the University of Minnesota Hospitals and will be available if desired.

The second of the additional Lomotil intoxication cases is that of James Hesse, St. Paul, Minnesota, who expired on 9/1/63. The attending physician was Dr. Leonard Phillips, St. Paul, Minnesota. This is a case of a two-year-old white male admitted to St. Joseph's Hospital, St. Paul, Minnesota, on 8/29/63 in a comatose state. According to Dr. Leonard Phillips, the child was receiving Lomotil for a chronic diarrhea thought to be caused by teething. The child ingested 10 to 20 tablets of Lomotil, and according to a consulting pediatrician, Dr. Shirley Lanske of the University of Minnesota Hospitals, the patient was unresponsive from the time of admission until the time of death. According to Dr. Lanske, there was a time lapse of 12 to 15 hours between the time of ingestion and the time she saw the patient in the emergency room of St. Joseph's Hospital. The patient was receiving Lomotil tablets at least several days prior to the time of the overdosage. According to Dr. Phillips, this is a litigation case. The chart from St. Joseph's Hospital, St. Paul, Minnesota, on James Hesse is exhibit #13.

A drug reaction report was made out by Dr. Jarvis for the Ehrich case for the G. D. Searle Company. A copy was obtained and is submitted as part of exhibit #1, with the autopsy report. The information not filled in was left out by Dr. Jarvis because it was either available in the autopsy report or in the charts. Drug reaction reports have been filled out for the other two cases as truly as is possible.

FRED S. HALVERSON, *Inspector.*

JUNE 29, 1966.

To: Acting Chief, DSB/DMR.
From: A. L. Kaminsky, M.D., Medical Officer, DSB/MBR.
Subject: Lomotil NDA12–462, 12–699. Toxicity and lethal effects in children.

(G. D. Searle & Co., Chicago, Ill., AF 13–505.)

Hospital records and autopsy protocols received in deaths of Terrence J. Erich 3 years old and James Besse 2 years old. The former due to toxicity to "therapeutic" (?) dose and the latter to overdosage.

Dr. Charles Jarvis, Pathologist to Children's Hospital, St. Paul, Minn., sums up the substance of the death in a letter to Dr. Goddard dated May 19, 1966 quote:

". . . I gather they (Searle & Co.) do not know what an overdose is, or how it reacts on the living organism. I find this state of affairs appalling. . . ."

Conclusion

It was recommended in a Summary of Supplement of September 16, 1965 dated April 27, 1966 signed Aaron L. Kaminsky, M.D. that:

1. "Dosage—Children: Delete entire section"

No studies have been performed using diphenexylate hydrochloride with 0.05 mg. atropine sulfate in children. The uncontrolled studies on children were accomplished using R1135 (diphenoxylate hydrochloride). Adverse reactions, including deaths, have been reported in children using therapeutic doses. Furthermore, fraction of tablets and teaspoons (varying from 4–5 cc.) are really not proper dosage forms for children who are very sensitive to the action of atropine.

2. "Summary: It is recommended that":

1. The drug be discontinued for children under 12 years of age. No valid, well controlled and double blind, studies were performed delineating the safety and efficiency of diphenoxylate hydrochloride with atropiue sulfate (0.025 mg.) for children.

2. A warning label to indicate the dangerous nature of the drug on children e.g. "Warning: Keep Out of Reach of Children, Dangerous Drug."

3. Labeling change are necessary as enumerated to labeling action. The labeling is in dire need of updating, correction, amendment, additions and deletion of dosage for children.

4. Atropine, even in subtherapeutic doses, should be removed from the mixture especially to obviate mortality in children.

It is the considered opinion of the undersigned, agreed to by G. M. Carroll, M.D. (Pediatrician), that Lomotil HC1 with atropine sulfate is not safe for children under 12 years of age. There are no adequate controlled studies for various age groups and for delineation of absorption, degradation, and excretion in children in a time sequence.

SUMMARY OF SUPPLEMENT

NDAs 12–462 (tablet), 12–699 (liquid).
G. D. Searle & Company, Chicago, Illinois AF 13–505.
App. Date: 9/29/60 (NDA 12–462); 1/17/61 (NDA 12–699).
Nov. 22, 1961 (Supplement).
Aug. 9, 1965 & Sept. 16, 1965—(Supplement).
Type of Drug.—Antidiarrheal.
Trade Name.—Lomotil.
Generic Name.—Diphenoxylate Hydrochloride and Atropine Sulfate 0.025 mg. (1/2400 gr.).
Dosage Form.—Tablets 2.5 mg.; Liquid 2.5 mg. per 5 cc.
Date of Supplement.—Nov. 22, 1961, Aug. 9, 1965 and Sept. 16, 1965
Chemist Summary.—see Chemist Summary
Pharmacologist Summary.—No new pharmacology. Vol. I three III, 130.13 report of September 14, 1965.
Clinical Evaluation.—Diphenoxylate Hydrochloride, a congener of meperidine (Demerol) with atropine sulfate 0.025 mg. (Lomotil) is indicated in the treatment of diarrhea secondary to motor disturbance, acute or chronic diseases of the gastrointestinal tract, and systemic disease. It is an adjuvant to specific and general therapy for the various functional, organic and post operative disorders of the gastrointestinal tract manifested by diarrhea.

All studies cited as part of the NDA's were performed with diphenoxylate hydrochloride without atropine sulfate, which is now included in the mixture called Lomotil. The original liquid form was deleted from NDA 12–462 because of stability problems. The company modified the liquid dosage from 2.5 mg. per 4 cc., in NDA 12–699, to 2.5 mg. per 5 cc. to conform with that enumerated, in the approval as an exempt narcotic, in the Federal Register, Tuesday, July 25, 1961. The same studies used for NDA 12–462 were used in the application of NDA 12–699. Labeling remained unchanged. The drug was approved as Lomotil, (diphenoxylate hydrochloride with atropine sulfate), without any clinical, pharmacological, (animal and human) and toxicological data and studies evaluating actions, safety and efficacy of the drug as a mixture.

The company reported on 521 patients evaluated by 31 clinicians in the United States and one (1) in Belgium; 830 cases by 88 investigators in Belgium, France and the Belgium Congo. The studies were poorly controlled to uncontrolled, and testimonial as noted in an "Evaluation and Summary" by John Nestor, M.D., Vol. I (7 pages) dated 5/14/64 and Vol. II (7 pages) dated 7/21/64. G. van Dorstoppen et al, used R1132 (diphenoxylate hydrochloride) in 10 ileostomy patient's and evaluated the drug against a placebo. The drug was effective in 8 patients.

Isbell and Fraser, in a beautiful study, evaluated the abuse potential and addicting dosage for diphenoxylate hydrochloride. They found the drug non-addicting in therapeutic doses.

The clinical reports indicated that the usefulness of the drug was greatest in the diarrhea associated with the irritable bowel syndrome, (functional bowel), and in the acute diarrhea. It was least effective in the diarrhea associated with moderate to severe regional enteritis, ulcerative colitis and other inflammatory disease of the bowels. The fact of that specific modalities of therapy were used must be noted, e.g. drug, supportive and psychologic. These, in themselves, may modify the diarrhea by either ameliorating and/or curing the underlying disorder. Lomotil is only an adjuvant in the treatment of diarrhea.

The only double blind study available to me was by H. Barowsky and S. A. Schwartz, JAMA 1962. They used Lomotil tablets, placebo and camphorated tincture of opium in 40 patients with varying diarrheal disorders. They concluded that, "at varying levels of daily dosage a 2.5 mg. dose of diphenoxylate hydrochloride (1 tablet) is equivalent in antidiarrhea efficacy to 4 cc. of camphorated tincture of opium." In mild cases, Lomotil tablets gave good results with a decreasing effectiveness with increasing dosage in moderate to severe conditions. The drug was found useful in chronic diarrhea where addiction to an opiate may be undesirable.

Clinical experience, as revealed in the reference section and the letter of Davis, DVM, (FDA) of the toxicology section, indicated safety and efficacy of the drug in tablet or liquid form for adults.

There are no valid or controlled clinical studies using diphenoxylate hydrochloride with atropine sulfate in children, pregnancy or lactation. Adverse reaction of serious import involving atropine toxicity have been reported in children; 13 with recovery, 6 with deaths, overdosage with tablet and liquid forms of the drug were responsible for 14 reactions with 4 deaths. Therapeutic dose regimens accounted for 2 deaths and 4 reactions with recovery; 1 child had permanent brain damage.

Review of Labeling.—Last approval date supplement September 24, 1965 and date of insert 1960 and 1961. The last, insert of 1961 reads as follows:

"References and a more detailed discussion of Lomotil are contained in Searle Physicians Product Brochure No. 81, available from the Medical Service Dept. G. D. Searle & Company, P.O. Box 5110, Chicago 80, Illinois." "September 5, 1961". The 1961 insert is an abbreviated 1960 new Product Brochure #81.

The physicians brochure and the insert are in dire need up updating, correction, amending with additions as noted below:

1. Contraindications.
2. Precautions.
3. Adverse reactions and deaths.
4. Overdose and treatment.
5. Antidotes.
6. Elimination of dosage for children.

A partial review of the Brochure #81 and drug insert dated in 1961 reveals the following deficiencies and need for change:

Page 1, par. 3 line 4:

Substitute: "but such agents have an addiction potential with long term use except in those individuals with a history of addiction or barbituation to narcotics in the past."

Instead of: "but such agents are frequently over constipating and they have a recognized addicting potential."

A double blind study concluded 2.5 mg. Lomotil was effective as 4 cc. of camphorated tincture of opium (Barowsky and Schwartz). Codeine was preferred by a few patients to Lomotil (Bachrach and Voigtlin). Codeine, tincture of opium and other narcotics are not more constipating than Lomotil, a congener of meperidine (Demerol).

The addiction potential of a narcotic is type, time and dose related. The longer the use of a narcotic the greater the addiction or abuse potential. *The only advantage of Lomotil, in therapeutic doses only, over the use of other narcotics for the treatment of a symptom, chronic diarrhea, it is minimal addicting potention on long term use.*

Page 2 Clinical Application: line 1 delete "excessive" after "undergone."

Line 2: Substitute: "It, as an adjuvant to specific therapy and a general treatment program" for: "It is the sole treatment or as part of a general treatment program."

Line 12: Add after "regional enteritis" mild. It has been shown that moderate and severe inflammatory disease of the intestinal tract, e.g. regional enteritis, ulcerative colitis, acute ileitis of varying etiologies, etc., react poorly, if at all, to the administration of Lomotil and other narcotics.

A compensated incomplete intestinal obstruction secondary to the intrinsic granulamatous disease process of regional enteritis may be converted to a complete obstruction by the use of this drug; and, an ileus created in ulcerative colitis. (Sleisinger and Almy)

Line 14: Add "mild" after "ulcerative colitis". Poor results were reported in the use of Lomotil in moderate and severe ulcerative colitis. Precaution must be exercised in the use of the drug to obviate ileus with possible complicating toxic megacolon, perforation, etc.

Page 3, par. 2 line 3 beginning "Machella" change "6" to "8".

Line 4: Change "9" to "8".

Line 17: Add, after "seen no undesirable sequelae", the statement: "There were no efficacious results even with high dosage (40 mg. daily) in sprue, regional enteritis and fair to poor results in 5 cases of ulcerative colitis".

Line 18: After "have ever used" add in parenthesis (1 case). The testimonial of one case questions the accompanying quote of "it is the best I have ever used" in the brochure.

Page 5 par. 1 line 8: After "treatment" add 8 patients benefited from treatment. See authors summary and conclusions.

Par. 2 line 6: Add "which is generally a self limiting disease" instead of "effect in acute diarrhea."

Dosage—Children: *Delete entire section.*

No studies have been performed using diphenoxylate hydrochloride with 0.05 mg. atropine sulfate in children. The uncontrolled studies on children were accomplished using R1135 (diphenoxylate hydrochloride). Adverse reactions, including deaths, have been reported in children using therapeutic doses. Furthermore, fraction of tables and teaspoons (varying from 4–5 cc.) are really not proper dosage forms for children who are very sensitive to the action of atropine.

Par. 6—Side effects: Add: headache, lightheadedness, toxicosis, angioneurotic edema, giant urticaris, lethargy, anorexia, atropine effects, respiratory difficulty and coma.

NOTE.—The statement that "Side Effects are relatively rare" is not accurate e.g.:

Schwartz, 24 side effects in 53 pts. 24/53.
Bachrach, 2 side effects in 6 pts. 2/6.
Voigtlin, 5 side effects in 11 pts. 5/11.
Klotz, 4 side effects in 24 pts. 4/24.
Texter, 3 side effects in 15 pts. 3/15.
McGlone, 5 side effects in 24 pts. 5/24.

(Severe enough to withdraw drug)

European study, 24/364.

This does not constitute, in any language, statistically or otherwise infrequent reactions, nor can one justify the appellation of "relatively rare" to the number and type of reactions. Nausea, as one (1) symptom, was corrected in many instances by withdrawing the drug or reducing the dose. Can this deserve the statement that most cases of nausea were due to the underlying condition or it is apparent the drug contributed its share to the production of nausea in both adults and children?

Summary

It is recommended that:

1. The drug be discontinued for children under 12 years of age. No valid, well controlled and double blind, studies were performed delineating the safety and efficacy of diphenoxylate hydrochloride with atropine sulfate (0.025 mg.) for children.

2. A warning label to indicate the dangerous nature of the drug on children e.g. "Warning: Keep Out of Reach of Children, Dangerous Drug."

3. Use in pregnancy and lactation is contraindicated unless studies are available to indicate safety.

4. Diphenoxylate hydrochloride with atropine sulfate is a safe and effective drug for diarrhea when used as an adjuvant to specific therapy for the underlying disorder causing diarrhea in adults.

5. Labeling changes are necessary as enumerated in labeling section. The labeling is in dire need of updating, correction, amendment, additions and deletion of dosage for children.

6. Lomotil is no more effective than other narcotics. The only advantage it enjoys is that of markedly decreased addiction potential over other narcotic drugs used in diarrheal disease.

7. Atropine, even in subtherapeutic doses, should be removed from the mixture especially to obviate mortality in children.

A. L. KAMINSKY, M.D.,
Drug Surveillance Branch/DMR.

SUMMARY OF REPORTS

Date Summary Completed: 10/24/67.
NDA 12-462 (tablets), 12-699 (liquid).
G. D. Searle & Co., Chicago, Ill., AF 13-505.
Original approval date: 9/15/60 (12-462); 1/17/61 (12-699).

Name of Drug.—Trade: Lomotil.

Generic: diphenoxylate hydrochloride and atropine sulfate.

Dosage forms and route of administration.—

1. Tablets, oral; diphenoxylate HCl 2.5 mg., atropine SO_4 0.025 mg.
2. Liquid, oral; diphenoxylate HCl 2.5 mg., atropine SO_4 0.025 mg. per 5 cc.

Category or Use of Drug.—Antidiarrheal (exempt narcotic)

Date of Reports.—

1. April 18, 1966
2. May 17, 1966
3. May 24, 1966
4. June 6, 1966
5. June 14, 1966
6. June 15, 1966
7. June 20, 1966
8. July 14, 1966
9. March 2, 1967
10. April 19, 1967
11. April 27, 1967

Reason for Reports.—Adverse reaction reports

Material Reviewed.—Report as follows:

Searle Case No.	*Dates of Reports*	*Searle Case No.*	*Dates of Reports*
A. LO 2-66	1. 4/18/66	G. LO 8-66	1. 6/20/66
	2. 6/15/66		2. 7/14/66
B. LO 3-66	1. 6/6/66	H. LO 2-67	1. 3/2/67
C. LO 4-66	1. 5/17/66		2. 4/19/67
D. LO 5-66	1. 5/24/66	I. LO 4-67	1. 4/19/67
	2. 6/15/66		2. 4/27/67
E. LO 6-66	1. 6/14/66		
F. LO 7-66	1. 6/20/66		
	2. 7/14/66		

Clinical Evaluation.

A. Searle Case #LO 2-66 dated 4/18/66 and 6/15/66.

Adverse reaction report follow-up (of 3/18/66 report) of fatality in a 3 year old child who had received Lomotil tablets under the supervision of C. W. Jarvis,

M.D., St. Paul, Minn. Analysis of blood samples submitted by the child's physician to G. D. Searle and Co. for serum diphenoxylate levels (Searle analytical #A–7202) revealed values for the sample of 3.9 mg. or 4.4 mg. per l. depending on whether the standard reference sample was a 2 mg. or a 1½ mg. standard, respectively. The former figure was believed to be the most accurate value (3.9 mg.). No conclusions regarding the blood level figures were made by the firm.

Autopsy of patient T. J. E., age 3, male at The Childrens Hospital, 311 Pleasant Avenue, St. Paul, Minn. 55102, yielded the following final diagnosis:

1. Complete bundle branch block with acute cardiac decompensation.
2. Diphenoxylate (Lomotil) toxicity.
3. Pulmonary edema.
4. Pneumonia.
5. Cerebral edema.
6. Acute passive congestion of the liver.

B. Searle Case #LO 3–66 dated 6/6/66.

Report of urinary retention in a 2 year old child (male with initials C. S. F.) following 4 doses of approximately ½ tsp. of Lomotil liquid given at 6 hour intervals because of diarrhea. The drug was discontinued and the child catheterized. Recovery followed.

Impression: Drug related adverse reaction.

C. Searle Case #LO 4–66 dated 5/17/66

A case of aplastic anemia in a 73 year old housewife (initials L. B. F.) was reported by George E. Clark, Jr., M.D., No. 1 Medical Arts Squire, Austin, Texas. The only drug taken by the patient prior to onset of the disease had been Lomotil tablets 1 to 2 daily taken intermittently since 5/10/65 for chronic diarrhea. A bone marrow study on 4/4/66 showed marked hyperplasia. The patient died on 4/30/66.

No past report similar to the above have been reported to this drug,

Impression: Cause and effect relationship considered uncertain.

D. Searle Case # LO 5–66 datel 5/24/66 and 6/15/66

Report of a death of a 2 year old child by Fred Heaton, M.D., 7000 Cutler Street, N.E., Albuquerque, N.M., who accidentally ingested between 12 to 22 tablets of Lomotil. (Death occurred despite intensive symptomatic and supportive therapy carried out at St. Joseph Hospital, Albuquerque, N.M.).

Impression: Cause due to accidental Lomotil overdosage.

Autopsy report on patient F. M. H., age 2, female from the Presbyterian Hospital, Albuquerque, N.M.

1. Intrapulmonic hemorrhages, moderate, bilateral.
2. Petechial hemorrhages, epicardium.
3. Reactive lymphadenitis, moderate, mesenteric.
4. Medullary and cerebral edema, moderate with a few petechial hemorrhages of the cerebellum.

No anatomical cause of death ascertained.

E. Searle Case # LO 6–66 dated 6/14/66

Report of a fatality involving a 3 year old child who ingested an overdosage of Lomotil and Hydrodiuril. (Two vials containing 30 Lomotil tablets and 10 Hydrodiuril tablets were found empty and it was assumed that the child had ingested them). Despite heroic measures at the local hospital in Elk River, Minn. and later at the University of Minn. Hospital, the child expired.

Death was considered to be due to an overdosage of Lomotil, with hydrochlorothiazide dosage a contributing factor.

F. Searle Case # LO 7–66 dated 6/20/66 and 7/14/66

Ingestion of 20 to 30 Lomotil tablets by a 19 month old child 12 hours prior to examination by Dr. A. P. Hartman, Box 2555, Billings, Montana on 6/15/66. Hospitalization, use of Nalline and artificial ventilation were advised. On 7/15/66, a follow-up report stated that the child had recovered.

Impression: Reaction from accidental Lomotil overdosage.

G. Searle Case # LO 8–66 dated 6/20/66 and 7/14/66

Ingestion of 10 Lomotil tablets by a 2 year old girl approximately 3 hours prior to hospital E. R. visit at Lutheran General Hospital, Park Ridge, Ill. Gastric lavage carried out and the patient was hospitalized. Nalline administration ad-

vised, as well as close observation and artificial respiration. A follow-up report dated 7/14/66 stated that the child had recovered.

Impression: Reaction from Lomotil overdosage.

H. Searle Case # LO 2–67 dated 3/2/67 and 4/19/67

Report of a fatality in a 2 year old child who accidentally ingested approximately 8 Lamotil tablets 12 hours prior to arriving at the Shawnee Mission Hospital, Shawnee, Kansas, D.O.A.

An autopsy was performed which revealed pulmonary congestion consistent with the picture of interstitial viral pneumonitis, reticuloendothelio hyperplasia, and a hypoplasia of the adrenal cortex. The final diagnosis of cause of death is listed as acute pneumonitis. "The results of toxological examination of the stomach contents show no atropine nor diphenoxylate to be present. The blood sample was insufficient for evaluation (quantitative) of diphenoxylate. Histological findings are consistent with those seen in children dying of acute viral pneumonitis and it is felt that the cause of death in this child is of this etiology."

Impression: Death probably not due to drug but viral pneumonitis.

I. Searle Case # LO 4–67 dated 4/19/67 and 4/27/67

Case of fatality from Lomotil overdosage in a 2½ year old girl treated at the University Hospital, Western Reserve University, Cleveland, Ohio. She allegedly ingested 8 tablets of Lomotil. Heroic symptomatic and supportive therapy given.

Follow-up autopsy by the Coroner's Office, Cleveland, Ohio yielded the following:

a. Lungs: Hemorrghagic bronchopneumonia.
b. Stomach: Acute ulcer.
c. Kidney: Renal tubular necroses. Protein casts. (Most of tubular epithelium is preserved).
d. Brain: Marked cerebral and cerebellar edema. Subarachnoid hemorrhage, focal, slight.

The tissue forwarded to Searle for laboratory analysis was received by the firm in such poor condition as to make them useless for analysis.

Impression: Possible death from Lomotil overdosage.

MARVIN SEIFE, M.D.,
Acting Director, Division of Cardiopulmonary Renal Drugs/ODS.

PHARMACOLOGIST'S SUMMARY

Date Summary Completed: July 21, 1967, NDA 12–699.
Company: G. D. Searle & Co., Chicago, Ill.
Original Effective Date: September 19, 1960 (12–699 OED 1/17/61).
Name of Drug.—Lomotil.
Generic Name.—Diphenoxylate hydrochloride with atropine sulfate.
Category.—Antiperistalic agent.
Dosage.—To 20 mg/day for adults in divided doses, orally.
Material Reviewed.—
Report of Acute Oral Toxicity of Lomotil Liquid dated July 12, 1967.

These are useless studies on the toxicity of the components of the vehicle of Liquid Lomotil. We requested "acute and subacute studies of toxicity in the newborn and adult to determine the relative toxicity of the mixture of drugs (2.5 mg diphenoxylate and 0.025 mg atropine sulfate) as the dry powder and as the syrup." Studies of the vehicle or components of the vehicle do not give any information as to a possible difference in absorption of the drug in the presence of the liquid vehicle.

The studies which were requested should be submitted.

LOUISE L. PHILLIPS, Ph. D.

ADDENDUM TO SUMMARY OF SUPPLEMENT NDA 12–699, DATED AUGUST 17, 1967, REGARDING REPORT DATED AUGUST 16, 1967

Report on NDA 12–699 (Lomotil Liquid) entitled "Acute Oral Toxicit Study—Weanling Rats, Diphenoxylate RCL–R1132, Lomotol Power, Lomotil Liquid—Final Report" dated 16 August 1967 and signed by Herbert Helling, Food and Drug Administration Liaison Coordinator. The report supplements the previous incomplete report.

The FDA pharmacologist, Dr. L. L. Phillips, has reviewed the above report concluding that "* * * Lomotil is more toxic to the young animal than to the adult and that the liquid form is more toxic than the powder—perhaps due to increased absorption from the gastro-intestinal tract." Her recommendation was that "* * * weight proportional doses should be prescribed for children and that lower doses of the liquid than the powder should be recommended."

The reviewer cannot but wonder whether the acute studies in weanling rats can be extrapolated to human infants and children. The majority of deaths with Lomotil were accidental. There have been a paucity of deaths on therapeutic—dosages after 6 years of use of the drug. The drug was approved 9/15/60 and 1/17/61. The study on dosages in a large number of children, supposedly near completion, is awaited before a request for dosage studies and absorption studies may be requested.

Conclusions

The drug is safe as originally approved. Efficacy is being evaluated by the appropriate NAS-NRC panel.

Recommendations

1. The supplement and reports reviewed be permitted under 130.9(d) of the regulations.
2. The company be requested to revise the package insert as recommended.

AARON L. KAMINSKY, M.D.,
Division of Cardiopulmonary Renal Drugs/ODS.

PHARMACOLOGIST'S SUMMARY

Name of Drug.—Trade: Lomotil.
Generic: Diphenoxylate hydrochloride with atropine sulfate.

Dates of Supplement.—Supplement August 9, 1965 and September 16, 1965. Annual Report August 30, 1966.

Therapeutic Indication.—Antiperistaltic agent.

Usual Human Dose and Route.—To 20 mg/day for adults in divided doses, orally.

Material Reviewed.—Two reproduction studies from Huntingdon Research Center, Huntingdon, England. One acute toxicity study from Searle Toxicity Lab. July 20, 1965.

Summary

Teratologic studies have been performed on three animal species: rabbit, rat, and mouse at doses of 0.4, 4.0 and 20.0 mg/kg/day of Lomotil equal to 1X 10X and 50X human theraupeutic dose (HTD). There was no evidence of anomalies in any of the fetuses. This included 69 rabbit, 91 rat, and 105 mouse fetuses at the two higher doses. Abnormalities in all species were found on thalidomide (150–200 mg/kg) used as a positive control in the ratio of 6/6 rabbits, 1/56 rats, and 4/32 mice. Resorptions and stillbirths were similar in the test and negative control groups but higher in the positive control in rabbits and rats. There was a slight reduction with borderline significance in fetal weight in the mice given Lomotil but the differences were not dependent.

In a different series on long term subacute toxicity studies carried out on male and female rats with feeding 10X and 50X HTD for 80 days prior to mating and then throughout three cycles of pregnancy and weaning there were no differences in mortality of the adult groups. Food consumption for the first 8 weeks did not vary significantly but was slightly elevated in males and slightly decreased in females of all test groups. Weight changes reflected the food consumption for this period with an increase for males and a decrease for females.

Fertility in terms of percent pregnancies and size of litters was depressed in animals receiving 20 mg/kg/day Lomotil, and thalidomide. Neonatal loss was also greater in these two groups but losses were high in all groups due to handling. The decreased fertility on the high dose of Lomotil and on thalidomide was nocentuated in the 2nd and 3rd matings. No anomalies were observed in 143 young at 4 mg/kg level or 45 young at 20 mg/kg level. Two abnormalities appeared in the first pregnancy on thalidomide and 4 in the second from a total of 33 offspring.

Acute toxicity studies of Lomotil and Neomycin showed LD_{50} in the adult mouse administered intragestrically to be greater than 1 gram/kg for either drug alone or as a mixture. Intraperitoneally, LD_{50} in the mouse was greater than 1 gram/kg for Lomotil, 240±24 mg/kg for neomycin and 315±32 mg/kg for the mixture (1 part of Lomotil to 50 parts Neomycin). In the rate a double peak of 50% mortality made precise LD_{50} calculation of Lomotil alone impossible. These peaks came at 130 mg/kg and 450 mg/kg both orally and I.P. LD_{50} for neomycin and in the mixture were greater than 1 gram/kg orally but 420±64 mg/kg for neomycin and 465±47 mg/kg for the mixture when given I.P. There appears to be no potentiation of LD_{50} between the two drugs.

Evaluation

Both reproduction studies indicate that there is no teratogenic effect of Lomotil when fed during pregnancy but that very high doses adversely affect the fertility of the adults (no studies on fertility of offspring) when fed for long periods (60 days prior to mating).

However, there is no evidence from the report of the laboratory as to the form in which the drug was given. If the studies were performed on the mixture (2.5 mg diphenoxylate to 0.025 mg atropine sulfate) then the results suggest a statisfactory margin for safe usage in pregnancy. If they were performed only on the diphenoxylate they should be repeated using the mixture. There is also no indication as to whether the syrup or dry material was used. There might possibly be an increased absorption of either or both drugs from the syrup. (The deaths in children, except those due to accidental ingestion of huge doses, followed administration of the syrup rather than the tablet form).

Acute and subacute studies of toxicity in the newborn should be run concurrently with adult studies to determine relative toxicity of the mixture in both forms—dry mixture and syrup. Until the comparative newborn vs. adult studies are reported and evaluated, it is urgently suggested that a stronger contraindication be placed in the labeling against administration to infants and young children.

L. L. PHILLIPS, Ph. D.

SUMMARY OF REPORT

Date Summary Completed: 9/11/67.
NDA 12-462 & 12-699. G. D. Searle, Chicago, Ill.
Original Approval Date: 12-462 9/19/60; 12-699 1/17/61.
Name of Drug.—Trade—Lomotil.
Generic—Diphenoxylate-HCl with atropine sulfate.
Dosage Forms and Route of Administration.—To 20 mg/day for adults, orally; children from 3 mg (3-6 months old); to 10 mg/day (10-12 years old).
Category or Use of Drug.—Antiperistaltic.

Material Reviewed

Report entitled "Acute oral toxicity study in weanling rats, of diphenoxylate MCl, Lomotil Powder, and Lomotil Liquid.

The report shows that diphenoxylate HCl alone has an LD50 of less than 117 mg/kg while the Lomotil Powder has LD50 of 47 (males) to 71 (females) mg/kg in 25 day old weanling rats. This is from 2 to 10 times the toxicity found in the adult LD50 (130-450 mg/kg).

The Lomotil Liquid has an LD50 equivalent to 22.8 ml/kg or 11.4 mg/kg in the weanling rats. This is 4 to 6 times the toxicity evinced by the dry powder.

Most of the deaths of rats with the powder occur within 2-5 days following administration of the drug and the dose response curve is flat. This tends to indicate that there may be occasional extreme susceptibility to the drug or increased absorption.

On the other hand after Lomotil Liquid the animals usually died within 24 hours of dosage and the dose-response curve was steeper. Both of these facts indicates absorption of the drugs to be more rapid and more uniform from the liquid than from the powder.

Clinical Evaluation

These studies make it evident that Lomotil is more toxic to the young animal than to the adult and that the Liquid form is more toxic than the powder—perhaps due to increased absorption from the gastro-intestinal tract. This increased

toxicity may explain the two deaths of children from relatively normal doses of the Lomotil Liquid.

Recommendations

The subacute toxicity studies which are supposedly in progress may add more information on the relative toxicity of liquid vs powder and child vs adult.

It would appear that less than weight proportional doses should be prescribed for children and that lower doses of the liquid than the powder should be recommended.

LOUISE L. PHILLIPS, M.D.

MEMORANDUM

DECEMBER 22, 1965.

To: R. J. Robinson, M.D., Chief, Drug Surveillance Branch/DMR.
From: L. V. Pascual, M.D., Medical Officer, DSB/DMR.
Subject: Report of overdose in association with the use of Lomotil.

(G. D. Searle & Co., Chicago, Ill. (A.F. 13–505) NDA 12–462)

This "Drug Reaction Report" from Dr. Miller was submitted by Adverse Reaction Branch/DMI on September 20, 1965. This report as well as two others was submitted by the company to FDA on July 20, 1965.

Lomotil went through the New Drug Application stage without the atropine added.

The marketed drug contains atropine sulfate supportably in sub-therapeutic quantity "to prevent overdosage". We are not aware of any pre-clinical or clinical trials performed with this combination. This combination should be considered a new drug. (Please see Memo of Dr. J. Nestor dated May 14, 1964).

Conclusions

The suggested warning statement pertaining to overdosage should be considered together with a complete revision of the labeling following evaluation of the data submitted in the NDA.

(The supplemental information submitted by Mr. Stetler, subsequently received, follows:)

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., December 12, 1967.

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

DEAR SENATOR NELSON: I respectfully refer you to pages 2269 to 2272 of the hearings conducted on November 16, 1967, before the Senate Monopoly Subcommittee of the Select Committee on Small Business.

On the cited pages Mr. Benjamin Gordon made certain statements alleging that the G. D. Searle & Co. added the active ingredient atropine sulfate to its drug LOMOTIL without first obtaining the approval of the Food and Drug Administration even though a new drug application covering the drug was, at that time, in effect. Mr. Gordon stated that his allegation was based upon information appearing in "a summary of the NDA. 12–462 Volume II . . ." The "summary" was "signed by John Nestor, Medical Director, FDA". (page 2272).

The document involving LOMOTIL is apparently not "a summary of the NDA." Instead, it appears to be an internal FDA memorandum prepared by Dr. John Nestor, to serve as a critique of the material in the NDA file. G. D. Searle & Co. holds an approved new drug application for LOMOTIL. The company has informed us that this application was originally approved on September 29, 1960, for a product *with atropine*, with exactly the same ingredients as those in the product now marketed. The product originally tested did not contain atropine, but this *was never marketed.* Atropine, in a non-therapeutic quantity, was added to the formula, prior to approval of the NDA, at the request of the Bureau of Narcotics. The Bureau's suggestion was in accordance with a recommendation of an advisory committee of distinguished scientists.

On November 16 you asked Mr. Gordon, "Are you saying that after a new drug application was granted, that the company involved added another active

ingredient without notifying the FDA?" Mr. Gordon stated that, "That is correct." (Page 2272) On the contrary, it appears that the active ingredients were not changed after the product was on the market.

I request that this letter be made part of the hearings and that in the final printed record it be inserted immediately after the materials presently contained on pages 2269 to 2272.

Sincerely,

C. JOSEPH STETLER.

Mr. STETLER. Are you saying this is a situation where they should have and did not have it approved by the FDA?

Mr. GORDON. That is right.

Mr. STETLER. What I am stating is, I cannot account for any exception. But the rule is that to make a change of significance of this type in a product it shall be cleared with a supplemental NDA. So this is not a free right the company has to make these decisions.

Mr. GORDON. Let me read part of the NDA summary on Lomotil:

> Laboratory work was practically nonexistent. That is such things as stool cultures. In many cases there was current therapy with other drugs, such as steroids, sulfanomides, tranquilizers. In many cases it was difficult or impossible to read and interpret the individual case histories which were lacking in significant detail—

and so on.

No mention is made of laboratory work, and there are no individual case histories. This is still about Lomotil:

> It immediately becomes apparent that the drug Lomotil as promoted is a combination of diphenoxylate and atropine sulfate whereas all of the investigational studies, both on man and animals, and all of the clinical work was done only on diphenoxylate hydrochloride.

This is an example where the FDA approved a drug and then the formula was changed.

Mr. STETLER. Obviously, I do not know what you are reading from.

Mr. GORDON. I am reading from the summary of NDA, which came from the files of the Food and Drug Administration.

Mr. STETLER. Is that an NDA that they filed and the FDA found that the evidence was inadequate? Is it a complaint against Searle that they did not file a supplemental NDA? My point is, it is required to be filed. If somebody did not do it properly, and you have one specific example of it, that does not prove the rule.

Mr. CUTLER. May we have the document you are reading from, Mr. Gordon?

Mr. GORDON. Yes; you can have it right here.

This is a summary of the NDA 12–462, volume II, on NDA 12–462, Lomotil, and it was signed by John O. Nestor, Medical Director, FDA.

Senator NELSON. Are you saying that after a New Drug Application was granted, the company involved added another active ingredient without notifying the FDA?

Mr. GORDON. That is correct.

Mr. STETLER. I am not saying they did or did not. All I am saying is that the rule requires that it be done.

Senator NELSON. That was not clear from what you were saying. I suppose the only point of that is that a substantial number of companies have had drug recalls, both brand- and non-brand-name firms. And the problem we deal with here continuously is the assertion by brand-name companies or supporters of brand-name companies that

all the problems—far and away the major problems that occur with respect to drug quality and quality control—are with generic drugs, and, therefore, everybody is out to prescribe brand names. I do not think the evidence we have been gathering support that assertion. I do not know that it would support an assertion either way.

Mr. STETLER. The last paragraph on page 12 in my statement is right on that point.

Let me state emphatically that we do not claim that all drug products marketed by brand name are high quality or that all products marketed generically are low quality. Many PMA member companies market some of their drugs under generic rather than brand names. We do claim that two drug products containing a specified amount of the same active ingredient may, depending on manufacturer capability and quality control know-how, vary in quality and therapeutic effect, and that this can be so whether one or both products are marketed by brand or generic name, and whether one or both manufacturers are members or nonmembers of PMA.

Senator NELSON. I do not think anybody will argue with that statement. It is true. That isn't the test of whether or not the drug meets a proper standard.

Mr. STETLER. May I go on?

Senator NELSON. Yes.

Mr. STETLER. On pages 13 and 14 we talk about various surveys, and the experience of the Department of Defense—all relating—for the next two or three pages, through 15—to really what we think are available or not available to the doctor in his actual prescribing.

Senator NELSON. I have read that, and I do not have a question on it.

Mr. STETLER. On the bottom of page 15 I would pick up and say, in summary on this point, that I do not presume to speak for the medical profession, but I cannot imagine there would be any substantial dissent within that body from the following propositions:

(1) A physician should consider first the known therapeutic effect and known quality of each drug product available to meet the particular needs of his patient.

(2) If a choice is available among effective drug products of satisfactory quality, the physician should take price as well as therapeutic effect and quality into consideration when prescribing.

(3) Unless the physician is satisfied that all drug products of the generic class he decides to prescribe are substantially therapeutically equivalent and of high quality, he should identify the source of the drug product on his prescription that he wants his patient to receive.

As we have said, we believe the doctor's most reliable guarantee of quality is his prior experience with the product of a particular manufacturer. Nevertheless, recognizing the importance of price, we would support effective methods of informing physicians, dentists, and other practitioners more fully than they already are about the comparative prices of different drug products containing substantially the same active ingredients.

Senator NELSON. What kind of idea do you have for supporting a more effective method of informing the physician?

Mr. STETLER. I was able this morning to talk about price in connection with the compendium. And I say that with a full realization

that it is easier to say why price should not be in the compendium than it is to come up with a satisfactory alternative.

I will say this however: Given the variations that exist in price from day to day and from store to store—and of course the doctor, if he is going to help his patient, has to be concerned with retail prices—it is difficult to suggest a practical current way.

I would just say as one possibility—and I have no great pride in this suggestion—possibly through the only organization that is available to him, through a county, possibly a local city or county medical society—they could assume some responsibility in making price information available. That is far from perfect, I am sure. But I believe it provides more chance of general distribution, and more chance of remaining current, than to try and bind it in a compendium or in a quarterly supplement to a compendium.

Senator NELSON. This morning we talked briefly about a compendium. You are aware of Dr. Goddard's testimony last week?

Mr. STETLER. Yes, I am.

Senator NELSON. At that time he said the industry and FDA would be conferring with the Drug Research Board on this matter.

And he also expressed some concern about the lack of progress since the first time this issue was raised 2½ years ago.

Is there any realistic prospect that some agreement may be reached on a compendium?

Mr. STETLER. I would have to say in terms of one more meeting of the Drug Research Board, the prospects are not good. Just let me mention a couple of reasons.

One I mentioned this morning, and that is I really have a very distinct feeling that the doctors, at least to the extent the American Medical Association speaks for them on this issue, do not believe the type of compendium that has been discussed for this last 18 months or 2 years is the kind of book they want.

Given that lack of enthusiasm by doctors for the book that is supposed to serve them, almost anything I had to say on the subject would not be binding.

Secondly, we really have not come to grips with the questions I identified this morning, on the format, the size. Until those things are resolved, it is going to be difficult to come to a decision.

Now, I am sure it is obvious that the industry is not interested in a completely generic compendium. First of all, it gives no identification to their products. It equates the worst manufacturer with the best manufacturer. Unless the manufacturer had some opportunity to indicate in the compendium where he might be different or excel—in other words, if he has done the clinical testing we have talked about if that could be identified, as contrasted with those that have not—if he has an opportunity in this compendium to capture or retain some of the differentiation that is possible in the package insert, I think there would be some enthusiasm in the industry for the compendium. But if he is just going to obtain anonymity in the book, it is going to be hard to expect him to put up the money to pay for it.

But I do think until the doctors are much more specific on what they want, it is going to be a tough question to resolve.

Now, as far as this meeting of the Drug Research Board is concerned, to get a little closer to the answers to these questions, and since

FDA is going to be the final authority on the approved language, it may be a worthwhile exercise to take the first 50 or 100 drugs in the Physicians' Desk Reference, and for the Food and Drug to put down how they would be handled. If I could see the format for the first 100 drugs in the Physicians' Desk Reference, how that is going to be handled, I think I could come to a much quicker recommendation to our industry as to our reaction to that kind of book. And I think maybe the doctors could say yes or no—that it is a good book, or that is a bad book.

Senator NELSON. What is your view of the problem that is sought to be resolved by the use of the compendium?

Mr. STETLER. I think there is a very legitimate desire to place in the hands of doctors information about available drug products—not necessarily every available drug product, but certainly the ones that are in common usage.

Now, I think it should be something less than a package insert, which is much too long and detailed in many respects.

But in fairness, again, to the manufacturer, and to the doctor who is going to be making some drug decisions from this book—we should give him some information that is going to let him make a better assessment of the producer or the source of these products.

I do not think that the doctor now gets that type of information readily from the package insert. But we should not necessarily jump from the package insert to something that also is not going to meet the problem.

I am not as impatient as Dr. Goddard is about trying to find out more specifically the answer to some of these questions. But that does not mean that we are opposed to a compendium.

We have looked very carefully, incidentally, at your bill, S. 720, which you have said you want to look at some more. But I think, as I said this morning, there is some desirability to the introduction of a new bill and to the conduct of some hearings on it.

Senator NELSON. Tell me this.

I don't have sufficient knowledge to know what the problem really is. But it is certainly a different problem for the physician who is practicing daily, say, in a university hospital, or in a big city hospital, with a formulary, and pharmacologists and pharmacists available for consultation. The problem of the physician practicing there is certainly dramatically different respecting the availability of information about the use of the drug in a particular instance than it is, to take the extreme case, of a country practitioner alone in a rural area. And it is quite different, I would suppose, for the specialist who deals only with heart patients or who deals only with allergies, or who is an ear, nose, and throat specialist using a very limited number of drugs, than it is for an internist, for example.

So, for each one of these specialties you have a different problem. And I suppose that the problem of getting information is not as serious for physicians practicing in the hospital as it is for one who does not; nor is it as difficult for one who is in a specialty which requires the use of a very limited number of drugs, as it is for a general practitioner.

So one problem that has concerned me is how the practicing physician who is alone, or in a very small group, or in a very small hospital,

or a small clinic, is informed about drugs. What is the basic, handy source?

How many drugs would the average internist use? Does anybody know?

Mr. STETLER. I suppose anybody could guess on that. I would say, if you had to pick a number, no more than 50 on the average.

Senator NELSON. So depending upon how broad his practice, and what kind of a circumstance——

Mr. STETLER. An average internist would have this experience in an average type of practice.

Senator NELSON. Well, is there any reason why a somewhat limited compendium of a couple of hundred drugs could not be put together that would solve the basic problem for an ordinary practicing physician? I am not sure that the specialist in the hospital is really worrying that much about it.

Mr. STETLER. I think that is one of our points. When people talk about a compendium of 7,000 or 10,000 products, this is what concerns the doctor. He says, "You are giving me a useless book that is going to be several volumes that I cannot use effectively."

I think you are right when you say that realistically we have to think in terms of a more limited type of compendium. Now, I do know that one difficulty between AMA and the type of compendium that has been discussed by Food and Drug is that any book they put out, such as New Drugs, or the one they are contemplating now for publication in 1968, involves comparative analyses between drugs. That is a different kind of a book, and it is really not the kind of compendium that the FDA is talking about. But I think if we could talk, and get the kinks out in terms of a more limited compendium, I think it would have some utility. And I want to make sure you understand we are not adverse to a compendium, depending on what the compendium is for and what it will do.

Senator NELSON. We are in the process of preparing another bill, because I am not satisfied with the one I put in.

Did I understand you to say this morning that you thought it might be of some value to conduct some hearings so that we could afford an opportunity to the physicians practicing in the various fields, as well as others, to comment on the idea of a compendium?

Mr. STETLER. Yes, and industry, and anybody else that is interested. Now, I don't know what might evolve from that, but I think you and Senator Javits have both said if you had your preference you would rather see the doctors or the industry put out such a book. Maybe through the process of these hearings we would end up there. If we did not and ended up with a Government compendium, so be it. But I think that might be the proper forum to get all of these attitudes and opinions out where they can be observed properly.

Senator NELSON. Thank you.

I think it might be of some value, too. This would be one way to get in the record the best testimony we could from the various specialties of medicine as well as industry and government.

Go ahead.

Mr. STETLER. I am at the bottom of page 16, under "Prices."

We have heard a great deal during these hearings about allegedly "high drug prices." The fact is, however, that all available price in-

dices show that drug prices are going down while other prices are going up.

Mr. GORDON. Mr. Stetler—I would like to put in the record an article entitled "Examination of Anomalies in Prescription Drug Prices and Utilization." It was written by Agnes W. Brewster and Juanita Horton. Mrs. Brewster is Chief, and Mrs. Horton is Pharmacist-Economist of the Health Economics Branch, Division of Medical Care Administration, Public Health Service. It was presented at the Drug Utilization Session, sponsored by the Medical Care Section of the American Public Health Association, in Florida, October 25, 1967.

I would like to read a couple of excerpts.

> Starting ten years ago, in 1957, what happened to this 1965 list in the way of price movement? More than half had no price change. For 57 the price advanced, sometimes more than once, and for 27 the price was reduced, sometimes twice. However, the increases in the prescription price (less than a dollar), were much smaller than the decreases, which were so large on a few products that the average was six dollars.
>
> The picture that emerges from this analysis is certainly not in conformity with the downward trend for the consumer price index for drugs. True, antibiotics such as Achromycin and Terramycin dropped dramatically. But most drugs remained unchanged, and the remainder rose in price. For the consumer to experience the price decline indicated by the CPI behavior, the drugs ordered for him would have been from a narrow list and not at all typical of the market as a whole.
>
> Generic prescriptions are used to provide the consumer price index even though more than 90 percent of prescriptions which consumers purchase are trade name drugs.

I ask, Mr. Chairman, that this document be put in the record at the appropriate place.[6]

Mr. CUTLER. May we have a copy, Mr. Gordon?

Mr. GORDON. I have only one, but I will have it Xeroxed.

Senator NELSON. Mr. Stetler, I have to run up to the Senate floor momentarily. Do you want to wait, or do you want to proceed with minority and majority counsel? I will be back soon.

Mr. STETLER. Do I understand as far as our other witnesses, they are not going to be going on today—they will be delayed until the 29th?

Senator NELSON. If that is satisfactory with you, we will conclude your testimony, and pick theirs up on the 29th. If it is not, I am available to go on later this evening.

Mr. STETLER. Since these people have spent a lot of time on their testimony, I would rather give them a time when they can put it on in sufficient detail for you and other members of the committee that might be present. So far as our next five witnesses are concerned, I would be agreeable to the 29th, assuming they can be available.

Senator NELSON. I would substitute these gentlemen for the witnesses you planned to have on the 29th.

Mr. STETLER. And then we would put them on our third day in December hopefully and have a fourth day for the ones that were due in December.

Senator NELSON. And a fifth and sixth day——

Mr. STETLER. Four will do it.

(At this point in the hearing Senator Nelson withdrew from the hearing room.)

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[6] See p. 1424, infra.

Mr. GORDON. In addition, I would like to read to you some of the testimony that Mr. Ross, Commissioner of the Bureau of Labor Statistics, gave before our committee at the beginning of our hearings.

I asked Mr. Ross, "But we do know that the consumer is paying more for his prescription; isn't that right?"

And Ross answered, "Yes, sir; there can be no doubt that average prices of prescriptions have risen. The four surveys listed above show increases of 6 to 10 percent."

Mr. STETLER. On this—as I indicated in my statement—we are familiar with that testimony by Mr. Ross. And two of the men that we had scheduled for the 29th—actually, now they will be put off—are men who we have selected to talk about the price indexes, to discuss Mr. Ross' testimony and the price performance of generic, brand, patented, nonpatented products. I do not really presume to have any expertise in this field, except to recite the statistics—I could do that. But in detail—I would prefer to wait until these men testified.

Mr. GORDON. I just wanted to bring up some of the statements which show the limitations of the Consumer Price Index to which you referred.

Mr. STETLER. Well, we referred to the statistics, Bureau of Labor statistics.

Now, that is the agency of Government that is responsible for deciding how price indexes shall be devised, and I think it is proper for our prices to be measured by the same criterion by which other prices are measured.

The statistics that are cited for——

Mr. GORDON. There is a great difference, Mr. Stetler. But since you are going to have experts come, let us postpone that.

Mr. STETLER. I will let them discuss this subject.

Mr. GORDON. In that case, why don't we take a break until the chairman comes back.

(Short recess.)

Mr. GORDON. Mr. Stetler, will you please resume with your testimony?

Mr. STETLER. As indicated, I am going to get to the tail end of my statement and conclude this in a couple of minutes.

As you know, we submitted with our statements some studies that go into fairly extensive detail about the contributions of the industry in a variety of areas. I will comment on that very briefly, and then give the conclusion as it is in my statement.

In the foregoing disscussion, I have tried to provide an insight into the achievements and aspirations of reputable pharmaceutical firms, the complexities of their operation, and their continued striving for excellence. I have tried to show the amount of effort and investment involved in research, in developing and marketing a new drug product, and the commercial risks that must be taken as the price of pharmaceutical advances.

Leading firms produce and stock certain so-called public service drugs which seldom yield a penny of profit. They are used in the treatment of rare, low-frequency diseases and the demand is simply not sufficient to justify the costly production process. They include antirabies serum, botulism antitoxin, gas gangrene antitoxin, Rocky Mountain spotted fever vaccine, and many others.

There is no question that these medications must be available whenever and wherever needed, and they are, thanks to the belief of many drug manufacturers that they have a moral responsibility to provide them. Usually they are provided without charge by the firms to the unfortunate persons who contract the diseases or to their physicians.

In conclusion I would like to say that in our continuing activities the pharmaceutical industry is pursuing the following aims, aims with which I believe this subcommittee would agree:

First, to provide doctors and their patients with drug products having the highest degree of safety, effectiveness and quality we can achieve for the lowest price at which these standards can be attained.

Secondly, to provide the doctor with a choice among such drug products as varied as the human idiosyncracies among the patients he treats and as divergent theories of medical therapy may require.

Third, to cooperate with the Government in assuring that these objectives are achieved at a reasonable cost.

We respectfully and urgently submit, however, that the way to attain these objectives is not to force physicians into generic prescribing or into prescribing the lowest price product regardless of the doctor's medical judgment as to its comparative quality and therapeutic effect.

Instead, we submit that the wise course for Government policy, in administering drug programs under various laws, is to assure:

(1) That physicians are provided with as much reliable information about the comparative effectiveness, quality, and price of drug products as our society can provide.

Mr. GORDON. Mr. Stetler, I think I can say fairly safely that the chairman and the rest of our subcommittee would agree with you completely. I certainly would like to underline the word "reliable." The information must be reliable. And I think that we are going to do everything possible to make sure it is so.

Mr. STETLER. Thank you.

(2) That physicians are left free to prescribe the particular product and manufacturing source they think best for particular patients; and

(3) That patients are provided with reliable information about comparative retail prices for that product.

In short, we urge that Government policy be aimed not at eliminating competition, but at making competition work as effectively as possible at all levels of the drug distribution system. I can assure you that the Pharmaceutical Manufacturers Association and its member companies will cooperate fully in all reasonable measures taken to achieve that end.

Thank you.

Mr. GORDON. Mr. Stetler, we certainly agree with you. This is a very fine statement. Practically every one of our previous witnesses have agreed with these points you have mentioned. We would appreciate it very much if you would submit to us any other ideas as to how we can implement this as early as possible.

Mr. STETLER. Thank you. We will do that.

Mr. GORDON. Do you have any questions, Mr. Grossman?

Mr. GROSSMAN. I have a couple of questions.

One—I think there was some confusion earlier during the questioning and colloquy with Senator Javits. I would like to ask you at this

time—to get back to the same issues we were talking about then, with regard to price differentials—you were talking I think at that time that a great deal of the reason for price differentials was the quality controls. I have been talking and I think he was talking about improving minimum standards, pushing up minimum standards.

Now, if we did push up minimum standards, could I assume or could we assume that the prices of the less expensive drugs would also go up to reach towards your quality control drugs? Is that fair to say?

Mr. STETLER. Yes; that is fair to say. That would be a demonstrable fact, I am sure. As the quality increased and the expense of providing that quality increased, it would have to be reflected in price.

Mr. GROSSMAN. Is there any evidence this has happened in the past when standards have been tightened or anything like that?

Mr. STETLER. I believe there is. I am not prepared to really document that fully today. But I think when our people testify about trends in generic and brand name prices, which might be as close as you can come to that, I think we will find that as the requirements of the Food and Drug Administration increased, there was more of an increase in price in the generic products than in the brand name products, which I think would be an index to the sort of thing you are talking about.

Mr. GROSSMAN. If you have any such information, could you supply it for the record?

Mr. STETLER. Yes; I will check to make sure—if it is going to be supplied by our group of witnesses, we will do it at that time. If it is not there, I will make sure I get it in connection with this day's hearings.

Mr. GROSSMAN. Yesterday the APhA testified as to a suggestion I think that has been made by other witnesses that generic patents be maintained, but that no trade names be attached. And I wondered if the PMA has any position on this. That is to say, that a doctor would just prescribe a generic, and if you wanted Schering or Upjohn, he could just put "Upjohn."

Mr. STETLER. I would like to make a brief comment on that, and let Mr. Cutler expand on it a little.

We definitely have a belief about that. We are not in agreement with the statement or the concept that the brand name era is dead. It certainly is not dead, should not be dead, and we hope we will not live to see the day when it is. As far as the drug products are concerned, when we are faced with the reality—and it is one—that doctors prescribe by brand names 95 percent of the time, obviously these names have utility to physicians. It is easier by the use of a brand name for a doctor to identify the source of the product than it is to use a generic name and indicate the manufacturer.

Now, this does not disparage a statement I made earlier—that we feel sincerely that doctors should have a right to prescribe any way they want to. But still the fact is that in the prescribing habits, and this has gone on for many years, they find it better and easier to use the brand name. Unless and until that situation is different, we cannot mandate different prescribing habits.

Mr. GROSSMAN. Do you think your position would be different if we had some kind of upgrading of minimum standards?

Mr. STETLER. I doubt that upgrading of minimum standards would affect significantly that problem but it might. Now, just on the brand

name item, and the brand name as a property right, I think Mr. Cutler might comment on that.

Mr. CUTLER. Mr. Grossman, as you know, trade names and trademarks are permitted under our laws for all products really as a means of encouraging competition enabling manufacturers to call attention to their mark which identifies their origin, and to enable them to help the customer differentiate their product and someone else's product. The problem is just the same in drugs as it would be in Coca-Cola, bikes, or Mustangs, or whatever other brand name or trademark you might select. There is no reason why drugs should be treated any differently.

Mr. GORDON. Are you saying that drugs can be compared with bicycles, shirts, shoes, and other things? Don't you see any difference at all in the drug industry?

Mr. CUTLER. Certainly I see difference in products.

Mr. GORDON. I do not mean just in products.

Mr. CUTLER. I believe the same competitive forces and competitive values in calling to the customer's attention, in this case the doctor, the difference between one manufacturing source and another apply in drugs as they do in automobiles, Coca-Cola, or food or whisky or anything else.

Mr. GORDON. But you do see, do you not, a certain social responsibility the drug industry has?

Mr. CUTLER. Absolutely.

Mr. GORDON. That other industries do not have?

Mr. CUTLER. No question. Drugs are one of the most important products we have. But there is no reason why competition, as Mr. Stetler has said, should not be the method by which different drug products win their way into the favor of the doctor who is making comparative judgments.

Mr. GROSSMAN. Would you not agree they should win their way based upon one product being better than another product?

Mr. CUTLER. No question about it. The presence or absence of a trademark would not affect that. The value of the mark or the trade name is to permit the manufacturer to call attention to his product.

Mr. GROSSMAN. I have just looked through some of the literature sent out by industry to doctors, and sometimes I just see a picture of some people looking very happy and healthy, and just a big trademark name right in front of it. That doesn't tell me or the doctor why that product is better than any other product.

Mr. CUTLER. It would be equally true if the same ad said "Merck's prednisone." The fact that it might or might not have a trade name does not really affect the point, it seems to me.

Mr. GORDON. I think there is another very important problem with respect to using a trade name. I think Dr. Modell and others have testified that trade names can cause certain confusion.

But from your point of view, you say it makes no difference whether you use a trade name, or whether you say reserpine-Ciba?

Mr. STETLER. We say the important thing is for the doctor to identify the source. If he does that more easily or more effectively by using a brand name, he should have the right to do it. But the important thing is the identification of the source. There is no question about that.

Mr. GROSSMAN. Thank you.

Mr. GORDON. I have a couple of additional questions, Mr. Stetler.

You discussed the differences at the beginning of your statement between the innovator and the non-innovator. The inevitable conclusion is that every licensee of a patent holder is a non-innovator, is that correct?

Mr. STETLER. That may be true with respect to that product. But, of course, most firms have a variety of products. They do an extensive job of research. But part of their product line may be a drug that has been researched and marketed or patented by someone else. But you cannot put them in the category of an innovator or a non-innovator, depending on what they do with just one product.

Mr. GORDON. As I understand your statement, you are saying that a person is an innovator, hence the quality of the product is necessarily better?

Mr. STETLER. No. If I have left that impression, it is wrong. There are two elements, obviously. One is innovation, the activity of the company which does the research, and does develop new products. That is a specific contribution which that type of a manufacturer makes. He cannot stop there. In addition, he has to do all of the quality control work that is essential to producing that product properly. But you will find, if you look at the manufacturers, that the companies engaged in significant research effort, those that have acquired this type of expertise and personnel, do not skip the quality process. They are more or less automatically in that role. But they are two distinct things. A company that does not do research can do a quality job.

Mr. GORDON. In other words, a certain company can also emphasize the manufacturing aspects, not the research aspects, and produce a drug of the same high quality as another company which may be an innovator. Is that reasonable?

Mr. STETLER. Quite possible.

Mr. GORDON. Now, Mr. Stetler, you justified the high cost of advertising as a necessary cost. Where would that be in your statement?

Mr. STETLER. Page 22.

Mr. GORDON. No; page 4.

The fact is that advertising is the most economical and efficient means of getting the facts about the new product to the physicians who need them.

Page 4, the third paragraph down.

Is it not a fact some of the most extensive advertising campaigns have been for old products, under a new name? For example—Noctec? A new name, relatively for an old product, choral hydrate. A lot of advertising is being done to advertise that particular name. This is not what you had in mind, though?

Mr. STETLER. Well, there are obviously some expenditures in advertising for old products, and if that is indicated—it gets the product back to the attention of the doctor, and the purpose of advertising is still to sell drugs.

But I think you will find that the larger proportion of the advertising budget is expended to get information available to physicians and pharmacists on new drugs rather than old drugs. As a general rule, I think that is a safe statement.

Mr. GORDON. We have also been told by Dr. Cluff, of the University of Florida Medical School, that another effect of advertising, both direct mail advertising and the efforts of detail men, is to cause serious

overprescribing of drugs. Is it your opinion that the type of advertising that causes this phenomenon would be in the public interest?

Mr. STETLER. I really do not believe it does come from that.

If there is overprescribing—and I am not prepared to say there is—I cannot speak on that with authority. I have read the statements and recent statements there is overprescribing. I doubt that that is so.

However——

Mr. GORDON. If it is so, what would be your answer?

Mr. STETLER. My answer is, I don't know the cause of it. But I have serious doubts that it would come from advertising.

No doctor, no good doctor is going to give a patient a drug that is not necessary or going to give a patient a drug in excessive quantities because he has happened to read a drug ad. I cannot believe that. I think the medical profession is a good deal more responsible than that.

Mr. GORDON. Have you any idea, Mr. Stetler, how many cases have been brought against drug firms in the last few years for false and misleading advertising?

Mr. STETLER. Yes, I do.

Mr. GORDON. Could you tell us what they are? How many PMA members were involved?

Mr. STETLER. Well, I am going to equate that to a claim that was made some time ago, since that is really the extent of the checking I have done.

I cannot tell you, because I do not know, how many questions have been raised by FDA with respect to ad violations or what categories they fall in. But, there was a statement made last year that one-third of the members of the PMA were found to have had ads in violation of the regulations. Now, when this statement was made—and I think it was in April or May of 1966—we attempted very diligently to find out exactly what the data was. We could not get that until September when we received it through a member of the press.

Now, as you know there are hundreds or maybe thousands of ads that are checked routinely, or at least annually, by FDA.

When we checked back—we had at that time I think 138 members—rather than one-third of the PMA members being found in violation, only nine PMA members were involved in ads that were forwarded to the HEW's lawyers for review.

That was less than 5 percent of PMA membership. Only 89 ads at that time in the period indicated were even questioned by FDA medical evaluators. And that was druing a 2-year period. The number of companies involved in these cases fell far below the one-third that was alleged.

In other words, that particular allegation was a gross overstatement of the problem.

I hasten to add—there are obviously companies that have been questioned. But when we talk about members being found to have ads in violation of the regulations, that is a case that has been queried and adjudicated. Those are relatively few. But when you are dealing with ad regulations that have subjective terminology, like "fair balance," "brief summary," you are dealing with language where two very reasonable, honest people can have distinct differences of opinion and still the one who may be with the company can have no intention of misleading.

The language of the 1963 advertising regulations is difficult to comply with. It is easy to see where there might be questions raised. But when you talk about ad violations you get down to a relatively small number.

Mr. GORDON. Mr. Stetler, I shall put into the record at this point some material that we have received from the Department of Justice—complaints of the Government in these nine cases you mentioned.

One criminal case closed—now there are two criminal closed—and three criminal cases pending, I think; four civil cases closed, and one civil case pending.[7]

Mr. STETLER. I think it should be clear many of these cases are still under consideration. Actually in terms of violations adjudicated, it is something like three, and nothing close to one-third of PMA membership involvement as was originally indicated.

Mr. GORDON. I shall also put into the record a large number of "Dear Doctor" letters which have been sent from 1961 to date.[8]

I notice that every one of these are from members of PMA.

Mr. STETLER. I think if we do 95 percent of the production and 95 percent of the drugs come from our firms, it is obvious that the good deeds and few mistakes will be dominant from those sources, too.

Mr. GROSSMAN. I have a question.

Talking about good deeds in the industry—yesterday we had testimony from Dr. Apple about the concept which he called the community formulary. Are you familiar with that concept?

Mr. STETLER. I have not read his statement. I am not familiar with how he used that terminology.

Mr. GROSSMAN. If I may, I will just read something.

"The local medical pharmaceutical societies would establish a pharmacy and therapeutic committee to develop a list of drugs to be utilized."

This might be in a community such as a disadvantaged area in New York or in Chicago, Watts in Los Angeles. In other words, what I am getting at here is what is the industry doing in areas like this? Has the industry made any contribution in disadvantaged areas?

Mr. STETLER. They have made significant contributions, but not of the type that would fall in the category of a formulary.

Mr. GROSSMAN. I am aware Smith, Klein & French has been helpful in Philadelphia in housing. What about in the particular field of drugs and lower cost to people in these areas?

Mr. STETLER. Well, I think it is probably spelled out pretty well in some of those blue books attached to my statement. But there are a great number of price concessions that have been made by firms to certain categories of beneficiaries under State, local, and Federal programs that would, I am sure, be pretty specific answers to your question.

Mr. GROSSMAN. What about this idea of a community formulary in an area such as Harlem or Bedford-Stuyvesant in New York?

Mr. STETLER. I think if you are going to talk in terms of a community formulary, it really would make no more sense or as much sense

[7] See p. 1427, infra.
[8] See p. 1450, infra.

in a disadvantaged area as in any other area. I do not think we should consider it just in terms of a disadvantaged area.

Now, if there is any rationale to such a formulary, it has to be based on medical considerations not price. If you base it strictly on price, you run a direct risk of ending up with a listing of second-class drugs, and you do not want that for your disadvantaged areas. Obviously—those people are entitled to the same quality of medical care, including drugs as anyone else. So I do not think you can think of a community formulary just in terms of a disadvantage area. If there is any rationale to the concept, I think it would go across the board.

Mr. GROSSMAN. You would not say that hospital formularies dispense second-class drugs?

Mr. STETLER. No. And I am not saying your concept would. I am just saying the further you get away from the individual doctor, and that individual medical decision, with a formulary, the better chance you have of making arbitrary decisions that do not reflect his individual views.

Mr. GROSSMAN. Let me just ask one final thing. It is kind of on a broader plane. I think I started on this this morning, and I am still concerned about it. I still foresee this controversy going on and on and on.

I can be assured when Dr. Goddard comes out with his new study—where are we going to be. Are we in any better position than we are right now? In other words, what is going to happen in the long run, what is the industry going to do?

Mr. STETLER. I think that is a very legitimate question. And again I will give you a personal reaction to this, because I want to make sure you understand this is not an industry concept.

I believe that one of these days or years soon we are going to have to take nother look at the theory or the rationale of the Food and Drug Act.

I do not believe that we are ever going to get to a position where we can say with assurance that there is equivalency among drug products, given the base from which we start.

Now, you can ask five people, and you will get five answers, as to how many manufacturers of prescription drugs there are in the United States. A good figure to use is 1,500. Now, when you realize that our 136 members make 95 percent of the prescription drugs, 5 percent are being made by some 1,374 drug companies.

Now, they must have some rather insignificant or small operations. They may be rather short in quality control. I am sure they are not getting the inspections that we get from Food and Drug, and let me say I would not do it any other way, if I was FDA.

Mr. GORDON. Dr. Goddard says there are not that many manufacturers.

Mr. STETLER. I said you can talk to five people and get five different answers. And that is true. But I think what we should have, so that this question could be resolved, in our registration of manufacturers, we should know, not guess, how many manufacturers there are, how many distributors there are, how many repackagers there are. The fact is today we do not know.

Mr. GORDON. How about intrastate manufacturers? Aren't there intrastate manufacturers?

Mr. STETLER. There are literally thousands.

Mr. GORDON. They do not come under the FDA regulations, do they?

Mr. STETLER. As for FDA controls, the answer is no. If they go across State lines, yes, but if they strictly manufacture and do an intrastate business, the answer is no.

I would like to go back just to the one concept, and that is I think personally, before we can get to the point where we can approach this problem differently, instead of looking every day at every manufacturer, how he does his job, we are going to have to establish some credentials and qualifications for being in the business of drug manufacturing, and to check that from time to time to make sure that they are still able to do the job.

Now, concomitant with that, I think the Government should stay away, at least on a day-to-day basis, from policing that qualified company, and let him assume, as he should, some of the responsibility for doing a good job. But if we start off with people that have had to comply with certain basic criteria to be in the business, then I think we have come a lot closer to ending up with products that deserve to be on the market.

Now, that is a personal view.

Mr. GROSSMAN. You do force the small businessman out.

Mr. STETLER. No necessarily. But, I do not want a small businessman or a big businessman making pills for me if he is not qualified for the job.

Mr. GROSSMAN. You see, the problem in a broad view from my point of view is that if we want to know about airports—I am talking about the committees of the Senate or the Congress—we usually get the Department of Transportation up here and they talk about it. If we want to know about something in another field, we usually get an executive agency to talk about it, and they tell us what they think.

Now, we call on the FDA, and they come up here and say there is therapeutic equivalency.

Mr. STETLER. Actually Dr. Goddard has not really said that. What he said is, "We cannot today say there is therapeutic equivalency. We hope soon to be able to say that with assurance, I have an idea there is and I am trying to validate it." I do not think if you were to ask him that question specifically that he would say, "We, the FDA, say there is therapeutic equivalency in drug products."

Mr. GROSSMAN. And this is the designated agency to oversee this job?

Mr. STETLER. Yes. Now, I do not want to say I am critical of them. I think that is an impossible job given today's circumstances for the FDA or anyone else.

Mr. GROSSMAN. Thank you.

Mr. GORDON. And yet according to the Sainsbury Committee recommendations, England might be getting a similar type of organization.

Mr. STETLER. That is right. But you have to look at what they have now, and what their problems are, and contrast it with what we have and what our problems are.

Mr. GORDON. Are you acquainted with the Sainsbury report recommendations on the elimination of brand names? Let me put it this way. What they suggest is that the first manufacturer adopt a name, a trade mark, and then every other manufacturer can use that name. That will be the name.

Mr. STETLER. "New drugs should be marked only under Commission approved names" they say. And I think they are talking in terms of a generic concept. But, of course, the 1962 Drug Amendments gave the authority to FDA to make the decision on generic names. So really we have this provision right now.

Mr. GORDON. Mr. Stetler, on behalf of the subcommittee I want to thank you very much for giving us a very fine statement. We are extremely sorry that we could not hear all of your people. We look forward to hearing the rest of them on the 29th.

Mr. STETLER. Thank you. And I really appreciate the chance to be here today to present our views.

(The complete prepared statement submitted by Mr. Stetler follows:)

STATEMENT OF C. JOSEPH STETLER, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. Chairman and Members of the Committee, I am C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association. Accompanying me are Lloyd N. Cutler, Special Counsel to the PMA, and Dr. A. E. Slesser, Associate Director, Quality Control, Smith Kline and French Laboratories.

I welcome the opportunity to appear today to answer charges made against the pharmaceutical industry during the current hearings of the Committee, and to describe how the industry serves the public health. I am not, of course, in a position to answer charges or questions addressed to any particular company. You have already heard testimony from representatives of five leading pharmaceutical firms, and I am confident that any other PMA member company you desire to hear will be willing to testify.

My statement and those of the other witnesses scheduled to appear on behalf of the Pharmaceutical Manufacturers Association will be addressed to the principal questions which have been raised here, as well as to other issues which we believe merit the Committee's consideration.

We have submitted, with our prepared statements, a considerable volume of additional material which we would like to have included in the printed record of the hearings. It consists mainly of the results of a broad range of studies by authorities in their respective fields, undertaken to provide the Committee with a comprehensive picture of the industry's operations and achievements, and to place in better perspective some of the testimony you have heard to date.

The PMA witnesses who follow me today and later will comment in greater detail on many of the points I will touch on briefly in my testimony. We will deal with the issue of prescribing and dispensing drugs by their generic names, and will discuss drug prices and profits. We will deal with research trends and expenditures. We will discuss the high-risk characteristics of the pharmaceutical industry and its need to attract capital for growth and for continued health progress. We will also discuss the vital aspects of production and engineering techniques and quality control in the manufacture of drugs, and the differences that may exist among drug products containing the same active ingredient, but which come from different manufacturing sources. We will set forth the unique importance of the industry's promotional efforts in the delivery of product information to physicians.

The backbone of this industry consists of the innovators—those firms that strive, through creative effort, to assure the continuing flow of valuable new pharmaceuticals, and to maintain the highest quality standards for their existing products. There are other companies in the pharmaceutical industry which engage only in the manufacture of drug products developed by others. I am not here to criticize these non-innovators. Theirs is a legitimate business undertaking. All firms marketing high quality drug products at competitive prices perform an important economic function. The fact remains, however, that their costs of

doing business and their contributions to the public health, are generally much less than those of the innovator companies.

The Innovator vs. the Non-Innovator

It is not an exaggeration to say that much of the misunderstanding that exists with respect to the drug industry arises from the failure to distinguish between these different types of manufacturers. The company which has the complex and extensive facilities and the highly-trained personnel necessary to discover and develop drugs which someone else has not already marketed maintains cost burdens which are reflected in its prices. The non-innovator does not support such effort and therefore does not incur the expense in time and dollars necessary to make comparable vital contributions to the health of mankind.

The innovator must assemble and support a highly specialized team of research scientists such as physicians, pharmacologists, toxicologists, virologists, biologists, chemists, biochemists, pharmacists, engineers and other technical specialists. When their knowledge and skills are applied to a disease problem, there is no way to tell in advance how much time and money will be required to find a solution, if, indeed, one is found at all.

The discovery of a new potentially useful product moreover is merely the beginning. It must then be developed, another long and costly procedure which often requires more people, more processes and more time than the original discovery. This stage requires years of animal and clinical testing, and the submission of a New Drug Application, plus exhaustive supporting data to the Food and Drug Administration.

The approval of the NDA, clearing the product for marketing, marks the point at which the manufacturer may begin for the first time to recoup his investment. This step, alone, from the time the NDA is filed, can take from 18 months to five years, sometimes longer.

Once cleared for marketing, an extremely costly, but necessary effort is then required to make the product known to the physician, the pharmacist, and other professionals who will be working with the new agent. While there are those who would suggest that the promotion effort is too costly, or not necessary, the fact is that advertising is the most economical and efficient means of getting the facts about the new product to the physicians who need them. Journals of medicine, pharmacy and nursing provide the vehicles. These promotion costs cannot be avoided if information is to be communicated. It is a necessary cost that the innovator must bear.

Because the innovator discovers new compounds and health-saving uses for them that have never before existed, he must be particularly sensitive to, and capable of, assuring purity, potency and safety through the uncompromising high quality of his products. Quality control and quality manufacture are the *sine qua non* of the research-oriented pharmaceutical industry. These precise disciplines are inextricably linked with the operation of the innovator firm. Briefly, they consist of indispensable specifications and tests for each ingredient in the formula, proper design and formulation of the product, multiple inspections and tests during processing and packaging, final product checks, and the preparation of detailed and meticulous records to show the complete manufacturing and control history of each batch, and to enable the manufacturer to trace his products after shipment. Quality firms are well organized to recall with precision from all commercial channels any particular lot of a suspected drug product at any time, or to provide emergency advice as to where a particular drug product can be obtained when needed.

The medical profession not only demands quality in drug products but it also expects the product to be available in every form and dose that might be needed to treat a wide variety of conditions—including capsules, tablets, injectables, oral and topical liquids, concentrates, suspensions, suppositories and ointments. Not all are commercially profitable, but a capsule cannot be used to fill a prescription for an ointment, nor a cencentrate when an injection has been ordered.

Innovator firms accept this responsibility as a matter of course. The non-innovator, in contrast, frequently does not feel obligated to provide the drug product in every possible form. Rather, his tendency is to concentrate on the most heavily prescribed and the simplest and most economical forms to produce.

Beyond the production process, the drug product, in all its forms and dosages, must be available when it is needed, where it is needed. Through his system of distribution points, the innovator reaches the entire nation. Furthermore, through the same system, he can cover an emergency within hours in virtually

any village, city or county in the United States. No matter what the market situation, his product—in its full line—is there whenever and wherever the physician needs it.

The Pharmaceutical Manufacturers Association

Turning now to the Association for which we are speaking today, let me quickly describe its structure and the companies that make up its membership, and tell you something of their accomplishments and aspirations.

The PMA is a non-profit trade association which traces its history through two predecessor organizations to 1907.

Its 136 active members engage in the production of prescription drug products—those which are primarily dispensed by licensed pharmacists at the direction of medical, dental and other practitioners who are licensed by state law to prescribe and administer them. These member firms account for upwards of 95 percent of the prescription drug products made and sold by the entire industry in the United States at the present time.

PMA firms currently have facilities in 44 states. In the United States, the prescription drug industry employs 125,000 workers, including a high percentage of scientists and research specialists. The annual payroll is more than $897 million. They pay taxes of approximately $506 million per year to federal, state and local governments in this country.

These figures do not take into account the activities of the thousands of supplier companies that depend wholly or in part on the prescription drug industry. The wages, dividends and taxes paid by the manufacturers of packaging materials, machinery and other equipment represent another sizable contribution to the economy.

Member companies vary greatly in size. Several do an annual business of less than $200 thousand, while others have drug sales of $100 million or more. Approximately one-half of our member companies would qualify as "small business" as that term is defined by the Small Business Administration.

Drug Industry—Competition and Accomplishments

No one company accounts for more than 7 percent of total domestic prescription drug sales, which last year reached more than $3 billion. This low degree of concentration is approached by very few other manufacturing industries of comparable size.

Constant striving for discovery and excellence has resulted from competitive rivalry in the marketplace and through such competition has come the strength and viability of the drug industry which has contributed so much to medical progress over the years.

The pharmaceutical industry as we know it today is very young—less than 30 years old. Within these three decades, we have seen the emergence of a variety of new drugs that have all but revolutionized the practice of medicine—sulfonamides and antibiotics, cardiovascular preparations and anti-depressants, vitamins, hormones, and tranquilizers—an impressive array of drug products that have virtually wiped out some killing diseases, have shortened the length of the average stay in hospitals, have reduced the space requirements of mental institutions, and have been a boon to doctors everywhere in the practice of their calling.

These developments reflect the results of an outstanding system for the discovery, production and distribution of drug products which have made a truly unprecedented contribution to human progress. The system may not be flawless. It is, however, the most efficient, the most dynamic and the most innovative of that of any country in the world.

From 1940 to 1966, an amazing total of 823 new single chemical entity drugs were introduced as prescription drugs in the United States.

Perhaps I should explain that a "single chemical entity" in the field of pharmaceuticals is a unique substance unlike any other drug. It becomes the active ingredient in one or more drug products, or it may be employed as one or two or more active ingredients in so-called combination products.

At this time, I would like to submit for the record a compilation of the 823 new drugs which have been introduced since 1940. The list[1] was prepared for PMA by Paul de Haen, Inc., the nation's foremost authority on the origins of drugs.

The compilation is significant in your consideration of this great industry for

[1] "Review of Drugs 1940–1966", *American Professional Pharmacist,* Paul de Haen, Inc., November, 1967.

it shows that the United States originated 502 of the 823 new weapons against disease and suffering which have been placed in the physician's armamentarium in the last 27 years. And the U.S. shares credit with foreign sources for several others. Of the U.S. discoveries, the laboratories of American manufacturers were responsible for 87 percent. The others came from university, non-profit or government sources.

The Issue of Generic Prescribing and Dispensing

A great deal has been said during these hearings about prescribing by the generic name of the drug. I would like the record to be perfectly clear that the prescription drug industry and the PMA do not oppose the physician's freedom to prescribe in this way. We believe a physician should be entirely free to prescribe as he wishes, whether by a manufacturer's brand name, by the generic name with the manufacturer identified, or by the generic name alone.

In a true generic prescription the physician delegates to a pharmacist or nurse the selection of the manufacturing source for the product prescribed. If the physician considers such a delegation not to be contrary to the interest of his patient, he should be free to prescribe in that manner. If the physician prefers, he should also be free to designate a brand name or to specify the manufacturing source by designating the generic name of the drug together with the name of the preferred manufacturer.

We also believe that, in prescribing, doctors should supplement their medical judgments and decisions regarding drug quality and effectiveness with considerations of cost to the patient. If the doctor believes that two manufacturers market drug products of substantially identical therapeutic effectiveness and quality, he should, of course, prescribe the less expensive one for his patient. Contrary to a general impression, most prescription products are not fair-traded, and therefore manufacturers impose no restrictions on the prices charged by retailers.

I would like to say a further word on the subject of prescribing by using the generic name of the drug. While we favor the right of the doctor to prescribe as he wishes, we emphatically disagree with the assumptions and statements advanced by certain earlier witnesses before your Subcommittee that generic and therapeutic equivalency go hand in hand. As has been pointed out in papers by a number of leading physicians and pharmacologists and in previous testimony before this Subcommittee, the term "generic equivalent" refers only to the name of a drug product and does not necessarily connote its safety or therapeutic effectiveness. Although two drug products may contain, or are supposed to contain, the same amount of the same active ingredient, this provides no assurance that both products will produce the same clinical effect in any particular patient.

Mr. Chairman, you have asked several previous witnesses whether they can present any scientific evidence that drugs with the same generic name do not have the same quality and therapeutic effect. The witnesses who follow me today have such evidence to present, and they are prepared to discuss it in depth.

Drug manufacturing is a complex and exacting process. In our member companies 18 percent of all production employees are directly engaged in quality control. Even that does not guarantee perfection, but these unflagging efforts provide the best means of achieving the highest degree of quality that is realistically possible.

On this subject, there appears to be a rather common, mistaken belief that the federal drug laws somehow guarantee a uniform high level of quality in all drug products which reach and are dispensed from the shelves of a pharmacy. This is not so and, as a practical matter, can never be so. Although Food and Drug Administration personnel do a conscientious job, it is impossible for them to inspect every manufacturer and distributor often enough to insure that every drug product meets even bare minimum quality standards. Maximum quality and reliability can only be built in by the manufacturer. Even antibiotic drug products, every batch of which FDA tests before shipment, have turned up with variations in quality and potency.

Clearly, the public interest must ultimately be served by private responsibility. Deeply ingrained in the business philosophy of the reliable manufacturer is the desire to excel in product quality as a competitive measure. This system of striving to produce only the best is the physician's and the patient's strongest safeguard.

Mr. Chairman, although our member firms strive for perfect quality, even the best companies do not always attain it. You have read into this record lists of drug recalls that illustrate that mistakes still are made. But the fact that

mistakes are made even by the best manufacturers only proves the importance to physicians and patients of selecting the manufacturing source that has the best record of achieving quality, and the least likelihood of making future errors. Medicine is an art as much as a science, and by prescribing the manufacturing source in which he has the most confidence, the physician minimizes one of the many elements of risk in therapy.

Let me state emphatically that we do not claim that all drug products marketed by brand name are high quality or that all products marketed generically are low quality. Many PMA member companies market some of their drugs under generic rather than brand names. We do claim that two drug products containing a specified amount of the same active ingredient may, depending on manufacturer capability and quality control know-how, vary in quality and therapeutic effect, and that this can be so whether one or both products are marketed by brand or generic name, and whether one or both manufacturers are members or nonmembers of PMA.

You have already heard significant testimony that the exacting laboratory tests run by the Department of Defense often turn up such differences. Congressman Durward Hall placed in the *Congressional Record* on August 9 a letter from the Defense Supply Agency stating that there had been 143 rejections of drug bids tendered by apparent low bidders in competitive Defense Department drug procurements during the 22-month period from August 1965 through June 1967. In each case the drug products were rejected either because the sample submitted failed to meet the specifications or because the bidder failed to meet quality control or housekeeping requirements. Some 58 different firms had apparent low bids rejected for one or both of these reasons. All of the 58 firms are on the Defense Department's list of responsible prospective contractors and many are frequently successful bidders who deliver products that meet all specifications. But in 143 instances these firms failed to meet the Defense Department's requirements. Some firms had as many as 10 and 20 rejections. Others had only one rejection each, and a great many firms, of course, had no rejections at all.

Thus, the experience of the principal procurement agency large enough to conduct rigorous tests of all products it considers buying and possessing a mammoth physician feedback of therapeutic experience shows clearly that drug products which are supposed to contain the same amount of the same active ingredient do differ in quality, and that some manufacturing sources are more consistently reliable than others.

For the physician and pharmacist who cannot conduct his own tests and inspections, manufacturer identification of drug products has proven itself to be the most practical and reliable measure of consistent quality. Approximately one billion prescriptions are dispensed by the nation's retail pharmacists every year in the United States. Surveys have shown that more than 90 percent of them signify a particular drug product of a specific manufacturer. Once a physician has identified a particular manufacturing source for a particular drug product which he considers, on the basis of his own recurring experience, as best for a particular patient, he can have a high degree of certainty that each succeeding prescription of the same drug product from the same source will carry the same built-in therapeutic performance.

Moreover, if anything does go wrong after the prescription is filled—if there is an unexpected side effect or a lack of effectiveness—the doctor who has specified the manufacturing source will be able to communicate promptly with the manufacturer, and obtain the prompt assistance of the company's medical staff in identifying and evaluating the problem and in taking proper corrective measures. He can also assist both the manufacturer and the FDA in maintaining an accurate and up-to-date record of adverse drug reactions for the information of the medical profession. But if the physician has prescribed generically, leaving it to a pharmacist to select the manufacturing source, the physician may or may not be able to take these important steps for the health of his patient and the advance of medical knowledge. He may be unable to ascertain promptly, if at all, the identity of the manufacturing source, particularly if the prescription has been refilled generically from a variety of sources. And if he does learn the producer's identity, the manufacturer may not have a medical staff qualified to evaluate the information. Indeed, many generic manufacturers or distributors have not filed New Drug Applications for the products they market, and under the law, are not even obliged to file periodic experience reports with the FDA.

The physician's identification of a particular brand of drug product, or a particular manufacturer, in turn, justifies the manufacturer's investment, his com-

mitment to superior performance in products and in services. It provides an incentive to compete for quality recognition which no set of government regulations will ever provide. For very direct and acute economic reasons, the producer cannot afford the loss of his good name in the marketplace. He must develop and improve methods of total quality control most likely to result in superior products and all-around performance, thereby earning for his products the continued confidence of the physician.

In summary on this point, let me say that I do not presume to speak for the medical profession, but I cannot imagine there would be any substantial dissent within that body from the following propositions:

(1) A physician should consider first the known therapeutic effect and known quality of each drug product available to meet the particular needs of his patient.

(2) If a choice is available among effective drug products of satisfactory quality, the physician should take price as well as therapeutic effect and quality into consideration when prescribing.

(3) Unless the physician is satisfied that all drug products of the generic class he decides to prescribe are substantially therapeutically equivalent and of high quality, he should identify the source of the drug product on his prescription.

As we have said, we believe the doctor's most reliable guarantee of quality is his prior experience with the product of a particular manufacturer. Nevertheless, recognizing the importance of price, we would support effective methods of informing physicians, dentists and other practitioners more fully than they already are about the comparative prices of different drug products containing substantially the same active ingredients.

Prices

We have heard a great deal during these hearings about allegedly "high drug prices". The fact is, however, that all available price indices show that drug prices are going down while other prices are going up. I will not attempt to discuss the intricacies of how price indices are or should be compiled. These points will be covered by two expert witnesses who will testify on November 29. But the Department of Labor's Consumer Price Index shows that the decline in retail prescription drug prices has continued to a point where these prices are now more than 10 percent under the 1957–59 base period. The latest government report with respect to prescription drugs for the first six months of this year shows a record low of 88.8 compared to the 1957–59 base of 100. For the same period, the index for all consumer items reached a record high of 116.

Moreover, the more comprehensive BLS Wholesale Price Index for Ethical Preparations also shows a significant current downward trend. Since this Index covers 55 leading drug products, it is far less subject to substantial variations due to the introduction of a few new products. Finally, of course, any of the defects ascribed to our Index system applies equally to the prices of the other commodities being measured—not just to drugs.

A computation based upon figures of the Department of Commerce shows that only 14 cents of the consumer's medical care dollar currently are required to pay for drug products of all types. Only seven years ago that figure was 19.5 cents. Prescription products, as distinguished from drug products in general, now account for only 9.8 cents of the consumer's medical care dollar as compared to 11.7 cents ten years ago.

As all of these figures show, and as the President's Economic Report for each of the last two years has expressly noted, prescription drug prices have behaved much better than most other prices, both in the medical care field and in the economy as a whole.

In June of this year, a national conference on health care costs was held under the auspices of the Department of Health, Education and Welfare. As was effectively illuminated throughout the proceedings by speakers and panel discussions, the principal medical cost problems relate to the other elements of health care, not to drugs.

Differences Between Brand and Generic Prices

There have been references during these hearings to "tremendous" price differences between brand name drug products and so-called "generic equivalents". As you know, from our earlier comments, we believe the doctrine of "generic equivalency" is at best a dangerous oversimplification of a complex

medical problem. Nevertheless, it should be well understood that the price differences paid at the retail level by consumers for drug products marketed by brand names and those marketed under a generic name are not nearly so high as statements of previous witnesses would have one believe.

Furthermore, price variations of the order of 50 to 100 percent and more between different manufacturers or sellers of "identical" or substantially similar consumer products are not at all unusual in most fields. Differences in quality, reliability and satisfaction are matters for the subjective and often differing judgments of consumers, and they are properly resolved and balanced against price in the marketplace.

The parallel between prescription drug product choices made by a trained physician and other consumer product choices made by the general public is admittedly far from exact. But it is significant that the general public regularly balances quality against price, and is often willing to pay a wide differential in price for compensating differences in quality. Product differentiation and price variations are hallmarks of our free market economy. The important thing is not to force this wide range of prices into some narrower band, but to give consumers, and in the case of prescription drugs to give doctors and other practitioners, as much information as they need about the variety of items available, the comparative merits of each and their differing prices to consumers.

The Issue of High Profits

Much has been made and continues to be made of the question of drug industry profits. Some, who on the one hand praise the pharmaceutical industry as the source of life-saving, health-giving drug products, on the other hand accuse it of making unconscionable profits at the expense of the ill and elderly.

It does not seem to matter that the price level of prsecription drugs, as indicated, has been declining in the last 10 years by more than 10 percent, while the prices of other necessities have been pushed up by inflationary pressures of the period.

In this high-risk industry, a high rate of profit is essential to attract the capital and other resources necessary to achieve further breakthroughs in medical progress. As you know, we have requested an opportunity for a team of economists to appear as a part of our presentation to discuss the "high-risk" nature of the industry and to present the results of studies which have been conducted for us this year comparing the drug industry with a number of other manufacturing pursuits. These men are now scheduled to testify on November 29.

They will point out that arbitrary reduction or elimination of the manufacturer's profit would not produce a substantial reduction in the price a patient pays for a prescription. We must look elsewhere than to manufacturers' profits in reducing prescription prices to the public.

Let me go further and ask this question: "Is the public interest served or harmed by the slight differential in retail drug prices caused by the fact that the profits of drug manufacturers are above the national average for industry generally?"

We think the public interest is served, not harmed, when quality-conscious and research-oriented prescription drug manufacturers earn enough to intensify their activities and to attract other like-minded firms to enter the field.

The development and marketing of new drug products is an uncertain enterprise at best. The percentage of the sales dollar which the research-oriented drug companies spend to discover and develop new products is by far the highest of any American industry.

Only one out of about 6,000 compounds tested by drug companies turns out to be a marketable product, and even then it can reach the market only after years of animal and clinical testing. In addition, a competitor's new or improved product for treatment of the same disease can appear at any moment to overshadow or make obsolete a profitable product perfected at great cost.

To illustrate, 16 drug products which were listed among the 200 most commonly prescribed products in 1965 had disappeared from the list when the 1966 annual audit of prescriptions filled in retail stores was completed. Three-quarters of those 16 products had been on the market 10 years or less. The same survey disclosed that 100 products dropped in frequency of prescribing rate between 1965 and 1966. Only 84 remained the same or rose in rank.

The struggle within the industry for success—the competition to be first with the new drug discovery—is costly and risky. Without the profit incentive it could not be continued. If it stops the public will be the loser.

We agree that the profitability of the drug industry is above average. We say this is not a unique phenomenon. It is one which characterizes rapidly growing industries generally where there is a high rate of new product innovation. Other innovative growth industries today, such as aerospace instruments and photographic goods, office equipment and computers, also return higher than average profits on capital invested.

On the other hand, the more stable, less dynamic industries, such as cement, iron and steel and textile products, tend to have lower profit margins. As a result, capital and management are attracted to the growth industries, intensifying the competitive nature of these industries and their rate of innovative progress. Above average profits in innovative growth industries perform a valuable economic function by serving to allocate capital and management resources where they can be most productively and beneficially employed.

We hold that the industry's profits are healthy and desirable. They provide the incentive to manufacturers to continue to operate their businesses the way they do, and the incentive to others to invest capital and resources in such companies.

With all the important and unfinished tasks that lie before the drug industry, we submit that it would be a grave mistake to arbitrarily reduce its profits and thus ruin the chance of reversing the major allocation of private capital resources to this industry that has proven so beneficial to the public over the past three decades.

The Issue of Promotional Expenditures

Some earlier witnesses have expressed the belief that pharmaceutical manufacturers spend "too much" in promoting their products and that they could materially reduce their prices by spending less. Their underlying theme seems to be that either the government or the manufacturers themselves should take steps to cut down the size of expenditures for advertising, sales representatives and other forms of conveying drug information to physicians.

We believe this to be a very strange and dangerous doctrine. Whether couched in terms of government regulation or in terms of collective arrangements among manufacturers, it goes to the heart of the competitive principle that our economy functions most effectively and efficiently when individual businessmen make individual decisions on how to make and market their products.

It is self-evident that no manufacturer spends money for the fun of throwing it away. Money is spent on promotion and marketing and on keeping physicians currently advised on drug products because, in the judgment of the manufacturer, the expenditures so made will have a direct favorable impact on sales volume and profits.

Individual decisions in these matters are the essence of a free market economy. Obviously our antitrust laws forbid any group of manufacturers from agreeing among themselves to reduce or eliminate competitive factors such as promotion expenditures, so that the same sales volume and market shares can be achieved with a lower competitive effort and a lower level of expenditure per manufacturer. Nor is there any way for the government effectively to regulate the volume of promotional expenditures or any other element of the cost of doing business. Regulation of this type is wholly impracticable, is bound to result in inequities, and is certain to deprive the public of the benefits of a free market economy. Only in times of gravest national emergency have we ever resorted to the regulation of manufacturing prices, and even then we have never been so foolish as to regulate the amounts individual manufacturers can spend to develop and manufacture their products.

Moreover, the professional judgment of the government official responsible for regulating the safety, efficacy and distribution of prescription drug products appears to be that the amounts spent on drug advertising and labeling serves an important public health purpose. On April 17, 1967, FDA Commissioner Goddard, in issuing "FDA Concepts for Proposed Revisions of Medical Advertising and Labeling Regulations," had this to say on the value of journal advertising and labeling: "We believe that good medical advertising is essential to good health in America today. The educational value of journal advertising and all forms of labeling is greater than the dollar outlay for it."

It should be borne in mind that the selling efforts of ethical drug products are made up of quite different activities and expenses from those of ordinary consumer products. You will hear from subsequent PMA witness about the activities of detailmen in supplying current information to doctors on the subject of drug

therapy. These detailmen are generally college graduates who have the backgrounds and capabilities for an intelligent understanding and presentation of developments in drug therapy.

The function of a detailman is both that of a salesman for his company's drug products and that of a quasi-educator. We make no claim that physicians rely on detail men for medical advice. It would be improper for them to do so. These men do, however, play a useful role in supplying physicians with accepted product literature and in referring a physician's inquiries to doctors on the staff of the company for reply. Neither the industry nor the medical profession will claim that the detailing system is free of faults. But I think on balance it has proved an effective solution to a difficult marketing and educational problem.

Other Contributions of the Pharmaceutical Industry

In the foregoing discussion, I have tried to provide an insight into the achievements and aspirations of reputable pharmaceutical firms, the complexities of their operation, and their continued striving for excellence. I have tried to show the amount of effort and investment involved in research, in developing and marketing a new drug product, and the commercial risks that must be taken as the price of pharmaceutical advances.

The record speaks for itself. Competition to develop new drugs has forced our industry to maintain an unparalleled rate of technological progress with untold benefits to the public.

But this is an enterprise of many unique dimensions. Its role of service to mankind goes far beyond the usual commercial concept of producing and marketing merchandise for profit, as desirable and beneficial as that merchandise may be. This is not to suggest for a moment that other commercial and industrial enterprises which bring to consumers the boons of modern creativity and technology are not performing an outstanding service to society.

But the responsible members of the pharmaceutical industry have long recognized that their obligations are special. Their products are required for illness. Their basic aims from the laboratory test tube to the end of the assembly line are the prevention of disease and the provision of aid and comfort for the afflicted.

These aims for years have found expression in the voluntary contributions regularly made by many firms toward enhancing the values of our society in a variety of ways.

Leading firms produce and stock certain so-called "public service drugs" which never yield a penny of profit. They are used in the treatment of rare, low-frequency diseases and the demand is simply not sufficient to justify the costly production process. They include anti-rabies serum, botulism antitoxin, gas gangrene antitoxin, Rocky Mountain spotted fever vaccine, and many others. There is no question that these medications must be available whenever and wherever needed, and they are, thanks to the belief of many drug manufacturers that they have a moral responsibility to provide them. Usually they are provided without charge by the firms to the unfortunate persons who contract the diseases or to their physician.

Among the most significant general public services rendered by the industry are those in the fields of education and research. Tens of millions of dollars in grants and aids for pharmacy and medical education have been donated by our member firms. These include scholarships, fellowships, and internships for medical and pharmacy students; science awards; post-graduate medical information programs for practicing physicians; and medical symposia for interns. Substantial amounts are channeled to medical, dental and pharmacy schools. The industry also provides many teaching aids—publications, films, tapes, etc.

In addition to their cash contributions to promote health and welfare and scientific progress, many firms support their own foundations through which considerable funds are made available to further the same basic objectives. They underwrite scholarships and fellowships, furnish both teaching and research grants, and allocate funds to universities and teaching hospitals.

I cannot leave this subject without specific reference to another foundation established almost three years ago by the Pharmaceutical Manufacturers Association and now being supported by the voluntary contributions of its members. In its way, it seems to me, this undertaking epitomizes the attitude of responsible manufacturers toward their industry, and their determination to go the exra mile when the need arises to produce better and safer drugs in the public interest. I believe, for this reason, I might discuss one or two details about the PMA Foundation and its highly specialized objectives.

The stated purpose of the Foundation is "to promote the betterment of public health through support of scientific and medical research with particular reference to the study and development of the science of therapeutics."

In its operations, the Foundation has very deliberately avoided duplicating or competing with the federal programs of research and other research already being supported by private sources, including industry contributions of various kinds. Its concentration is currently in two areas of interest—fundamental research in drug toxicology, and research and training of personnel in the field of clinical pharmacology and drug evaluation.

The Foundation has already authorized grants of more than $1,000,000 from funds derived from PMA firms, plus added support from organizations related to the drug industry and individuals. There will not be a dime of monetary return to the contributors. No product research is involved.

What will be returned is new scientific knowledge, better methodology in the field of drug testing, and trained scientists who have had the opportunity to study drug toxicity and pharmacology. The PMA Foundation represents an effort by the members of our Association to solve pressing problems in the public interest. We are confident of its future and look for it to become an outstanding force for progress in the medical and scientific community.

These have been merely the highlights of a wide range of activities of the pharmaceutical industry which are not generally known or appreciated outside the industry and the scientific community. Yet we believe they are important in the consideration of the role of responsible drug manufacturers in modern society. Their direct contribution to the common good through the medicines they discover and produce simply cannot be questioned. Interestingly, these same discoverers—the innovators, or originators of new drugs—have been the ones who have made the extra efforts I have outlined to extend the frontiers of knowledge and contribute to the health and well-being of society here and abroad.

In order that you might have the full details, too voluminous to recite here, of the vast array of these activities, the PMA commissioned the management consultant firm of Klein and Saks, Inc. to make studies of several fields of particular interest and compile their findings in convenient form. I have their reports here and would like at this time to introduce them in the record.[2]

Conclusion

Mr. Chairman, in conclusion I would like to say that in our continuing activities the pharmaceutical industry is pursuing the following aims, aims with which I believe this Subcommittee would agree:

—First, to provide doctors and their patients with drug products having the highest degree of safety, effectiveness and quality we can achieve for the lowest price at which these standards can be attained.

—Second, to provide the doctor with a choice among such drug products as varied as the human idiosyncracies among the patients he treats and as divergent theories of medical therapy may require.

—Third, to cooperate with the government in assuming that these objectives are achieved at a reasonable cost.

We respectfully and urgently submit, however, that the way to attain these objectives is not to *force* physicians into generic prescribing or into prescribing the lowest priced product regardless of the doctor's medical judgment as to its comparative quality and therapeutic effect.

Instead, we submit that the wise course for government policy is to assure:

(1) that physicians are provided with as much reliable information about the comparative effectiveness, quality and price of drug products as our society can provide;

(2) that physicians are left free to prescribe the particular product and manufacturing source they think best for particular patients; and

(3) that patients are provided with reliable information about comparative retail prices for that product.

In short, we urge that government policy be aimed not at eliminating competition, but at making competition work as effectively as possible at all levels of

[2] (a) Contributions of American Prescription Drug Manufacturers in the United States—Klein and Saks, Inc.—March 1967.
(b) Contributions to Medical Education by American Prescription Drug Manufacturers—Klein and Saks, Inc.—August 1967.
(c) Contributions of American Prescription Drug Manufacturers in International Development—Klein and Saks, Inc.—November 1966.

the drug distribution system. I can assure you that the Pharmaceutical Manufacturers Association and its member companies will cooperate fully in all reasonable measures taken to achieve that end.

(The supplemental information submitted by Mr. Gordon follows:)

EXAMINATION OF ANOMALIES IN PRESCRIPTION DRUG PRICES AND UTILIZATION*

Agnes W. Brewster, B.A., F.A.P.H.A.; Juanita P. Horton, B.S., R.Ph., M.S., F.A.A.A.P.E.

From time to time the Health Economics Branch of the Public Health Service is asked to examine seeming anomalies in medical care prices, expenditures, use rates and cost. One such recent study related to prescription drugs.

Totally and per capita, consumer expenditures for drugs have been rising, reflecting increased numbers of prescriptions per capita and a rise in the average cost of a prescription (table 1). Yet the Consumer Price Index for prescription drugs has shown an almost continual decline over the past 10 years (table 2). How does one explain this seeming contradiction?

To better understand the elements of price movement and increased utilization as they might affect the consumer, we undertook a study using the 200 drugs most frequently prescribed in 1965 as a point of departure. This list—published annually—is prepared by R. A. Gosselin and Company. It is reported to reflect about two-thirds of all non-compounded prescriptions filled in the given year. The 200 most frequently prescribed products are part of a list that runs to thousands of different drugs. Since the 200 also represent about two-thirds of the prescription dollar market of $2.9 billion for 1965, the list provides an adequate base for observing trends in prices.

This study pertains to the 188 trade name products in the listing. A word of explanation is in order. Generically prescribed drugs were excluded because there is no way of determining their prices or price changes since the various manufacturers of the generic products are not specified in the Gosselin listing. The top twelve generic products listed among the 200 most prescribed drugs for 1965 accounted for approximately 6.2 percent of all 550 million prescriptions making up the top 200 drugs. Their removal does not appreciably affect the results of the study.

The *Drug Topics Red Books* for the years 1957–1967 were used for determining wholesale price. Any changes in wholesale price would very shortly be reflected in price to the consumer. One dosage form, strength, and quantity was selected for each of the 188 trade name products in the study. The price of the described item was found in the *Red Book* for the appropriate years. As you know, this is the standard source for pharmacists to determine the wholesale price of drugs. For example, the price of 100 one-grain Proloid tablets was traced from 1957 to 1967. The 1957 *Red Book* listed the price as $0.75; the 1961 and subsequent *Red Books*, $0.85. In our analysis, this represents one product which had a single price increase. Some products had more than one price change in the period under review.

Usually a product carries a higher price when first introduced; therefore, our first step was to sort the 188 drugs by the date they were introduced. Eighty-six percent had been on the market five or more years by 1967. Interestingly, 1959 was a year marked by new drugs—20 of our top 200 were introduced that year. Relatively few drugs—26 in number, or 14 percent—could be classified as really recent, introduced after 1962 (table 3a). Thus, the majority of the drugs leading in popularity are old standbys of the physicians' practice, available on the market for quite a span of years.

Starting 10 years ago, in 1957, what happened to this 1965 list in the way of price movement? More than half had no price change. For 57 the price advanced, sometimes more than once, and for 27 the price was reduced, sometimes twice (table 4). However, the increases in the prescription price (less than $1.00) were much smaller than the decreases, which were so large on a few products that the average was over $6.00.

The picture that emerges from this analysis is certainly not in conformity with a downward trend for the Consumer Price Index for drugs. True, antibiotics

*Presented at the Drug Utilization Session, sponsored by the Medical Care Section of the American Public Health Association at the Ninety-Fifth Annual Meeting in Miami, Florida, October 25, 1967. Mrs. Brewster is Chief and Mrs. Horton is Pharmacist-Economist of the Health Economics Branch, Division of Medical Care Administration, Public Health Service.

such as Achromycin and Terramycin, dropped dramatically; but most drugs remained unchanged and the remainder rose in price. For the consumer to experience the price decline indicated by the CPI behavior, the drugs ordered for him would have been from a narrow list and not at all typical of the market as a whole.

The Consumer Price Index for drugs has been under close scrutiny and subsequent revision a number of times throughout the lifetime of the Index. During the period 1935–March 1960, the Index was based on first two, and later three relatively simple compounds. Over the entire period, the prices of these prescriptions advanced 77 percent while the overall Consumer Price Index showed a rise of 114 percent.

The Bureau of Labor Statistics came to realize that the original list of drugs was no longer adequate to represent the type and kind of prescriptions consumers purchase. The Bureau then embraced the concept of therapeutic categories under which a number of prescriptions could be priced. Beginning in April 1960, prices were collected for a new list of 13 drugs sold on prescription within the seven end-use categories. After 9 months of pricing prescriptions under the new procedures, indexes of prices for the three old prescriptions and the 13 new prescriptions were computed. The Index, based on the revised list, was 2.4 percent lower than it would have been if just the previous three items had been continued.

In 1964, the Consumer Price Index was again revised to include 14 prescription drugs and a new sampling technique was instituted. The Index continued to show a decline.

In March 1967, the sample for prescription drugs was once again revised to include nine instead of seven end-use categories with no change in the number of drugs priced. The antiarthritic group has been dropped while internal analgesic, anti-obesity and hormone categories have been added. Even so, the CPI for June 1967 shows an overall decline of 1.2 percent from the March Index—a much greater percentage than for any three month period in 1966 under the prior sample.

Unlike the drugs in the top 200 list, only two drugs in the Consumer Price Index since 1964 were introduced after 1957 (table 3b).

Generic prescriptions are used to price the Consumer Price Index even though more than 90 percent of the prescriptions which consumers purchase are trade name drugs. Six of the 14 drugs in the CPI 1964–1966 were among the top 12 generic products in 1965 and five others could be purchased generically. The three remaining drugs in the Consumer Price Index are available from only one manufacturer because their patent rights are still in effect even though the prescription order specifies the generic name. Only one drug in the Consumer Price Index had an increase in its wholesale price. Pencillin G, tetracycline, and prednisone all had dramatic decreases.

CHANGES IN DRUG PATTERNS AS AN EXPLANATION OF PRICE MOVEMENT

Since the Consumer Price Index for prescribed drugs is necessarily altered so slowly to reflect newer drugs, we decided to examine how much alteration there had been in the pattern of the 200 "best-sellers". Comparison of the 1962 and 1965 drug lists indicates that 31 drugs were dropouts and 31 drugs were replacements. The terms "dropouts" and "replacements" are not intended to imply that the new drugs in the listings were substituted therapeutically for those dropped. Two thirds of the replacements were recent drugs introduced between 1963 and 1965. A comparison of the prices of the replacements with the prices of the dropouts indicates an overall upward trend in expenditures associated with changes in utilization for prescription drugs.

The analysis of dropouts and replacements by therapeutic categories reveals 28 pattern changes in utilization of drugs. The greatest number of replacements occurred in the hormonal category with seven oral contraceptives and one thyroid preparation added (table 5). There were no dropouts in the hormonal class. On the other hand, no replacements occurred for the five anti-spasmodic dropouts and for the one dropout in each of the antihistamine, dermatologic, and oxytoxic categories. The categories with the greatest amount of activity are: anti-infectives, cough and cold preparations, and cardiovasculars. It is interesting to note that three of the cardiovascular and one of the cough and cold replacements had been on the market prior to 1961.

The analysis of price by therapeutic category shows that the replacement drugs generally cost more than their predecessors in popularity for the same

therapeutic purpose. For example, in the antibiotics, the average price of the two trade name replacements was $25.64 while the average price of the three dropouts was $12.39. It should be noted, however, that the third replacement in this group was generic tetracycline for which the wholesale price could not be determined. This finding, coupled with the price changes already reported, seem to bear out the intuitive reaction of the consumer that drug prices have not fallen, albeit they have not risen as fast as other items in the Consumer Price Index for medical care.

We are of the opinion that the day is getting much closer—thanks to electronic data processing—when the Consumer Price Index for prescribed drugs could be refined. With drugs becoming increasingly significant items of out of pocket consumer medical expenditures, the Consumer Price Index should become a more sensitive instrument.

TABLE 1.—TOTAL AND PER CAPITA PRESCRIPTION DRUG EXPENDITURES, NUMBER OF PRESCRIPTIONS PER CAPITA AND AVERAGE PRESCRIPTION PRICE, 1959–66

Year	Total consumer expenditure (in billions)	Per capita expenditure	Number of prescriptions per capita	Average price per prescription
1959	$2.0	$11.12	3.54	$3.14
1960	2.0	11.33	3.52	3.22
1961	2.1	11.75	3.65	3.22
1962	2.3	12.30	3.83	3.21
1963	3.4	12.37	3.83	3.23
1964	2.6	13.33	4.09	3.26
1965	2.8	14.37	4.29	3.35
1966	3.1	15.47	4.51	3.43

Source: Derived from American Druggist, Mar. 19, 1962; Mar. 15, 1965; and Mar. 13, 1967.

TABLE 2.—CONSUMER PRICE INDEX FOR PRESCRIPTION DRUGS, 1958–66

Year	All items	Prescriptions	Antiinfectives	Sedatives and hypnotics	Ataractics	Antispasmodics	Antiarthritics	Cough preparations	Cardiovascular and antihypertensives
1958	100.7	100.7	--------	--------	--------	--------	--------	--------	--------
1959	101.5	103.0	--------	--------	--------	--------	--------	--------	--------
1960	103.1	102.6	98.5	100.4	99.5	100.6	99.9	99.7	99.6
1961	104.2	99.2	91.9	99.4	96.5	99.2	99.9	98.3	97.6
1962	105.4	95.3	86.2	97.0	93.8	97.7	97.7	95.8	94.7
1963	106.7	93.0	82.2	96.4	93.2	97.1	97.6	95.6	93.7
1964	108.1	91.8	80.3	95.6	92.2	97.4	95.6	94.8	93.2
1965	109.9	90.8	77.4	95.7	91.2	97.7	91.9	95.7	93.6
1966	113.1	90.6	75.1	97.0	90.9	98.5	90.4	97.2	93.7

Sources: Consumer Price Indexes for Selected Items and Groups, annual averages, December 1958–December 1966; and annual averages computed from fiaures published in Consumer Price Index Components of Prescription Drugs, as prepared by the U.S. Department of Labor, Bureau of Labor Statistics, quarterly averages 1958–67.

TABLE 3a.—NUMBER AND PERCENT OF TRADE NAME PRODUCTS IN LIST OF 200 MOST FREQUENTLY PRESCRIBED DRUGS FOR 1965 BY DATE OF INTRODUCTION, 1927–65

Year of introduction	Number of drugs	Percent of total
Total	188	100
1927–56	79	42
1957–61	83	44
1962–65	26	14

TABLE 3b.—NUMBER AND PERCENT OF DRUGS IN THE CONSUMER PRICE INDEX FOR 1964–66 BY DATE OF INTRODUCTION, 1927–65

Year of introduction	Number of drugs	Percent of total
Total	14	100
1927–56	12	86
1957–61	2	14
1962–65		

TABLE 4.—NUMBER OF DRUGS BY YEAR OF INTRODUCTION, NUMBER OF PRODUCTS WITH PRICE INCREASES, DECREASES AND NO PRICE CHANGE AND NUMBER OF PRICE INCREASES AND DECREASES, 1957–67

Year of introduction [1]	Number of drugs	Number of drugs with price increases	Number of drugs with price decreases	Number of drugs with no price change	Number of price increases [2]	Number of price decreases
Total	188	57	27	104	78	38
1927–56	79	35	7	37	55	8
1957–61	83	19	20	44	20	30
1962–65	26	3	0	23	3	0

[1] Prepared from list of 200 most frequently prescribed drugs, 1965, R. A. Gosselin & Co., Dedham, Mass.
[2] Some drugs had more than one price increase or decrease.

TABLE 5.—DROPOUTS AND REPLACEMENTS IN THE LISTS OF THE 200 MOST FREQUENTLY PRESCRIBED DRUGS FOR THE YEARS 1962 AND 1965 BY THERAPEUTIC CATEGORY

Therapeutic category	Number of dropouts	Number of replacements
Total	31	31
Analgesics	4	2
Antibiotics	3	3
Antihistamines	1	0
Anti-infectives	2	6
Antiobesity	0	1
Antispasmodics	5	0
Ataractics	3	1
Cardiovasculars	3	4
Cough and cold	5	3
Dermatologics	1	0
Hormones	0	8
Psychostimulants	2	1
Sedatives and hypnotics	1	2
Oxytoxics	1	0

In the United States District Court for the District of New Jersey

Criminal No. ——— [21 U.S.C. 331(a), 333(a), 352(n)]

UNITED STATES OF AMERICA,

v.

WALLACE LABORATORIES, A DIVISION OF CARTER PRODUCTS, INC., A CORPORATION, DEFENDANT

Information

COUNT I (39–859 A)

The United States Attorney charges:

That within the period from on or about June 15, 1964, to on or about June 17, 1964 Wallace Laboratories, Division of Carter Products, Inc., a Maryland Corporation, the defendant herein, did, within the District of New Jersey, in viola-

tion of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Cranbury, New Jersey, for delivery to Dallas, Texas, consigned to the Great Southwest Warehouses, Inc., a number of bottles containing a drug designated by the name "Pree MT";

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

"50 tablets Pree MT Each tablet contains meprobamate. . . . 200 mg. hydrochlorothiazide. . . . 25 mg. Caution: Federal law prohibits dispensing without prescription. Wallace Laboratories Division of Carter Products, Inc., Cranbury, N.J."

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was a drug required to be dispensed only upon prescription as provided by 21 U.S.C. 353(b)(1) since it was a drug intended for use by man and covered by an approved new drug application which became effective under 21 U.S.C. 355 prior to October 10, 1962, and which limited said drug to use under the professional supervision of a practitioner licensed by law to administer such drug;

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(n) in that said drug was a prescription drug distributed and offered for sale in the United States and said defendant, the manufacturer of said drug, failed to include in advertisements, caused to be issued by said defendant with respect to said drug in the editions of June 1, 1964, and June 8, 1964 of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects and contraindications of said drug as required by Section 1.105(f)(2) of the regulations published in the Federal Register of January 10, 1964 (29 F.R. 257), to wit, the aforesaid advertisements did not present, from the labeling accepted in the aforesaid new drug application, as required by said regulations, information concerning certain side effects and contraindications of said drug that were pertinent with respect to the use recommended and suggested in said advertisements, namely, premenstrual tension, and with respect to the uses for which the dosage form advertised was commonly prescribed, namely, hypertension and congestive heart failure, since (1) the aforesaid advertisements did not state in brief summary or at all with respect to the side effects of said drug and its ingredients, namely hydrochlorothiazide and meprobamate, that excessive response and resulting undesirable electrolyte imbalance may be caused by the administration of said drug, that azotemia may be precipitated or increased by hydrochlorothiazide, that it may be necessary to discontinue administration of said drug to patients with severe liver or renal disease, that gout has been precipitated, that all patients on hydrochlorothiazide should be carefully followed to detect side reactions or unusual manifestations of drug idiosyncrasy, such as leukopenia, agranulocytosis, or aplastic anemia, that from the use of meprobamate allergic reactions most often in form of a skin rash, have been reported and, less frequently, more severe reactions (fever, angio-neurotic edema and bronchial spasm) have occurred, that other allergic effects from use of meprobamate though rarer, include nonthrombocytopenic purpura, chills, edema and arthralgia, and that said drug should be discontinued when hypersensitivity develops; and (2) the aforesaid advertisements contained the statement "Contraindications: None known" which was false and misleading as applied to said drug for which contraindications were known; and (3) the aforesaid advertisements did not state in brief summary or at all with respect to the contraindications of said drug and its ingredients, namely hydrochlorothiazide and meprobamate, that hydrochlorothiazide is contraindicated in the presence of anuria, that therapy with hydrochlorothiazide should not be reinstituted in patients who have had toxic reactions to hydrochlorothiazide, and that therapy with meprobamate should not be reinstituted in patients who have had an allergic reaction to meprobamate.

COUNT II (98–706 A)

The United States Attorney further charges:

That on or about June 26, 1964, Wallace Laboratories, Division of Carter Products, Inc., a Maryland Corporation, the defendant herein, did, within the District of New Jersey, in violation of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for

introduction into interstate commerce at Cranbury, New Jersey, for delivery to South San Francisco, California, consigned to J. F. Coffman and Sons, a number of bottles containing a drug designated by the name "Pree MT";

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

"50 Tablets Pree MT Each tablet contains meprobamate. . . . 200 mg. hydrochlorothiazide. . . . 25 mg. Caution Federal law prohibits dispensing without prescription. Wallace Laboratories Division of Carter Products, Inc., Cranbury, N.J."

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was a drug required to be dispensed only upon prescription as provided by 21 U.S.C. 353(b)(1) since it was a drug intended for use by man and covered by an approved new drug application which became effective under 21 U.S.S. 355 prior to October 10, 1962 and which limited said drug to use under the professional supervision of a practitioner licensed by law to administer such drug;

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(n) in that said drug was a prescription drug distributed and offered for sale in the United States and said defendant, the manufacturer of said drug, failed to include in advertisements, caused to be issued by said defendant with respect to said drug in the editions of June 1, 1964, June 8, 1964, June 15, 1964, and June 22, 1964, of the Journal of the American Medical Association, a true statement of informaion in brief summary relating to the side effects and contraindications of said drug as required by Section 1.105(f)(2) of the regulations published in the Federal Register of January 10, 1964 (29 F.R. 257), to wit, the aforesaid advertisements did not present, from the labeling accepted in the aforesaid new drug application, as required by said regulations, information concerning certain side effects and contraindications of said drug that were pertinent with respect to the use recommended and suggested in said advertisements, namely, premenstrual tension, and with respect to the uses for which the dosage form advertised was commonly prescribed, namely, hypertension and congestive heart failure, since (1) the aforesaid advertisements did not state in brief summary or at all with respect to the side effects of said drug and its ingredients, namely hydrochlorothiazide and meprobamate, that excessive response and resulting undersirable electrolyte imbalance may be caused by the administration of said drug, that azotemia may be precipitated or increased by hydrochlorothiazide, that it may be necessary to discontinue administration of said drug to patients with severe liver or renal disease, that gout has been precipitated, that all patients on hydroclorothiazide should be carefully followed to detect side reactions or unusual manifestations of drug idiosyncrasy, such as leukopenia, agranulocytosis or aplastic anemia, that from the use of meprobamate allergic reactions most often in form of a skin rash, have been reported and, less frequently, more severe reactions (fever, angioneurotic edema and bronchial spasm) have occurred, that other allergic effects from use of meprobamat though rarer, include nonthrombocytopenic purpura, chills, edema and arthralgia, and that said drug should be discontinued when hypersensitivity develops; (2) the aforesaid advertisements contained the statement "Contraindications None known" which was false and misleading as applied to said drug for which contraindications were known; and (3) the aforesaid advertisements did not state in brief summary or at all with respect to the contraindications of said drug and its ingredients, namely, hydrochlorothiazide and meprobamate, that hydrochlorothiazide is contraindicated in the presence of anuria, that therapy with hydrochlorothizide should not be reinstituted in patients who have had toxic reactions to hydrochlorohiazide, and that therapy with meprobamate should not be reinstituted in patients who have had an allergic reaction to meprobamate.

———— ————,

United States Attorney for the District of New Jersey.

FEBRUARY 16, 1966.

Re *U.S.* v. *Wallace Laboratories*, criminal No. 322–65 DJ#FMV : JWD : ajw 21–48–334.

(Attention of Harold P. Shapiro, Chief, Administrative Regulations Section, Criminal Division.)

DEPARTMENT OF JUSTICE,
Washington, D.C.

SIRS: Reference is made to your letter dated February 9, 1966.

Please be advised that the Honorable Arthur S. Lane sentenced the above-named defendant to a fine of $1,000.00 on each of counts I and II of the information.

Respectfully,

DAVID M. SATZ, Jr.,
U.S. Attorney.

By MARK E. LITOWITZ,
Assistant U.S. Attorney.

In the United States District Court for the Northern District of Illinois Eastern Division

No. ———

(21 U.S.C. 331 and 333)

UNITED STATES OF AMERICA

v.

ABBOTT LABORATORIES, A CORPORATION

COUNT I

The United States Attorney charges:

That on or about May 6, 1965, Abbott Laboratories, a corporation, organized and existing under the laws of the State of Illinois and trading and doing business at North Chicago, Illinois, the defendant herein, did, within the Eastern Division of the Northern District of Illinois, in violation of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at North Chicago, Illinois, for delivery to Milwaukee, Wisconsin, consigned to St. Mary's Hospital, a number of bottles containing a drug designated by the name "Eutonyl";

[2]

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

100 No. 6876 Filmtab EUTONYL 10 mg. PARGYLINE HYDROCHLORIDE

Caution. Federal (U.S.A.) law prohibits dispensing without prescription. Each tablet contains: Eutonyl (Pargyline Hydrochloride), N-Benzyl-N-methyl-2-propynylamine hydrochloride—10 mg. Lot No. 771–1413–22, Abbott Laboratories, North Chicago, Ill., U.S.A.

That said drug when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, the monograph relating to said drug set forth in the 1965 Edition of the Physician's Desk Reference, was not, as required by regulations, 21 CFR 1.106(b)(4)(i), substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

[3]

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid was further misbranded within the mean-

ing of 21 U.S.C. 352(n) in that said defendant, the manufacturer of said drug, failed to include in the advertisement caused to be issued by said defendant with respect to said drug in the February 8, 1965 Edition of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications and effectiveness of said drug as required by regulations, 21 CFR 1.105(e) and (f), to wit, the aforesaid advertisement did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisement, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in said advertisement, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications.

United States Attorney for the
Northern District of Illinois.

In the United States District Court for the District of New Jersey

UNITED STATES OF AMERICA v. CIBA PHARMACEUTICAL COMPANY, DIVISION OF CIBA CORPORATION

Criminal No. 391–66 (21 U.S.C. 331(a) and 333(a))

Information

COUNT I

The United States Attorney charges:

That on or about September 30, 1964, CIBA Pharmaceutical Company, Division of CIBA Corporation, a corporation organized and existing under the laws of the State of Delaware, and trading and doing business at Summit, New Jersey, the defendant herein, did, within the District of New Jersey, in violation of the Federal Food, Drug and Cosmetic Act, [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Summit, New Jersey, for delivery to Glendale, New York, consigned to Barry Division of Ketchum & Co., Inc., a number of bottles containing a drug, Esidrix-K.

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

Esidrix-K 50/1000. Each tablet contains Esidrix Brand of Hydrochlorothiazide 50 mg. Potassium Chloride 1000 mg. Caution: Federal law prohibits dispensing without prescription. Lot No. 282 305 CIBA Pharmaceutical Company, Summit, N.J.

That said drug when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug, which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, a mailing piece identified as A/9507 February 1964 entitled in part "For 'K-Losers' in edema Esidrix-K," was not, as required by regulations, 21 CFR 1.106(b)(4)(i) substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was further misbranded within the meaning of 21 U.S.C 352(n) in that said defendant the manufacturer of said drug, failed to include in the advertisement caused to be issued by said defendant with respect to said drug in the September 21, 1964 Edition of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications and effectiveness of said drug as required by regulations, 21 CFR 1.105(e) and (f), to wit, the aforesaid advertisement did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisement, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in said advertisement, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications.

COUNT II

The United States Attorney further charges:

That on or about November 13, 1964, CIBA Pharmaceutical Company, Division of CIBA Corporation, a corporation organized and existing under the laws of the State of Delaware, and trading and doing business at Summit, New Jersey, the defendant herein, did, within the District of New Jersey, in violation of the Federal Food, Drug and Cosmetic Act, [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Summit, New Jersey, for delivery to New York, New York, consigned to New York Division Ketchum & Co., Inc., a number of bottles containing a drug, Esidrix.

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

Esidrix Hydrochlorothiazide U.S.P. 25 mg. Each tablet contains Esidrix, brand of Hydrochlorothiazide USP 25 mg. Caution: Federal law prohibits dispensing without prescription. Lot No. 282281 Ciba Pharmaceutical Company, Summit, N.J.

That said drug when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug, which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, a mailing piece identified as A/9507 February 1964 entitled in part "For 'K-Losers' in edema Esidrix-K," was not, as required by regulations, 21 CFR 1.106(b)(4)(i) substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was further misbranded within the meaning of 21 U.S.C. 352(n) in that said defendant the manufacturer of said drug, failed to include in the advertisement caused to be issued by said defendant with respect to said drug in the September 21, 1964, Edition of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications, and effectiveness of said drug as required by regulations, 21 CFR 1.105(a) and (f), to wit, the aforesaid advertisement did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisement, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in said advertisement, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications.

COUNT III

The United States Attorney further charges:

That on or about April 8, 1965 CIBA Pharmaceutical Company, Division of CIBA Corporation, a corporation organized and existing under the laws of the State of Delaware, and trading and doing business at Summit, New Jersey, the defendant herein, did, within the District of New Jersey, in violation of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Summit, New Jersey, for delivery to New York, New York, consigned to New York Division of Ketchum & Co., Inc., a number of bottles containing a drug, Esidrix.

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

Esidrix Hydrochlorothiazide U.S.P. 50 mg. Each tablet contains Esidrix, brand of Hydrochlorothiazide USP 50 mg. Caution: Federal law prohibits dispensing without prescription. Lot No. 282 944 Ciba Pharmaceutical Company, Summit, N.J.

That said drug when caused to be introduced and delivered for introduction into interstate commerce as foresaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug, which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, the monograph relating to said drug set forth in the 1965 Edition of the Physicians' Desk Reference was not, as required by regulations, 21 CFR 1.106(b)(4)(i) substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was further misbranded within the meaning of 21 U.S.C. 352(n) in that said defendant the manufacturer of said drug, failed to include in the advertisement caused to be issued by said defendant with respect to said drug in the April 5, 1965, Edition of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications and effectiveness of said drug as required by regulations, 21 CFR 1.105 (e) and (f), to wit, the aforesaid advertisement did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisement, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in said advertisement, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications.

COUNT IV

The United States Attorney further charges:

That on or about April 8, 1965, CIBA Pharmaceutical Company, Division of CIBA Corporation, a corporation organized and existing under the laws of the State of Delaware, and trading and doing business at Summit, New Jersey, the defendant herein, did, within the District of New Jersey, in violation of the Federal Food, Drug, and Cosmetic Act, [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Summit, New Jersey, for delivery to New York, New York, consigned to New York Division of Ketchum & Co., Inc., a number of bottles containing a drug, Esidrix.

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

Esidrix Hydrochlorothiazide U.S.P. 25 mg. Each tablet contains Esidrix, brand of Hydrochlorothiazide USP 25 mg. Caution: Federal law prohibits dispensing without prescription. Lot No. 282 982 Ciba Pharmaceutical Company, Summit, N.J.

That said drug when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug, which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, the monograph relating to said drug set forth in the 1965 Edition of the Physicians' Desk Reference, was not, as required by regulations 21 CFR 1.106(b)(4)(i) substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was further misbranded within the meaning of 21 U.S.C. 352(n) in that said defendant the manufacturer of said drug, failed to include in the advertisement caused to be issued by said defendant with respect to said drug in the April 5, 1965 Edition of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications and effectiveness of said drug as required by regulations, 21 CFR 1.105 (e) and (f), to wit, the aforesaid advertisement did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisement, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in said advertisement, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications.

DAVID M. SATZ, JR.,
United States Attorney, District of New Jersey.

In the United States District Court for the District of New Jersey

Criminal No. 391–66 Bill of Particulars

UNITED STATES OF AMERICA *v.* CIBA PHARMACEUTICAL COMPANY, DIVISION OF CIBA CORPORATION

Now comes the United States of America by David M. Satz, Jr., United States Attorney, and Matthew J. Scola, Assistant United States Attorney for the District of New Jersey, and pursuant to Order of the Court, under Rule 7(f) of the Federal Rules of Criminal Procedure, provides the following Bill of Particulars:

COUNT I

1. The mailing piece referred to was not substantially the same as the labeling authorized by the approved new drug application effective with respect to the drug Esidrix-K in the following respects:

(a) Taken as a whole, the mailing piece would leave the prescribing physician with a different interpretation of the effects of the drug than he would have by reading the authorized labeling, in that the mailing piece implies that the drug would protect all patients against potassium electrolyte imbalance.

(b) The mailing piece omits the caution statement: "Combined therapy: When necessary, other hypertensive agents may be added cautiously. Since this drug potentiates the antihypertensive effect of other agents, such additions should be gradual. Dosages of ganglionic blockers in particular should be halved."

(c) The mailing piece omits these factors which predispose to hypokelemia (hypopotassemia): "intensive and prolonged diuretic therapy," "restricted sodium chloride intake" and "corticosteroid therapy."

(d) The mailing piece omits the information expressed in the approved labeling: "Since these tablets may not provide all the potassium required by some patients, a diet rich in this element will help obviate depletion."

(e) The mailing piece misleadingly claims that the drug affords "protection" by the following two statements: "Nearly twice the potassium protection offered by any other combination tablets for edema/hypertension" and that the drug "provides the most potassium protection", thereby inviting unwarranted reliance in the use of the drug, by leading the reader to believe that Esidrix-K, in recommended dosage, can prevent or correct potassium electrolyte imbalance in all patients, whereas there are some patients who require much more potassium than can be supplied by the upper range of the usual dose of Esidrix-K recommended (1.048 grams of potassium, or 2 grams of potassium chloride in two tablets), and, therefore, some patients who may not be protected at all from potassium imbalance by the highest recommended daily dose of this drug.

(f) The mailing piece states that the drug provides an "amount [of potassium] well within recommended prophylactic range (1–3 Gm.)," which statement is misleading and at variance with the approved labeling in that only the higher recommended maintenance daily dose of two tablets of Esidrix-K 1000 supplies sufficient potassium (1.048 Gm.) to be within the lower part of this prophylactic range. The statement is further misleading and at variance with the approved labeling because even 1.048 Gm. of potassium daily would not protect all patients against potassium electrolyte imbalance.

(g) The mailing piece states, as one reason for the claim that Esidrix-K provides the most potassium protection, that the 50/1000 tablet "dissolves completely and consistently in the upper intestine within 17 to 20 minutes, facilitating rapid absorption and full therapeutic benefits," which statement has not been approved for package insert labeling, and is contrary to fact, since the work described in the new drug application to which the statement refers was on simulated intestinal fluid *in vitro* and not in the actual upper intestine of men or animals.

(h) The mailing piece distorts the scientific article of R. E. Ray (Reference No. 6) to an extent that it implies approval of a more prolonged administration of the drug than the author in fact gave it, in that the article is quoted incompletely to imply that Ray gave Esidrix-K, with good results and without untoward reactions, to 45 women with obesity and cyclic edema

in continuous prolonged therapy for 6 months, whereas the article reported in fact that Esidrix-K was not administered continuously over that period, but was given intermittently, two weeks on and two weeks off during the first 3 months and thereafter only as required.

2. The advertisement in the September 21, 1964 edition of the Journal of the American Medical Association failed to present a brief summary relating to side effects, contraindications and effectiveness of the drug Esidrix-K as follows:

(a) The advertisement omits the following essential information:

(1) That the drug potentiates the antihypertensive effect of other agents, that additions of such agents should be gradual, and that dosages of ganglionic blockers, in particular, should be halved.

(2) That some of the factors predisposing to hypokalemia (hypopotassemia) are intensive and prolonged diuretic therapy, restricted sodium chloride intake, and corticosteroid therapy.

(3) That "In severe hypokalemia, large oral doses of potassium may be necessary to correct the deficit" and "Since these tablets may not provide all the potassium required by some patients, a diet rich in this element will help obviate depletion."

(b) In the statement "Important . . . for doctors who want to be sure their patients on diuretic antihypertensive therapy have potassium protection: Be sure to prescribe Esidrix-K . . ." the advertisement does not fairly show the effectiveness of the drug and lacks fair balance in presenting information as to such effectiveness, since it implies that the drug, in recommended dosage, can prevent or correct potassium electrolyte imbalance in all patients, while in fact there are some patients who may not be protected at all from potassium imbalance by the highest recommended daily dose of Esidrix-K.

(c) The advertisement claims that Esidrix-K "dissolves consistently and completely in intestinal juices within 17 to 20 minutes . . .", accompanied by a sketch of part of the gastrointestinal tract, thereby implying, unfairly and falsely, that this dissolution occurs in intestinal fluid within the intestines of patients, contrary to results of investigations made by defendant which report that the earliest complete disintegration time of Esidrix-K observed in the actual intestines of a patient was two hours.

COUNT 2

1. The mailing piece was not substantially the same as the labeling authorized by the approved new drug application effective with respect to the drug Esidrix in the following respects:

(a) The combined therapy warning set out above in Count 1, g1(b) is omitted.

(b) The mailing piece distorts scientific reports to an extent that they appear to say something that was not in fact reported, as follows:

(1) The findings reported in the 1959 article by Hejtmancik, Hapmann and Kroetz (Reference No. 4) are misrepresented so as to exaggerate efficacy, in part by failing to mention that 7 of the 19 patients rereferred to were given a daily maintenance dose of 50 mg. three times daily, contrary to the claim that "Effective maintenance dosage was 50 mg. twice daily," and further, that these 7 patients were given an initial dose of 300 mg. rather than the recommended initial dose of 50–100 mg.; and the mailing piece further fails to mention that the authors' patients suffered such side effects as depression of serum potassium levels below normal, including one case of clinical hypopotassemia with marked weakness, and elevation of blood urea nitrogen levels, which prompted the authors to warn that "the rise in the values of blood urea nitrogen observed in some indicate a need for caution in the administration of this drug."

(2) The mailing piece reports only the satisfactory clinical responses noted in the 1959 article by Zuspan, Barnes and Bell (Reference No. 5), but fails to mention the unsatisfactory effects reported by the authors, including the fact that 18% of the group of patients treated with the drug experienced adverse reactions, as compared to no adverse reactions among a group receiving a placebo.

(3) The mailing piece quotes the 1959 article of Kemp and Findley (Reference No. 7) to show that Esidrix is "completly effective" in treat-

ing 26 out of 30 patients with edema, but fails to disclose the fact that these authors utilized concomitant adjunctive therapeutic measures in those patients where required (including bed rest, digitalis, codium restriction, etc.), and further that they reported side effects of hypokalemia, mild azotemia with weakness and postural hypotension, a tendency toward hypontremia and hypochloremic alkaloris, and salt depletion.

(4) The mailing piece, in citing the 1959 statement by Clark (Reference No. 8), fails to make clear that this statement reported observations based not on an acceptable clinical study, but on only two patients with edema whom he treated with Esidrix in the course of his practice. Further, the mailing piece cites the Clark statement to support efficacy in diuresis of "steroid-induced edema", while the Clark statement discloses that he did not know whether the edema was caused by the disease itself or the steroid therapy.

2. The advertisement in the September 21, 1964 edition of the Journal of the American Medical Association failed to present a brief summary relating to side effects, contraindications and effectiveness of the drug Esidrix, as follows:

(a) The advertisement omits the essential information set out above at Count I, § 2(a)(1).

(b) The advertisement did not present a fair balance of information on effectiveness and side effects and contraindications in that the advertisement distorts scientific reports, as follows:

(1) With respect to the 1959 article by Dr. B. Calesnick (Reference No. 1) the advertisement gives the general impression that the author minimized the potential dangers of Esidrix, although he, in fact, stressed the potential dangers of the drug, particularly the side effect of potassium depletion; and further the advertisement misrepresents both the extent of initial transient hypokalemia observed by the author by stating that it was noted in a "few patients", whereas the author does not so limit its occurrence, and the effect of continued medication on potassium level by stating that the potassium levels returned to "normal" with continued medication, whereas the author reported only a "trend toward a return to the control level" with continuous medication.

(2) With respect to the 1959 article by Drs. Kemp and Findley (Reference No. 2), the advertisement misleadingly implies that in all of the 30 patients in that study serum potassium levels were slightly elevated and that danger of a lowered blood potassium in all those patients was non-existent, whereas serum electrolyte studies were made on only 18 patients and, although the average serum potassium level showed a slight increase after 10 days of Esidrix therapy, five patients showed a decrease in serum potassium and one of the five was diagnosed as having hypokalemia.

COUNTS III AND IV

1. The monograph relating to the drug Esidrix in the 1965 edition of the Physicians' Desk Reference omits the caution statement on combined therapy set out above at Count I, § 1(b).

2. The advertisement in the April 5, 1965 edition of the Journal of the American Medical Association failed to present a brief summary relating to side effects, contraindications and effectiveness of the drug Esidrix as follows:

(a) The advertisement fails to contain in brief summary a warning relating to the possibility of the drug's causing bowel lesions.

(b) The advertisement omits in brief summary the caution statement on combined therapy set out above at Count I, § 1(b).

_____ _____,
United States Attorney.

_____ _____,
Assistant United States Attorney.

In the United States District Court for the Western District of Michigan
Southern Division

UNITED STATES OF AMERICA

v.

THE UPJOHN COMPANY, A CORPORATION

No. ———

21 U.S.C. 331 and 333

COUNT I

The United States Attorney charges:

That on or about August 26, 1965 the Upjohn Company, a corporation, organized and existing under the laws of the state of Delaware and trading and doing business at Kalamazoo, Michigan, the defendant herein, did, within the Southern Division of the Western District of Michigan, in violation of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Kalamazoo, Michigan for delivery to Cleveland, Ohio consigned to the Upjohn Company warehouse at 1740 Chester Avenue, Cleveland, Ohio, a number of bottles containing a drug designated by the name "Orinase";

That displayed upon each of said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

200 Tablets No. 5849, Orinase (tolbutamide) 0.5 Gm. Each tablet contains Tolbutamide . . . 0.5 Gm. Caution: Federal law prohibits dispensing without prescription. The Upjohn Company, Kalamazoo, Michigan.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since it was a prescription drug which was a new drug subject to 21 U.S.C. 355 and its labeling, namely, the monograph relating to said drug set forth in the 1965 Edition of the Physician's Desk Reference, was not, as required by regulations, 21 CFR 1.106(b)(4)(1), substantially the same as the labeling authorized by the approved new drug application effective with respect to said drug.

HAROLD D. BEATON,
United States Attorney.

In The United States District Court for The Eastern District of New York

No. 66-M-163

UNITED STATES OF AMERICA, LIBELANT

v.

WARNER-LAMBERT PHARMACEUTICAL COMPANY, *Claimant*

An article of drug consisting of 68 bottles, more or less, of an article labeled in part: "100 80 mg. Tablets Peritrate SA Sustained Action (pentaerythritol tetranitrate) (Warner-Chilcott Laboratories Div., Morris Plains, N.J.)"

DECREE

On the 28th day of February, 1966, a Libel of Information against the above-described article was filed in this Court on behalf of the United States of America by the United States Attorney and the Assistant United States Attorney for this District. The Libel alleges that the article, namely 68 bottles of Peritrate SA, proceeded against is a drug which was shipped in interstate commerce and is in violation of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355(a) and 21 U.S.C. 352(a), 352(f)(1) and 352(n)].

Pursuant to monition issued by this Court, the United States Marshal for this District seized said article on the 28th day of February, 1966. Thereafter, Warner-Lambert Pharmaceutical Company of Morris Plains, New Jersey, intervened and

filed claim to said article. Now without admitting any of the allegations of the Libel, Claimant consents that a decree, as therein prayed for, be entered.

It is therefore ordered, adjudged and decreed That, based on the consent of the Claimant which does not admit any of the allegations of the Libel, the said article, namely 68 bottles of Peritrate SA, under seizure, is in violation of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355(a) and 21 U.S.C. 352(a), 352(f)(1) and 352(n)] and it is hereby condemned pursuant to 21 U.S.C. 334(a);

And it is further ordered, adjudged and decreed That the United States Marshal shall destroy the said condemned article; costs of which shall be taxed and paid by the Claimant subsequent to destruction.

And it is further ordered, adjudged and decreed That the bond for costs executed and filed herein be and the same hereby is canceled upon payment by Claimant of Court costs of $35.00, and $25.88 Marshal's fees.

Dated this 12th day of May, 1966.

GEORGE ROSLING, U.S.D.J.

We hereby consent to the entry of the foregoing decree.

WARNER-LAMBERT PHARMACEUTICAL COMPANY
By ROBERT B. CLAIL, *Vice President.*
ROGERS, HOGE & HILLS,
By JAMES S. HOGE,
Attorneys for Claimant Warner-Lambert Pharmaceutical Company.
UNITED STATES ATTORNEY,
By CARL GOLDEN,
Assistant United States Attorney.

STATE OF NEW YORK
County of New York, ss:

Personally appeared before me Robert B. Clark who being duly sworn deposed and said that he is the Vice President of Warner-Lambert Pharmaceutical Company and the seal affixed hereto is the seal of said corporation and that his signature is duly authorized.

LEONORE H. WICHMANN,
Notary Public, State of New York.

District Court of the United States, Eastern District of New York

THE PRESIDENT OF THE UNITED STATES OF AMERICA

To the Marshal of the Eastern District of New York—Greetings:

Whereas, a libel of information hath been filed in the District Court of the United States for the Eastern District of New York, on the 28th day of February, in the year of our Lord one thousand nine hundred and sixty-six by Joseph P. Hoey, Esquire, United States Attorney, on behalf of the United States of America, against An article of drug consisting of 68 bottles, more or less, of an article labeled in part:

(btl.) "100 80 mg. Tablets Peritrate SA Sustained Action (Pentacrythritol tetranitrate) Caution: Federal law prohibits dispensing without prescription. Warner-Chilcott Laboratories Div., Morris Plains, N.J. Usual Adult Dose: b.i.d. 1 tablet immediately on arising and 1 tablet 12 hours later *** Read accompanying directions *** Quality Control No. 3264115B"

(Package insert) "349G243 Peritrate SA (pentacrythritol tetranitrate) peritrate with Phenobarbital SA Sustained Action Each tablet contains: Phenobarbital 45 mg. (¾ gr.) *** Pentacrythritol Tetranitrate 80 mg. ***"

(For breach of the provisions of 21 U.S.C. 301 et seq.) for the reasons and causes in the said libel of Information mentioned, and praying the usual process and Monition of the said Court in that behalf to be made, and that all persons interested in the said above-entitled article may be cited in General and Special, to answer the premises, and all proceedings being had that the said above-entitled article may, for the causes in the said libel of Information mentioned, be condemned as forfeited to the use of the United States.

You are therefore hereby commanded, to attach the said above-entitled article and to detain the same in your custody until the further order of the Court respecting the same, and to give due notice to all persons claiming the same, or knowing or having anything to say why the same should not be condemned and sold pursuant to the prayer of the said libel of Information, that they be

and appear before the said Court, to be held in and for the Eastern District of New York on the 23rd day of March, 1966, at 10:30 a.m. of the same day, if the same shall be a day of jurisdiction, otherwise on the next day of jurisdiction thereafter, then and there to interpose a claim for the same, and to make their allegations in that behalf. And what you shall have done in the premises do you then and there make return thereof together with this writ.

Witness, the Honorable Joseph C. Zavatt Chief Judge of said Court, at the Borough of Brooklyn, in the Eastern District of New York, this the 28th day of February, in the year of our Lord one thousand nine hundred and sixty-six, and of the Independence of the United States of America the one hundred and ninetieth.

LEWIS ORGEL, *Clerk.*
By MARIE R. BARETTI,
Deputy Clerk.

In the United States District Court for the Eastern District District of New York

No. ——

UNITED STATES OF AMERICA

v.

An article of drug consisting of 63 bottles, more or less, of an article labeled in part: (btl.) "100 86 mg. Tablets Peritrate SA Sustained Action (Pentaerythritol tetranitrite) Caution: Federal law prohibits dispensing without prescription. Warner-Chilcott Laboratories Div., Morris Plains, N.J. Usual Adult Dose: b.i.d. 1 tablet immediately on arising and 1 tablet 12 hours later * * * Read accompanying directions * * * Quality Control No. 3264115B" (package insert) "3490243 Peritrate SA (pentaerythritol tetranitrate) Peritrate with Phenobarbital SA Sustained Action Each tablet contains: Phenobarbital 45 mg. (¾ gr.) * * * Pentaerythritol Tetranitrate 80 mg. * * *"

LIBEL OF INFORMATION

To The Honorable Judge of the United States District Court For The Eastern District of New York.

Now comes the United States of America, by Joseph P. Racy, United States Attorney for the Eastern District of New York and shows to the Court:

1. That this libel is filed by the United States of America and prays seizure and condemnation of a certain article of drug, as hereinafter set forth, in accordance with the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

2. That there is at Glendale, New York, in possession of Barry Division of Ketchum and Company, Inc., 80–00 Cooper Avenue, an article of drug consisting of 63 bottles, more or less, of an article labeled in part: (btl.) "100 80 mg. Tablets Peritrate SA Sustained Action (Pentaerythritol tetranitrate) Caution: Federal law prohibits dispensing without prescription. Warner-Chilcott Laboratories Div., Morris Plains, N.J. Usual Adult Dose: b.i.d. 1 tablet immediately on arising and 1 tablet 12 hours later * * * Read accompanying directions * * * Quality Control No. 3264115B" (package insert) "3490243 Peritrate SA (pentaerythritol tetranitrate) Peritrate with Phenobarbital SA Sustained Action Each tablet contains: Phenobarbital 45 mg. (¾ gr.) * * * Pentaerythritol Tetranitrate 80 mg. * * *" which were shipped, on or about February 4, 1966, by Warner-Chilcott Laboratories, Inc., 201 Tabor Road, Morris Plains, New Jersey, via Parcel Delivery Service, Inc.

3. That the aforesaid article is a new drug which may not be introduced or delivered for introduction into interstate commerce, under said Act, 21 U.S.C. 355(a) since it is a new drug within the meaning of 21 U.S.C. 321(p) in that it is not generally recognized as safe and effective for the uses recommended or suggested in the labeling, and no approval of an application filed pursuant to 21 U.S.C. 355(b) is effective with respect to such drug for all of such uses, since the labeling of the drug, namely, the aforesaid package insert and the mailing piece which is identified "490T718 October, 1965," and contains the reprints entitled "Pentaerythritol Tetranitrate, As Adjunct Therapy In The Immediate Pastinfarction Period," reprinted from Angiology, Vol. 15, 11, November 1964, and "The Use Of Coronary Vasedilators In Acute Coronary Occlusion," reprinted

from "A Scientific Exhibit Presented at The American College of Cardiology, Boston, Mass., February 17–21, 1965," offers the drug for the following purposes for which the drug is not generally recognized as safe and effective, and under the following representations of safety and efficacy, which purposes and representations are not contained in the labeling accepted by the Food and Drug Administration under the presently approved new drug application for the article:

(Package insert)—

1. "This drug increases blood flow and oxygen supply to the myocardium . . .

2. ". . . the dilation of the capillaries of the postarteriolar bed with a resultant greater flow of blood through the arteries and arterioles to supply these capillaries . . .

3. "This drug, because of its gradual onset of action, is safe for prolonged use in all patients with coronary artery disease, because it does not significantly change the blood pressure, cardiac output, or pulse rata . . .

4. ". . . for adequate, sustained increase in blood flow and oxygen supply to the myocardiam . . ."

(mailing piece identified "490T718 October, 1965")

1. that the drug is for use in the immediate postinfarction period and in acute coronary occlusion.

2. that a purportedly well-controlled clinical investigation, comparing patients treated with Peritrate SA with similar patients treated with a placebo beginning at a time closely following the onset of acute myocardial infarction, proved that the fact that 22 percent more patients treated with Peritrate SA remained alive after two years than patients treated with a placebo was due to the action of the drug.

4. That the aforesaid article was misbranded when introduced into and while in interstate commerce within the meaning of said Act, 21 U.S.C. as follows:

352(a) in that its labeling, namely, the mailing piece identified "498T718 October 1965," contains statements which represent and suggest that a purportedly well-controlled clinical investigation comparing patients treated with Peritrate SA with similar patients treated with a placebo beginning at a time closely following the onset of acute ayecardial infarction, proved that the fact that 22 percent more patients treated with Peritrate SA remained alive after two years than patients treated with a placebo was due to the action of the drug, which statements are false and misleading since they are contrary to fact; and in that said mailing piece also contains statements which represent and suggest that the referenced study by Lumb, G. D., and Hardy, L. B., Circulation (Pt. II, Cardiovascular Survery) 27:717, 1963, supports the claim in said mailing piece that "from the first sign and throughout the course of coronary artery disease . . . Peritrate SA (pentaerythritol tetranitrate) 80 mg. Sustained Action . . . stimulates development of collateral circulation," which statements are false and misleading since they are contrary to fact.

352(f)(1) in that its labeling fails to bear adequate directions for use and it is not exempt from such requirement, since it is a prescription drug within the meaning of 21 U.S.C. 353(b)(1)(C), and a new drug subject to the provisions of 21 U.S.C. 355, and its labeling, namely, the package insert, is not the labeling authorized in an approved new drug application as required under the exempting regulation 21 CFR 1.106(b)(3)(ii), and the mailing piece identified "4981718 October 1965," which is labeling within the meaning of (21 CFR 1.105(1)), is not substantially the same as the labeling authorized in an approved new drug application, as required under the exempting regulation 21 CFR 1.106(b)(4)(i).

352(n) in that it is a prescription drug distributed and offered for sale in the State of New York, and the advertisement for the drug appearing in the *Journal of the American Medical Association* from December 6, 1965 through January 3, 1966 and in the *Journal of the American Medical Association* for February 7, 1966, identified "PE–OP–527–4C December 1965," caused to be issued by the manufacturer, packer, or distributor of the drug, failed to include a true statement of information in brief summary relating to the effectiveness of said drug as required by regulations 21 CFR 1.105(e) in that the advertisement lacks fair balance in its presentation and does not fairly show the effectiveness of the drug in the conditions for which it is recommended or suggested in the advertisement since the advertisement represents (1) that a purportedly well-controlled clinical investigation, comparing patients treated with Peritrate SA with similar patients treated with a placebo beginning at a time closely following the onset of acute mycardial infarction, proved that the fact that 22

percent more patients treated with Peritrate SA remained alive after two years than patients treated with a placebo was due to the action of the drug, which representation is false and misleading since it is contrary to fact; and (2) that the referenced study by Lumb, O. D., and Hardy, L. B., Circulation (Pt. II, Cardiovascular Surgery) 27:717, 1963, supports the claim that "Peritrate SA (pentaerythritol tetrenicrate) 80 mg. Sustained Action . . . stimulates development of collateral circulation," which representation is misleading in that the advertisement fails to reveal the material fact that the research involved the use of young pigs in a manner which in no way approximates the human disease situation.

5. That the aforesaid article is in the possession of Barry Division of Ketchum and Company, Inc., 60–80 Cooper Avenue, at Glendale, New York, or elsewhere within the jurisdiction of this Court.

6. That by reason of the foregoing, the aforesaid article is held illegally within the jurisdiction of this Court, and is liable to seizure and condemnation pursuant to the provisions of said Act, 21 U.S.C. 334.

Wherefore, libellant prays that process in due form of law according to the course of this Court in cases of admiralty jurisdiction issue against the aforesaid article; that all persons having any interest therein be cited to appear herein and answer the aforesaid premises; that this Court decree the condemnation of the aforesaid article and grant libellant the costs of this proceeding against the claimant of the aforesaid article; that the aforesaid article be disposed of as this Court may direct pursuant to the provisions of said Act; and that libellant have such other and further relief as the case may require.

Dated: Brooklyn, New York, February 28, 1966.

JOSEPH P. HOEY,
United States Attorney, Eastern District of New York, Practor for Libellant, 521 United States Court House, Brooklyn, New York.

By CARL GOLDEN,
Assistant United States Attorney.

DEPARTMENT OF JUSTICE,
U.S. MARSHAL,
EASTERN DISTRICT OF NEW YORK,
Brooklyn, N.Y., March 2, 1966.

NOTICE OF ATTACHMENT

U.S. Marshal's No. 20166
U.S. Court No. 66–M–163

Hon. JOSEPH P. HOEY,
U.S. Attorney,
Brooklyn, N.Y.:

Notice is hereby given that on February 28, 1966, this office libeled the article of drug consisting of 68 bottles, more or less, of an article labeled in part: (btl.) "100 80 mg. Tablets Peritrate SA Sustained Action(Pentaerythritol tetranitrate) Caution: Federal law prohibits dispensing without prescription. Warner-Chilcott Labs. Div., Morris Plains, N.J., etc. of which you are reputed to be the proctor. Process returnable in the U.S. District Court, 225 Washington Street, Brooklyn, New York, on the 23rd of March, 1966. Libeled by United States of America for breach of the provisions of 21 U.S.C. 301 et seq.

Respectfully,

GEORGE J. WARD,
U.S. Marshal, E.D.N.Y.

In the United States District Court for the District of New Jersey

No. ——

UNITED STATES OF AMERICA

v.

An article of drug consisting of 100 bottles, more or less, labeled in part: (btl.) capsules 14747 Serax (Oxerepam) * * * 10 mg. Caution: Federal law prohibits * * * See accompanying information. Usual Dosage: Use or two

capsules 3 or 4 times daily. Wyeth Laboratories, Inc. Philadelphia, Pa. * * *" Control No. 1660711 * * * (insert) "Serex (Oxerepam), Serex is 7-chloro-1, 3-dihydro-3-hydroxy-5-phenyl-23-1, 4-benzediazepin-2-one. Wyeth Laboratories, Inc. Philadelphia, Pa., Cir. 2473, January 24, 1966 * * *"

LIBEL OF INFORMATION

To The Honorable Judge of the United States District Court for the District of New Jersey.

Now comes the United States of America, by David N. Sats, United States Attorney for the District of New Jersey and shows to the Court:

1. That this libel is filed by the United States of America and prays seizure and condemnation of a certain article of drug, as hereinafter set forth, in accordance with the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

2. That there is at Secaucus, New Jersey, in possession of Wyeth Laboratories, Division of American Drug Products Corporation, 555 Secaucus Road (warehouse), or elsewhere within the jurisdiction of this court, an article of drug consisting of 150 bottles, more or less labeled in part: (bottle) "100 Capsules 13737 Serea * * * 10 mg. Caution: Federal law prohibits * * * see accompanying information. Usual dosage: one or two capsules 3 or 4 times daily. Wyeth Laboratories, Inc., Philadelphia, Pa. * * *

3. That the aforesaid article was misbranded when introduced into and while in interstate commerce, within the meaning of said Act, 21 U.S.C. 352(a) in that it is a prescription drug within the meaning of 21 U.S.C. 353(b)(1)(C), it is distributed in the State of New Jersey, and the advertisement for the drug appearing in the April 25, 1956 issue of the *Journal of the American Medical Association*, in the March 1956 issue of *American Journal of Psychiatry*, and in the April 18, 1956 issue of Medical Economics, caused to be issued by the manufacturer, packer, or distributor of the drug lacks fair balance in its presentation and does not fairly show the effectiveness of the drug in the conditions for which it is recommended in the advertisement, as required by regulations 21 CFR 1.105(e), in that:

(A) The advertisement emphasizes use of Serex by elderly persons, and implies that Serex is quite safe for elderly persons through use of such statements as "Possesses extraordinary safety margin" and "stamia, drowsiness, dizziness rare," but fails to provide fair balance in that the advertisement does not emphasize the fact that Serox should be used cautiously in the elderly, particularly because of the possibility of serious hpotessive reactions in elderly persons.

(B) The advertisement refers to a study by Chesrow, et al., as one involving "145 elderly patients," but fails to show that the patient group of 145 ranged in ages from 33 to 97 (men) and 33 to 89 (women).

(C) The advertisement is false and misleading in that it quotes from the Chestos, et al paper a dosage of the drug up to 40 mg. a day; while the approved package labeling for _____ limits the initial damage of the drug in "older patients" to 30 mg. a day; the advertisement thus misleadingly promotes a dangerous use in the age group on which the promotion is based.

(D) The advertisement promotes effectiveness of Serax by the closis "controls . . . anxiety-linked depression," which claim is not permitted in the approved package labeling; further, aluco "depression" may vary between neuresis and psychosis (Serax being contraindicated in psychotic patients), the claim is dangerous.

(E) The advertisement lacks "fair balance" since it selects one paper to emphasize favorable aspects of Serex therapy, in relation to a competitive product, while failing to mention other studies which present different views; and the advertisement falsely implies that the Chesrow et al paper represents the medical consensus as to the performance of Serex in comparison to chlordiozopozide.

4. That by reason of the foregoing, the aforesaid article is held illegally within the jurisdiction of this Court, and is liable to seizure and condemnation pursuant to the provisions of said Act, 21 U.S.C. 354.

Wherefore, libellant prays that process is due form of law according to the course of this Court in cases of admirality jurisdiction issue against the aforesaid article; that all persons having any interest therein be cited to appear herein and answer the aforesaid premises; that this Court decree the condemnation of the

aforesaid article and grant libellant the cost of this proceeding against the claimant of the aforesaid article; that the aforesaid article be disposed of as this Court may direct pursuant to the provisions of said Act; and that libellant have such other and further relief as the case may require.

UNITED STATES OF AMERICA

By ——— ———

United States Attorney.

———

United States District Court, Southern District of Ohio, Western Division

Civil No. 6273

UNITED STATES OF AMERICA

v.

14 Cases, More or Less, of an Article Labeled in Part "24 Capsules * * * LINCOCIN"

CONSENT DECREE

On the 27th day of October, 1966, a Complaint in the form of a Libel of Information against the above-described article was filed in this Court on behalf of the United States of America by the United States Attorney for this District. The Complaint alleges that the article, namely 14 cases of Lincocin capsules, proceeded against is a prescription drug which was shipped in interstate commerce and is in violation of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 352(n)) because of an advertisement which it was claimed failed to comply with 21 CFR 1.105(E) and 21 CFR 1.105(G).

Pursuant to monition issued by this Court, the United States Marshall for this District seized said article on the 27th day of October, 1966. Thereafter, The Upjohn Company, of Kalamazoo, Michigan, intervened and filed claim to said article. Now, without admitting the allegations of the Complaint, Claimant, having discontinued the advertisement, consents that a decree, as hereinafter provided, be entered.

It is therefore ordered, adjudged and decreed that, based on the consent of the Claimant which does not admit the allegations of the Complaint, the said article, namely 14 cases, more or less, labeled "24 Capsules * * * LINCOCIN" under seizure, is in violation of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 352(n)) and it is hereby condemned pursuant to 21 U.S.C. 334(a);

And it is further ordered, adjudged and decreed that the United States Marshal shall deliver the said condemned article in equal amounts as follows:

(a) to the Bellvue Hospital Center, First Avenue and 27th St. New York City (A. Wyman) 7 cases of Lincocin for its use;

(b) to the Los Angeles County General Hospital, 1200 N. State Street, Los Angeles, California (A. Witherill) 7 cases of Lincocin for its use.

And it is further ordered, adjudged and decreed that Claimant shall pay Court costs of $——, and Marshal's fees of $——.

Dated this 6th day of December, 1966.

TIMOTHY S. HOGAN,
United States District Judge.

We hereby consent to the entry of the foregoing decree.

DINSMORE, SHOHL, BARRETT, COATES & DEUPREE,
By THOMAS S. CALDER,
Attorneys for Claimant, The Upjohn Company.

UNITED STATES ATTORNEY,
By THOMAS R. SMITH,
Assistant United States Attorney.

United States District Court, Southern District of Ohio, Western Division

Civil No. 6273

UNITED STATES OF AMERICA *v.*

14 cases, more or less, of an article labeled in part "24 capsules * * * Lincocin"

CLAIM OF OWNER

The Upjohn Company, a corporation duly organized and existing under the laws of the State of Delaware, with its principal place of business in Kalamazoo, Michigan, appears before this Court, intervening in this proceeding for the interest of itself as owner of the articles above described, and makes claim to the said articles which have been attached by the United States Marshal for this District under process of this Court at the instance of the United States of America, libelant;

And said claimant avers that it is the true and bona fide owner of the said articles and that no other person is the owner thereof; wherefore it prays to defend accordingly.

THE UPJOHN COMPANY,
By GERARD THOMAS,
Vice President.

AFFIDAVIT

STATE OF MICHIGAN
County of Kalamazoo, ss:

Gerard Thomas, being duly sworn, deposes and says that he is the Vice President of The Upjohn Company, the corporation which is described herein and which executed the foregoing claim; that he has authority to act on behalf of the corporation in this matter and that he signed said claim pursuant to said authority; that he has read said claim and knows the contents thereof, and that the same is true to the best of his knowledge, information and belief.

GERARD THOMAS, *Vice President.*

Subscribed and sworn to before me this 2nd day of December, 1966.

HOWARD D. KALLEWARD, *Notary Public.*

My commission expires December 8, 1967.

PROOF OF SERVICE

A copy of the attached Claim of Owner and Affidavit of Gerard Thomas was delivered to the Office of Thomas R. Smith, Assistant United States Attorney, this 6th day of December 1966.

THOMAS S. CALDER.

Hon. ROBERT M. DRAPER,
U.S. Attorney,
Cincinnati, Ohio.

DEAR SIR: There is at Cincinnati, in possession of The Upjohn Company, 4910 Para Drive (warehouse), an article of drug consisting of 14 cases, more or less, each containing 48 24-capsule bottles of an article labeled in part: (btl.) "24 capsules * * * Lincocin (lincomycin hydrochloride monhydrate) equiv. to 500 mg. lincomycin. * * * Caution: Federal Law * * * Usual Adult Dosage: 500 mg. three or four times daily * * * Lot No. WG969E6 * * * Expires May 1, 1969, * * * The Upjohn Co., Kalamazoo, Michigan." which were shipped, on or about October 4, 1966, by The Upjohn Company, 9171 Portage Road, Kalamazoo, Michigan, via Holland Motor Express.

No analysis has been made. It is assumed that the article contains the ingredients declared on its label and labeling.

The aforesaid article was misbranded when introduced into and while in interstate commerce, within the meaning of the Federal, Food, Drug, and Cosmetic, 21 U.S.C. 352(n) in that it is a prescription drug which is subject to certification and is distributed and offered for sale in the State of Ohio, and the advertisement for the drug appearing in the *Journal of the American Medical Association for October* 3, 1966, identified "C 1966 by The Upjohn Company J66-6375-2"

caused to be issued by the manufacturer, packer, or distributor of the drug, failed to include

(A) a true statement of information in brief summary relating to the effectiveness of said drug as required by regulation 21 CFR 1.105(e) in that the advertisement lacks fair balance in its presentation and does not fairly show the effectiveness of the drug in the conditions for which it is recommended or suggested in the advertisement since the advertisement represents,

(1) That therapy may be initiated parentally and then followed through orally without switching to another antibiotic but fails at this point to refer to the sensitivity study requirement contained in the labeling accepted under the certification requirements for the drug that " . . . in vitro sensitivity studies should be performed before Lincocin is utilized as sole antibiotic therapy;"

(2) That reactions are rare, even for patients sensitive to penicillin—does not share antigenicity with the penicillin group of compounds, "which representation is misleading, and fails at this point to refer to the "adverse experience" information contained in the labeling accepted under the certification requirements for the drug that "A few cases of hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported;"

(3) That there are "no serious renal or neurologic abnormalities, no ototoxicity" and "no tooth discoloration to date" which representations are misleading in that the audience for whom the advertisement is intended is not advised at this point or with equal prominence or in reasonably close association with this information the facts that hematologic toxicity, manifested by neutropenia or leukopenia can occur and that the frequency of severe diarrhea is a unique feature of Lincocin therapy.

(B) a true statement of information in brief summary concerning those side effects and contraindications that are pertinent with respect to the uses recommended or suggested in the advertisement and any other use or uses for which the dosage form advertised is commonly prescribed as required by regulation 21 CFR 1.105(g) in that the advertisement failed to include the following information from the labeling covered by the certification, or the applicable certification regulations (21 CFR 148.3 and 148X):

(1) The precautionary information that "With B-hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis:"

(2) The side effect information which specifies the serious nature of the cases of hypersensitivity reactions, i.e., . . . "Angioneurotic edema, serum sickness and anaphylaxis" and fails to identify the usual agents which should be available for emergency treatment, i.e., "antihistamines, pressor amines, corticosteroids;"

(3) The precautionary information that ". . . in vitro sensitivity studies should be performed before Lincocin is utilized as sole antibiotic therapy."

(4) The statement "Other adverse reactions observed in a small proportion of patients . . ." appearing in the labeling is not included and is misleadingly changed in the advertisement to read "Side effects of small proportion . . ."

The aforesaid article misbranded when introduced into and while in interstate commerce, is subject to seizure and condemnation under 21 U.S.C. 334. Immediate seizure is requested. Please advise the action taken.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel, Food and Drug Division.

In the United States District Court for the Eastern District of Pennsylvania

No. ——

UNITED STATES OF AMERICA, PLAINTIFF

v.

An article of drug consisting of 45 individually cartoned bottles, more or less, labeled in part:

(bottle and ctn.)

"Lasix 40 Mg. Furosemide 100 Tablets Caution: Federal law prohibits * * * Directions: * * * 1 or 2 tabs. see insert * * * Hoechst Pharmaceuticals, Inc. Formerly Lloyd Bros., Inc. Cincinnati, Ohio 45229 * * * Control 600376B"

(insert)

"Lasix Brand of furosemide * * * Original Printing June 3, 1966"

DEFENDANT

COMPLAINT FOR FORFEITURE

To The Honorable Judge of the United States District Court For The Eastern District of Pennsylvania.

Now comes the United States of America, by Drew J. T. O'Keefe, United States Attorney for the Eastern District of Pennsylvania and shows to the court:

1. That this complaint is filed by the United States of America and prays seizure and condemnation of a certain article of drug, as hereinafter set forth, in accordance with the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

2. That there is at Philadelphia, Pennsylvania, in possession of Drug House, Inc., 1011 West Butler Street, or elsewhere within the jurisdiction of this Court, an article of drug consisting of 45 individually cartoned bottles, more or less, labeled in part: (bottle and carton) "Lasix 40 Mg. Furosemide 100 Tablets Caution: Federal law prohibits * * * Directions: * * * 1 or 2 tabs. See insert * * * Hoechst Pharmaceuticals, Inc. Formerly Lloyd Bros., Inc. Cincinnati, Ohio 45229 * * * Control 600376B" (Insert) "Lasix Brand of furosemide * * * Original Printing June 3, 1966" which were shipped, on or about November 3, 1966, by Hoechst Pharmaceuticals, Inc., Cincinnati, Ohio, via unknown carrier.

3. That the aforesaid article was misbranded when introduced into and while in interstate commerce, within the meaning of 21 U.S.C. 352(n) in that it is a prescription drug distributed and offered for sale in the State of Pennsylvania, and the advertisements for the drug appearing in the Journal of the American Medical Association for October 10, 1966, Medical World News of October 21, 1966, Medical Economics of October 31, 1966, and MD Medical News Magazine of November 1966, caused to be issued by the manufacturer, packer, or distributor of the drug, fail to include a true statement of information in brief summary relating to the effectiveness and contraindictions of said drug as required by regulations 21 CFR 105 as follows:

(A) the advertisements lack fair balance in their presentations on effectiveness and contraindications, and do not fairly show the effectiveness of the drug in the conditions for which it is recommended or suggested in the advertisements, as required by regulations 21 CFR 105(e) since the advertisements represent,

(1) That when the drug was compared with hydrochlorothiazide substantial increases in water and sodium excretion were shown in the case of furosemide (by reference to a paper by Dr. H. Kleinfolder, published in German M. Month. (8:459, 1963) but fail to reveal that the studies were conducted with only eight patients, and that the overlap of the standard errors of the means derived from the data is so great that the data do not permit their unspecified repetition in the advertisements and the implied extrapolation to experience to be expected in the general population;

(2) That a paper by R. J. Timmerman, M.D. published in *Curr. Therap. Rea.* 6:88, 1964, pertains to the time of onset and length of action of the drug in edematous patients but misleadingly fail to reveal that the studies reported by the paper were not conducted on edematous patients;

(3) That two references, namely, a paper by L. B. Berman, M.D. et al., published in *Proc. Soc. Exp. Biol. Med.* 118:333, 1965, and a paper by L. Bencomo, M.D. et al., published in *Cur. Therap. Res.* 7:339, 1965, pertain to use of the drug when other diuretic regimens have failed when in fact the papers do not show that the patients in the studies were refractory to other diuretic therapy;

(4) That two references, namely a paper by D. E. Hutcheon, M.D. et al., published in *Arch. Int. Med.* 115:542, 1965, and a paper by H. Kleinfelder, M.D. published in *German M. Month.* 8:459, 1963, support the claim that natriuresis with furosemide far exceeds that of the thiazides and that there is no parallel increase in kaliuresis, but misleadingly fail to reveal that the papers also show that the 24-hour urinary potassium excretion is essentially no different with furosemide than with thiazide in most patients, and that potassium depletion and hypokaklemia do occur with furosemide;

(5) That there is a "highly favorable urinary Na/K ratio" and "greatly enhanced Na, proportionately low increase in K excretion": but fail to present in fair balance (a) that there is almost always a marked increase in urinary potassium when furosemide is given as compared to potassium excretion with no diuretic, (b) that the 24-hour urinary potassium excretion is usually the same or greater with furosemide as compared with thiazide or mercurial diuretics, and (c) that notwithstanding the quoted claims, hypokalemia may develop during the use of furosemide;

(6) That data in graphic form obtained from two papers, namely, by R. J. Timmerman, M.D. published in *Curr. Therap. Res.* 6:88, 1964 and by H. Kleinfelder, M.D. published in *German M. Month.* 8:459, 1963, accurately reflect general experience concerning effectiveness of the drug but fail to reveal that the data are from studies conducted on only 15 patients in the former and four patients in the latter study;

(7) That furosemide is a "non-thiazide diuretic" but misleadingly fail to present at this point in fair balance that furosemide shares many important contraindications, warnings and side effects with the thiazides and in this important sense the two classes of compounds ar quite similar; and

(8) In the advertisements in *Medical World News of October* 21, 1966, *Medical Economics* of October 31, 1966, and *MD Medical News Magazine* of November 1966, it is claimed that, "When the effects of Lasix (furosemide) and hydrochlorothiezide were compared over a 24-hour period, fluid output produced by Lasix (furosemide) was 200% greater, and sodium excretion was 167% greater," which claim is not a true statement in that the data in the paper by H. Kleinfelder, M.D. German M. Month, 8:459, 1963, show that the correct percentages are 105% and 67%, respectively; and

(B) Each of the aforesaid advertisements suggest, contrary to the requirements of regulation 21 CFR 1.105(f)(1), uses for the drug that are not in the labeling accepted in the approved new drug application for the drug since the advertisements represent that the drug is for use in a variety of conditions "from the easy to control to the severe and thiazide refractory edemas . . ." and "Throughout the spectrum, from the mild to the most severe and refractory edema," which representations exceed the indications for use as specified in the labeling accepted in the approved new drug application.

4. That by reason of the foregoing, the aforesaid article is held illegally within the jurisdiction of this Court, and is liable to seizure and condemnation pursuant to the provisions of said Act, 21 U.S.C. 334.

Wherefore, plaintiff prays that process in due form of law according to the course of this Court in cases of actions in rem issue against the aforesaid article; that all persons having any interest therein be cited to appear herein and answer the aforesaid premises; that this Court decree the condemnation of the aforesaid article and grant plaintiff the costs of this proceeding against the claimant of the aforesaid article; that the aforesaid article be disposed of as this Court may direct pursuant to the provisions of said Act; and that plaintiff have such other and further relief as the case may require.

UNITED STATES OF AMERICA,
DREW J. T. O'KEEFE,
United States Attorney.

_____,
Assistant United States Attorney.

In the United States District Court for the Eastern District of Pennsylvania

No. 56 of 1966

UNITED STATES OF AMERICA, PLAINTIFF

v.

An article of drug consisting of 45 individually cartoned bottles, more or less, labeled in part: (btl. and ctn.) "Lasix 40 mg. Furosemide 100 Tablets Caution: Federal law prohibits * * * Directions: * * * 1 or 2 tabs. see insert * * * Hoechst Pharmaceuticals, Inc. Formerly Lloyd Bros., Inc. Cincinnati, Ohio 45229 * * * Control 600376 B"

(insert)

"Lasiz Brand of furosemide * * * Original Printing June 3, 1966"

DEFENDENT

DECREE OF CONDEMNATION

And now, to with, this 5th day of April, 1967, on motion of DREW J. T. O'KEEFE, United States Attorney for the Eastern District of Pennsylvania, it appearing to the Court that upon the Complaint for Forfeiture filed in the within cause on November 21, 1966, a warrant of attachment duly issued and was served; that proclamations were duly made in accordance with law and no one having filed an Answer to the Complaint or filed a Claim to the property mentioned in said Complaint and attached by the Marshall, it is ordered, adjudged and decreed

1. That said property, to wit: An article of drug consisting of 45 individually cartoned bottles, more or less, labeled in part: (btl. and ctn.) "Lasix 40 mg. Furosemide 100 Tablets Caution: Federal law prohibits * * *" is misbranded.

2. That said property be, and the same is hereby condemned and forfeited to the United States for the cause set forth in said Complaint and it is further ordered, adjudged and decreed that the United States Marshall deliver said condemned article to Jefferson Medical College Hospital, Department of Pharmacy, Philadelphia, Pennsylvania, for use by them solely pursuant to the package insert and not for resale.

By the Court:

(s) RALPH C. BODY.

In the U.S. District Court for the Northern District of Illinois

No. L7C686

United States of America, Plaintiff

v.

An article of drug consisting of 34 cartons, more or less, each containing 4 plastic boxes, each box contains 6 ampules, labeled in part:

(carton):

"4 Boxes, 6 Ampules, Each of 2 cc.
Warning: Not for Injection
Indoklon
Flurothyl
(bis) 2,2,2-trifluoroethyl ether
* * *
Distributed by
Ohio Chemical
Ohio Chemical and Surgical
Equipment Company
(A Division of Air Reduction Company, Inc.)
Madison 10, Wis. * * *
Control No. 7155"

(plastic box) :

"6 Ampules, 2 cc Each
Warning: Not for Injection
Indoklon
* * *
Distributed by
Ohio Chemical
Ohio Chemical and Surgical
Equipment Company
* * *
Madison 10, Wis. * * *
Control No. 7155"

(Insert in plastic box) :

"Indoklon
Fluorothyl
* * *
A convulsant agent for psychiatric use * * *

(Ampule) :

"2 cc Ampule
Indoklon
Flurothyl
For Inhalation Only
Caution: * * *
Warning: * * *
Ohio Chemical
Madison, Wisconsin
Control No. 7155", Defendant

COMPLAINT FOR FORFEITURE

The United States of America, by Edward V. Hanrahan, United States Attorney for the Northern District of Illinois, shows to the Court:

1. This complaint is filed by the United States of America and prays seizure and condemnation of a certain article of drug, as hereinafter set forth, in accordance with the Federal Food, Drug, and Cosmetic Act, (21 U.S.C. 301–392).

2. There is at Chicago, Illinois, in possession of The Ohio Chemical and Surgical Equipment Company Branch Warehouse, 3100 South Homan Street, or elsewhere within the jurisdiction of this Court, an article of drug consisting of 34 cartons, more or less, each containing 4 plastic boxes, each box contains 6 ampules, labeled in part:

(carton)

4 Boxes, 6 Ampules Each of 2 cc., Warning: Not For Injection, Indoklon, Flurothyl, (bis) 2,2,2-trifluoroethyl ether, * * *, Distributed by Ohio Chemical, Ohio Chemical and Surgical Equipment Company (A Division of Air Reduction Company, Inc.) Madison 10, Wis. * * *, Control No. 7155

(plastic box)

6 Ampules, 2 cc each, Warning: Not For Injection, Indoklon, * * *, Distributed by Ohio Chemical, Ohio Chemical and Surgical Equipment Company * * *, Madison 10, Wis. * * *, Control No. 7155

(Insert in plastic box)

Indoklon, Flurothyl, * * *, A convulsant agent for psychiatric use * * *

(Ampule)

2 cc Ampule, Indoklon, Flurothyl, For Inhilation Only, Caution: * * *, Warning: * * *, Madison, Wisconsin, Control No. 7155

which were shipped, on or about February 20, 1967, by The Ohio Chemical and Surgical Equipment Company, Cleveland, Ohio, via the company's own truck.

3. The aforesaid article was misbranded when introduced into, while in, and while held for sale after shipment in interstate commerce, within the meaning

of said Act, 21 U.S.C. 352(a), in that it is a prescription drug offered and distributed for sale in the State of Illinois, and the advertisements for said drug appearing in the February, 1967, and April, 1967, issues of the *American Journal of Psychiatry* and in the February, 1967, issue of the journal, *Diseases of the Nervous System*, reading in part:

> When convulsive therapy is indicated * * * Indoklon * * * Eliminates patient fear and anxiety of electroshock, Indoklon pharmacoconvulsive Therapy is safe and dependable * * *

failed to include a true statement of information relating to the side effects and contraindications of said drug as required by the regulations, 21 C.F.R. 1.105, since said advertisements failed to include any information relating to said side effects and contraindications.

4. By reason of the foregoing, the aforesaid article is held illegally within the jurisdiction of this Court, and is liable to seizure and condemnation pursuant to the provisions of said Act, 21 U.S.C. 334.

Wherefore, plaintiff prays that process in due form of law according to the course of this Court in cases of actions in rem issue against the aforesaid article; that all persons having any interest therein be cited to appear herein and answer the aforesaid premises; that this Court decree the condemnation of the aforesaid article and grant plaintiff the costs of this proceeding against the claimant of the aforesaid article; that the aforesaid article be disposesd of as this Court may direct pursuant to the provisions of said Act; and that plaintiff have such other and further relief as the case may require.

Dated ————, 1967.

EDWARD V. HANRAHAN,
U.S. Attorney.

STATE OF ILLINOIS
County of Cook, ss:

AFFIDAVIT

Roger J. Balla, Assistant United States Attorney, being first duly sworn on oath, deposes and says that he has been appointed by Edward V. Hanrahan, United States Attorney for the Northern District of Illinois, to represent the United States of America in the instant cause; and that he has read the above complaint, and the complaint is true in substance and fact.

ROGER J. BALLA,
Assistant U.S. Attorney.

Subscribed and sworn to before me this ———— day of April, 1967.

————— ————,
Notary Public.

LAKESIDE LABORATORIES,
DIVISION OF COLGATE-PALMOLIVE CO.,
Milwaukee, Wis., November 1967.

DEAR DOCTOR: The Food and Drug Administration have requested that we call your attention to the monograph for Norpramin (desipramine hydrochloride) in the 1967 *PDR:* page 687, white section. The FDA consider this monograph incomplete (in relation to the official labeling, the package insert), and therefore potentially misleading as prescribing information to allow safe and effective use of the drug.

To provide you with the necessary adequate reference, we enclose a revised monograph for 1967 Physicians' Desk Reference in which the changes have been emphasized by italics. Please insert this revision opposite page 687.

Sincerely yours,

WILLIAM C. JANSSEN, M.D.

THE S. E. MASSENGILL CO.,
Bristol, Tenn., November 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for our products, Predsem, Salcort and Salcort-Delta, in the current (1967) *Physicians' Desk Reference.* The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and thherefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion at page 812 of your current (1967) PDR. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely,

ROBERT P. EWING,
Vice President, Marketing.

ORGANON INC.,
West Orange, N.J., October 27, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for *Cortrophin® Gel, Cortrophin® Zinc, Hexadrol® Phosphate Injection and Hexadrol®* Tablets and Elixir in the current *Physicians Desk Reference.* The FDA considers these monographs to be incomplete in presenting necessary information for the safe and effective use of these drugs, and, therefore, potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your *PDR.* The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely yours,

JOSEPH D. CUONO, M.D.,
Director, Professional Services.

E. R. SQUIBB & SONS INC.,
New York, N.Y., October 24, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to certain advertisements for Mysteclin ®–F products which the FDA regards as misleading. The main theme of the advertising, which we have stopped, suggests that "almost every candidate for broad-spectrum antibiotic therapy, is a candidate for Mysteclin–F."

We wish to emphasize that those patients selected for tetracycline therapy who are know to be particularly susceptible to candidal superinfection are the potential candidates for Mysteclin–F therapy.

The FDA points out that recent journal advertisements for these products suggested that candidal superinfection is a serious problem with the use of ampicillin. This was not supported by the reference used in the ads. Although the reference cited included the statement that candidal overgrowth may follow ampicillin therapy, the FDA has asked that we point out that the significance of this overgrowth has not been established.

Further, the same ads omitted important warning information relating to precautions and side effects. The nature and extent of the omission are capitalized in the enclosed "Brief Summary".

Sincerely,

SQUIBB.

ENDO LABORATORIES INC.,
Garden City, N.Y., October 14, 1967.

DEAR DOCTOR: Undoubtedly you are aware of the unfortunate widespread confusion which surrounds the recall which we are presently conducting of certain specific packaging lots of our Coumadin Tablets 2 mg., 2½ mg., and 5 mg.

We enclose:

1. A copy of a public statement issued yesterday, October 13, 1967, by James L. Goddard, M.D., Commissioner of Food and Drugs.
2. A copy of a letter which is today being sent to every hospital pharmacy, retail pharmacy and drug wholesaler throughout the country.

We, of course, also regret that this confusion has arisen, and we feel that the attached letters will reassure you and your patients concerning Coumadin.

Very truly yours,

LEONARD S. BRAHEN, M.D.,
Medical Director.

OCTOBER 13, 1967.

From: James L. Goddard, M.D., Commissioner of Food and Drugs.

There has been widespread confusion among heart patients, their physicians, and the public generally, since it was reported yesterday that approximately

30 million tablets of Coumadin, a brand of the anticoagulant sodium warfarin, are being recalled from the market. I would like to explain as clearly as I can what the facts of the situation are.

The recall was requested by the Food and Drug Administration because assays of samples showed that some tablets were above or below required potency levels—but the variations found *do not* pose an imminent danger to the health of the user. It could be *more hazardous* to abruptly halt use of the medication. The safest course the patient can follow is to continue the medication his doctor prescribed.

The recall covers 16 packaging lots of Coumadin tablets in three dosages. For the information of physicians, 2 mg. and 2.5 mg. Coumadin tablets being recalled were slightly *below* allowable potency levels. Only the 5 mg. tablets were found to be *above* the allowable potency limits, ranging in strength from 5.49 to 5.56 mg.

Excessive potency is likely to be more hazardous than subpotency with this particular drug, but the variations found in this case *do not* represent an immediate hazard to patients for whom the drug has been prescribed.

However, the manufacturer, Endo Laboratories, agreed that the tablets should be withdrawn from the market since they do not meet potency standards of the U.S. Pharmacopeia. Pharmacists will be notified of the lots to be returned. The recall involves only a small part of the supply of this drug on the market.

ENDO LABORATORIES INC.,
Garden City, N.Y., October 14, 1967.

IMPORTANT—DRUG RECALL

Re Coumadin (sodium warfarin).

We are recalling from the market certain specific lots of Coumadin Tablets 2 mg., 2½ mg., and 5 mg., because recent re-assays have shown these lots to be above or below the allowable limits of label strength as follows:

Product	Packaging lot No.	Package size
Coumadin, 2 mg	5020	Bottles of 100 and 1,000.
Do	7C0140	Bottles of 100.
Do	7C0141	Do.
Do	7C0142	Bottles of 1,000.

Whereas the allowable lower limit of 2 mg. Coumadin Tablets is 1.90 mg., the above lots range from 1.68 mg. to 1.86 mg. per tablet.

Product	Packaging lot No.	Package size
Coumadin, 2½ mg	5171	Bottles of 25, 100, and 1,000.
Do	6129	Do.
Do	7B0105	Bottles of 100.
Do	7C0156	Do.
Do	7C0157	Bottles of 25.
Do	7C0158	Bottles of 1,000.
Do	7D0236	Bottles of 100.
Do	7F0235	Do.

Whereas the allowable lower limit of 2½ mg. Coumadin Tablets is 2.375 mg., the above lots range from 2.29 mg. to 2.32 mg. per tablet.

Product	Packaging lot no.	Package size
Coumadin, 5 mg	5191	Bottles of 100.
Do	6152	Do.
Do	7E0118	Do.
Do	7E0322	Do.

Whereas the allowable upper limit of 5 mg. Coumadin Tablets is 5.25 mg., the above lots range from 5.49 mg, to 5.56 mg. per tablet.

Only the above packaging lots are involved.

Please return *only these lots* of Coumadin immediately as follows:

1. Fill out and *enclose* the packing slip with the merchandise.
2. Use the enclosed postage paid address label on the package. No stamps required. Do not insure.

We will immediately replace the merchandise returned.

This recall is being made with the knowledge of the Food and Drug Administration.

We appreciate your assistance.

Sincerely yours,

ENDO LABORATORIES INC.

ASTRA PHARMACEUTICAL PRODUCTS, INC.,
Worcester, Mass., August 23, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call to your attention two of our recent mailing pieces for Citanest® which the FDA regards as so substantially misleading and lacking in adequate professional use information that in its view they represent potential hazards to health. These mailing pieces, identified as 118–67 and 119–67, should be discarded if still in your possession.

1. Intravenous Regional Anesthesia

Mailing piece 118–67 recommended the use of Citanest in intravenous regional anesthesia. The FDA regards use of this drug by that technique as experimental. The package insert for Citanest contains no information for its use in intravenous regional anesthesia and the drug has not been approved for used in that procedure.

2. Maxiumum Single Dosage

Mailing pieces 118–67 and 119–67 contained statements which implied that dosages of Citanest in excess of the maximum single dose (600 mg.) could be employed in clinical use. No such implication was intended by Astra, and Astra reaffirms that no more than 600 mg. of the drug should be used during any two-hour period.

3. Professional Use Information

Both booklets omitted essential and required professional use information. The attached page contains the warning, precautionary, and adverse reaction information which was omitted from the "full disclosure" sections of the booklets.

The safety and effectiveness of Citanest (prilocaine), when used in accordance with the conditions specified in the enclosed package insert, are not in question.

Sincerely yours,

ASTRA PHARMACEUTICAL PRODUCTS, INC.

NEISLER LABORATORIES, INC.,
SUBSIDIARY OF UNION CARBIDE CORP.,
New York, N.Y., August 11, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement for Diutensen-R which the FDA regards as misleading.

The Food and Drug Administration regards the warning information in the ad to be so substantially deficient that the ad represents a potential danger to health. Therefore, we have rewritten our "Brief Summary", and the nature and extent of the changes are shown in capital letters in the attached revision. We have discontinued the ad in question and all future ads will carry the new "Brief Summary".

The safety and efficacy of Diutensen-R are not in question when used in accordance with the prescribing information in the official package insert.

Sincerely,

NEISLER LABORATORIES.

SMITH KLINE & FRENCH LABORATORIES,
Philadelphia, Pa., July 1967.

DEAR DOCTOR: Smith Kline & French has recently received reports of auditory and visual hallucinations and of disorientation and confusion which occurred in patients during the administration of "Vontrol" (brand of diphenidol), our drug for control of vertigo, and nausea and vomiting.

Approximately twenty such cases have been reported. In most of these, the reaction occurred within two days after the start of "Vontrol" in the recommended dosage and subsided spontaneously, usually within 24–48 hours after the drug was stopped. Although most of these patients had been receiving other drugs, "Vontrol" is believed to be the causative agent. We have not been able to establish a correlation between the reaction and any concomitant therapy nor have we been able to relate the reaction to sex or any specific age group.

Because it is impossible at this time to identify the individual patient in whom this reaction might occur, and because there is no specific treatment for this reaction other than allowing it to run its course (usually 24–48 hours after stopping the drug), the benefit to be derived from the use of this drug must be weighed against the risk of this serious and potentially dangerous reaction.

In view of the above, the use of "Vontrol" (brand of diphenidol) should be limited to hospitalized patients or to patients under comparable continuous close professional supervision. We shall continue to study the cause and the frequency of this adverse effect.

We have revised the package insert for "Vontrol" (brand of diphenidol) to indicate this limitation and to include a warning regarding this reaction. A copy of the revised package insert is enclosed bearing the limitation legend and warning as follows:

Vontrol (brand of diphenidol)

Use Limited to Hospitalized Patients or Patients Under Comparable Continuous Close Professional Supervision

Warning: Use limited to hospitalized patients or patients under comparable continuous close professional supervision. Auditory and visual hallucinations, disorientation and confusion have been reported associated with the use of "Vontrol". The frequency of this reaction is unknown. Thus far, the reaction has occurred within two days of starting the drug in recommended dosage and has subsided spontaneously usually within 24 to 48 hours after discontinuation of the drug. Patients on 'Vontrol' (brand of diphenidol) should be observed closely and in the event of such a reaction the drug should be stopped.

We are continuing to report the available information to the Food and Drug Administration. If you should observe a similar reaction during treatment with "Vontrol" (brand of diphenidol) please send us full information concerning your case.

Sincerely yours,

MAURICE R. NANCE, M.D.,
Medical Director.

FLINT LABORATORIES,
DIVISION OF TRAVENOL LABORATORIES, INC.,
Morton Grove, Ill., July 20, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the initial advertisements for Choloxin® (sodium dextrothyroxine), currently appearing in several journals, which are regarded by the FDA as misleading.

The headline, "A significant new advance in the management of hypercholesterolemia", does not include the qualification that Choloxin is indicated for the treatment of hypercholesterolemia in selected patients, i.e., euthyroid patients with no known evidence of organic heart disease. Also, the ads fail to stress that Choloxin is not intended to replace or to lessen the desirability of considering dietary regulation in the management of hypercholesterolemia.

The FDA points out that, while the ads emphasize that Choloxin effectively lowers blood cholesterol levels, they fail to emphasize that this effect has not been proven to alter the morbidity and mortality of atherosclerotic disease. The claim in the ads that Choloxin (sodium dextrothyroxine) is "significant in its accepted physiologic mode of action" is considered to oversimplify the extent of knowledge of its mode of action. Further, the reference to "over 6,000 patients

treated in clinical studies" overstates pertinent clinical experience, since only 2,967 patients were in the diagnostic categories for which the drug is currently indicated.

The FDA also considers the summary of warning information in the ads to be incomplete. The enclosed "Brief Summary" contains information in capital letters that was not present in the current ads, but will be incorporated into future ads for Choloxin. We are discontinuing the ads in question. The safety and efficacy of Choloxin are not in question when used in accordance with the official package circular, which remains unchanged.

Sincerely,

THOMAS A. GARRETT,
Vice President, Medical Affairs.

EATON LABORATORIES,
Norwich, N.Y., July 10, 1967.

Urgent: Drug Recall—Furacin® Solution Aerosol, 1 oz., all lots.

DEAR DOCTOR: There is a possibility that absorption of hexylene glycol, one of the components of the base used in Furacin *Aerosol* may cause coma if used in relatively large quantities on severely burned patients.

We have discontinued sales of the product and are withdrawing all existing stocks of Furacin *Aerosol* from the market.

Please destroy any of the *Aerosol* which you have in your possession. (Do not incinerate.) Prescriptions for the product will not be filled.

This problem concerns only the base of the *Aerosol* formulation. No other Furacin formulation contains hexylene glycol. This notice does not involve any other Furacin product.

We have had two reports of possible reactions of this class involving the use of the *Aerosol*, both occurring in infants with large area burns. Both children recovered upon cessation of therapy. In both cases, there is evidence to indicate that other causes may have been involved.

We regret that this action is necessary. Your cooperation is sincerely appreciated.

EATON LABORATORIES.

MEAD-JOHNSON LABORATORIES,
Evansville, Ind., June 30, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to current medical journal advertisements for Oracon and Questran which the FDA regards as misleading.

Oracon®

The ad claims that the drug provides ". . . oral contraception with effects which closely parallel those of the natural hormonal cycle" and also contains a related slogan implying such effects are "So Close to Nature." The FDA points out that not neary all effects of oral contraceptives parallel those of the natural hormonal cycle and that some of the effects of these drugs are of profound or undetermined nature.

The ad emphasizes the low incidence of certain less serious side effects such as amenorrhea, breakthrough bleeding, weight gain, etc. However, it fails to give adequate emphasis to more serious known side effects—or adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism or cerebral vascular accident.

The FDA points out that the pregnancy rates claimed in the ad were incorrectly based on 1065 women instead of only 880, and that the ad improperly features a pregnancy rate of 0.2 per 100 woman-years. While available data do not provide a reliable scientific basis for a statement of true pregnancy rates, experience reported to us shows that the unadjusted rate for all women who were given Oracon was 2.0 per 100 woman-years. The rate of 0.2 used in the ad included only those patients who insisted that they had adhered to the regimen.

Questran®

The FDA considers the summary of warning information in the journal advertisement for Questran to be inadequate in that it did not contain any information on precautions and warnings. We have attached a revised "Brief Sum-

mary," which contains the omitted precautions and warning information in capital letters.

We are discontinuing the ads in question, and future advertising will incorporate the above corrections. The safety and effectiveness of Oracon and Questran are not in question when the drugs are used in accordance with the official package inserts.

Sincerely,

P. A. WALTER, M.D.,
Director, Medical Research Deparmtent.

GEIGY PHARMACEUTICALS,
DIVISION OF GEIGY CHEMICAL CORP.,
Ardsley, N.Y., June 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to recent journal advertisements for our products (Hygroton® and Regroton®) which the FDA considers to be misleading.

Hygroton advertisement

This ad is headlined, "Do your patients shell out too much for a diuretic?". It states that a published report on a new short-acting diuretic supports the claim that "If one considers maximum recommended doses for each product, tablet for tablet Hygroton was clearly superior. Two tablets of Hygroton were found to produce almost 40% more natruresis and 20% more weight loss than five tablets of the other diuretic."

The FDA points out that the studies were based on small numbers of patients (6 to 13), that the actual differences repored were clinically insignificant, and that the ad's claim for superiority was not supported by the data or by the authors' conclusions. Further, the report was not a direct comparative study of the two drugs, but rather a comparison of data obtained on the new diuretic with data obtained on Hygroton in a previous study.

In addition, the table-for-tablet comparison in the ad is not regarded as sound because single tablets of Hygroton and the other diuretic do not contain comparable therapeutic dosages.

Regroton advertisement

This ad displays a single Regroton tablet in relation to two sets of five tablets representing drug regimens for treating hypertension. The ad states that "in moderate hypertension" Regroton was "better than reserpine+hydralazine+hydrochlorothiazide in 41 of 43 patients and better than reserpine+methyldopa+hydrochlorothiazide in 34 of 37 patients". These numbers, taken from a paper referenced in the ad, refer specifically to a comparison of average mean blood pressures after two years on Regroton with responses to prior therapy utilizing the other drug combinations.

The FDA points out that the differences observed in the blood pressure response to the various treatments were neither statistically nor clinically significant. Further, the study was not done on patients diagnosed as "moderate hypertension", and the authors did not state that the effect of Regroton on the patients' blood pressure was "better".

The FDA also considers the summary of prescribing information in each ad to be inadequate. Each enclosed "Brief Summary" contains information in capital letters that was not included in our current ads. We are discontinuing the ads in question and future advertising will incorporate the revised "Brief Summary". The safety and effectiveness of the products are not in question when used in accordance with the official package inserts.

GEIGY PHARMACEUTICALS.

PFIZER LABORATORIES,
DIVISION, CHAS. PFIZER & CO., INC.,
New York, N.Y., May 22, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to recent promotional messages for our products (Rondomycin, Renese, and Renese-R) which the FDA regards as potentially misleading.

Renese and Renese-R

The monograph in the 1967 *Physicians' Desk Reference* for Renese and Renese-R is considered inadequate in presenting information necessary for their safe and effective use. To provide you with the necessary additional information, we are enclosing a revised monograph for insertion into your *PDR*. The changes include additional warnings and precautions concerned with electrolyte imbalance, hepatic coma, maintenance dosage, and, in the case of Renese-R, the possibility of Parkinsonism and confusion.

Rondomycin

The FDA has also asked us to call to your attention certain features of our current advertising for the broad spectrum antibiotic, Rondomycin. The ad does not disclose that it is a member of the bacteriostatic tetracycline family and that administration for ten days is especially important in the treatment of Beta-hemolytic streptococcal infections. In referring to the "Protective dose (PD_{50}) tests," the ad did not specify that they were performed in mice utilizing laboratory strains of organisms injected intraperitoneally. While demonstrating the activity of Rondomycin against these test strains, the PD_{50} tests cannot be extrapolated directly to the clinical situation, in which sensitivity testing is recognized to be important for selection of the most appropriate antibiotic for a specific patient's infection.

In addition, the "Brief Summary" of warning information in the above ad, and also in the current journal ad for Renese-R, is considered inadequate. We are modifying the advertisements in question and future advertising will include the requested additional warning information.

Sincerely yours,

JOHN L. WATTERS, M.D.,
Medical Director.

ABBOTT LABORATORIES,
North Chicago, Ill., April 13, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement on Enduron® (methyclothiazide) and Enduronyl® (methyclothiazide and deseripidine). The advertisement, headlined "Thiazide-potassium problems, doctor?" is regarded by the FDA as misleading.

The ad states that the advertised drugs provide "excellent sodium output with less potassium loss than either chlorothiazide or hydrochlorothiazide."

The consensus of expert medical opinion is that there is no significant difference in the amount of potassium loss caused by thiazide agents, including methyclothiazide (Enduron).

The ad suggests that any physician taking a patient off a thiazide-potassium combination may wish to consider Enduron as alternative therapy. It states that the product will "do an outstanding job for you, *without* routine potassium supplementation," and that it has "potassium-sparing characteristics." The FDA believes that these claims could lead to the erroneous conclusion that hypokalemia is less likely to occur, and consequently, that potassium supplementation is less often necessary with Enduron than with other thiazides.

In point of fact, the need to consider proper potassium supplementation, dietary or otherwise, is no less with Enduron or Enduronyl than with any other thiazide drug.

Because the ad's "brief summary" of warning information was considered inadequate, a new one is enclosed. The information capitalized in the attached revised "brief summary" is not present in current ads, but will be incorporated into future ads for these products.

ABBOTT LABORATORIES.

WALLACE PHARMACEUTICALS,
DIVISION OF CARTER-WALLACE, INC.,
Cranbury, N.J., March 31, 1967.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are calling your attention to one of our recent advertisements captioned, "*The published clinical studies indicate: 3 of 4 non-psychotic depressions respond to 'Deprol'.*" The FDA considers that this advertising may have been misleading.

In the advertisement, we listed 21 studies comprising the total published "Deprol" literature containing data on *non-psychotic* depressions. While the ad does not reflect the fact, data from these studies were *excluded* in whole or in part if—

(*a*) the diagnosis was not entirely clear;

(*b*) the recommended maximum dose of 6 "Deprol" tablets per day was exceeded;

(*c*) other psychotropic drugs or electroshock were part of therapy.

Moderate, marked, excellent, and complete responses were counted as favorable, while mild, fair, slight, and no responses were counted as unfavorable.

Using the above criteria, the final number of patients included was 323 selected from ten of the 21 listed studies. Nine of the ten studies were uncontrolled, and most patients in the ten studies concomitantly received informal or structured psychotherapy. The reported therapeutic results (ranging from 0% in a study with two non-psychotic depressed patients, through 64% in a study with 53 such patients, to 90% in two studies with 38 and 41 such patients respectively) also include, to an undetermined degree, placebo responses and spontaneous remissions known to occur in the therapy of neurotic depression.

The factors noted above represent problems that exist in working with any literature and are present in some "Miltown" advertisements carrying the theme "one of a series". In order to avoid any misunderstanding, we have discontinued the use of these "Miltown" advertisements as well as the described "Deprol" advertisement.

Sincerely,

WALLACE PHARMACEUTICALS.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., March 15, 1967.

IMPORTANT PRESCRIBING INFORMATION

DEAR DOCTOR: The association of ulcerative stenotic lesions of the small bowel with the use of coated tablets of potassium chloride alone or combined with thiazide diuretics has been generally recognized by the medical community.

In March 1965 a warning paragraph was placed in the labeling of coated potassium chloride products, including those combined with thiazides, and of the thiazides themselves, pointing out this hazard. Since that time there has been a decline in the number of reported cases of this lesion.

That the hazard still exists is shown by the 75 cases reported to have occurred since the warning was issued. Of these, 63 were associated with the combined thiazide-potassium chloride products, 6 with thiazide where coated potassium chloride tablets were administered separately, and 6 with thiazide where it is not known if potassium chloride tablets were administered. Of the cases reported, 54 involved surgery, 51 of which were associated with the combination preparations. Among these cases, 12 deaths were reported, but as yet a definite causal relationship to the medication has not been established. Current data provide neither a determination of the frequency of occurrence of the lesion, nor conclusive evidence of a dose-related effect. Animal studies do suggest that the important etiologic factor is a high concentration of potassium chloride in contact with the mucosa. All the thiazide-potassium preparations are capable of causing the lesion in the monkey.

In view of this, the Food and Drug Administration has directed the manufacturers of thiazide-potassium chloride preparations to limit the indications for use in the package insert and other labeling to the following:

(Trade Name-Generic Name) is indicated for Thiazide-Responsive Edema of Cardiac, Rental or Hepatic failure, chronic steroid administration, and for hypertension, but only where development of even a mild degree of Hypokalemia might have serious consequences.

Note: (Trade Name-Generic Name) in the recommended dosage may not alone provide sufficient potassium to prevent hypokalemia in chronic Diuresis. (Trade Name-Generic Name) should never be used for the treatment of Hypokalemia.

We have further directed that the package insert and other labeling for potassium-thiazide preparations which also contain reserpine or rauwolfia be similarly revised. These preparations will be limited in their indications to the

treatment of hypertension where the development of mild hypokalemia might have serious consequences.

The following preparations will be affected by these required labeling changes:

Merck Sharp & Dohme

HydroDIURIL-Ka (hydrochlorothiazide with potossium chloride); Hydropres-Ka (hydrochlorothiazide reserpine, potassium chloride).

Eli Lilly & Co.

Anhydron K (cyclothiazide with potassium chloride); Anhydron KR (cyclothiazide with potassium chloride and reserpine).

E. R. Squibb & Sons

Naturetin c K (bendroflumethiazide with potassium chloride); Rautrax (rauwolfia serpentina whole root, flumethiazide potassium chloride); Rautrax-N Modified (rauwolfia serpentina whole root, bendroflumethiazide with potassium chloride); Rautrax-N (rauwolfia serpentina whole root, bendroflumethiazide with potassium chloride).

Ciba Pharmaceutical Co.

Esidrix-K (hydrochlorothiazide and potassium chloride).

It should be noted that the labeling for all capsules or tablets which provide 100 mg. or more of potassium per dosage unit or in the case of liquid preparations 20 mg. of potassium per milliliter are required to contain the warning concerning the occurrence of ulcerative-stenotic bowel lesions or directions for dissolving or diluting the preparation adequately to minimize the possibility of gastrointestinal injury. Potassium preparations with this potential hazard should be used only when adequate dietary supplementation is not practical.

To assist us in further evaluation of this problem, the Food and Drug Administration would appreciate your reporting to us any cases of the small bowel lesion associated with the use of thiazide and potassium preparations either alone or in combination.

Your cooperation will be greatly appreciated.

Sincerely yours,

HERBERT L. LEY, Jr., M.D.,
Director, Bureau of Medicine.

ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LA ROCHE, INC.,
Nutley, N.J., March 10, 1967.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are extending the "brief summary" of prescribing information for Librium® (chlordiazepoxide HCl) which appears in medical journal advertisements by adding several phrases and items from the unchanged official package circular.

The revised "brief summary" for medical journals is attached, indicating by capitalization the requested added material. Prescribing information in all Librium (chlordiazepoxide HCl) package circulars, direct mail information and brochures is complete and requires *no* change. The safety and effectiveness of the product are *not in question.*

In addition, in future medical journal advertisements for Librium (chlordiazepoxide HCl) in geriatric patients, we are amplifying statements which have appeared concerning possible side effects and initial dosage:

The statement that "Side effects in most instances are mild in degree and readily reversible with reduction of dosage," will be extended by the observations made in our package circular which point out that drowsiness, ataxia and confusion have been reported in some patients, particularly the elderly and debilitated, occasionally at lower dosage ranges, and that in a few instances syncope has been reported.

Whereas in geriatrics, the *usual daily dosage* is 5 mg, two to four times daily, the *initial dosage* in elderly and debilitated patients should be limited to 10 mg or less per day, adjusting as needed and tolerated.

We hope the additional detail in medical journal advertising clarifies the use of the product in accordance with the enclosed package circular.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

ORTHO PHARMACEUTICAL CORP.,
Raritan, N.J., February 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that a claim in our recent advertising of ORTHO-NOVUM SQ* may be misleading.

In our introduction of this product to the medical profession we featured the theme, "The Most Effective Sequential", based on a comparison of pregnancy rates published in manufacturers' package inserts. The Food and Drug Administration has pointed out that such a comparison is invalid because there has been neither a direct comparative study of the efficacy of the three sequential oral contraceptives in the same population nor individual studies of the three products in population groups shown to be comparable. We are therefore discontinuing the promotional theme in question.

ORTHO PHARMACEUTICAL CORPORATION.

CARNRICK LABORATORIES,
DIVISION OF G. W. CARNRICK, CO.
Summit, N.J., January 10, 1967.

IMPORTANT NOTICE

DEAR DOCTOR: This is to bring to your attention a *possible incorrect identification of sample tables* mailed to you.

During the latter part of December you were mailed an extra long (11 inch) envelope which contained an almost equally long product sample folder and the Carnrick Classified.

This sample folder was actually three product samples in one, which could be detached from one another by simply separating at the perforated lines.

The 3 product samples contained were Bontril Timed No. 1, 3-layer (yellow, white and orange) tables for obesity; Hormonin No. 2, 2-layer (blue and white) tablets for menopause; and Sinulin (peach colored) tablets for sinus headache.

However, a small number of the sample folders were produced with the Bontril Timed tablets attached to the Sinulin segment of the folder and vice versa.

We regret this error and would sincerely appreciate your cooperation in discarding this sample material.

A new mailing will be reaching you soon.

Sincerely yours,

ROBERT G. DAVIS,
Medical Service Department.

MERCK SHARP & DOHME,
DIVISION OF MERCK & CO., INC.,
West Point, Pa., December 20, 1966.

DRUG SAFETY INFORMATION

DEAR DOCTOR: From time to time, we have sent you new information regarding "Indocin" (indomethacin) as greater clinical experience is gained. At this time, I would like to reiterate that the drug should be used only in those conditions which are indicated in the package circular and it should not be prescribed for children because safe conditions for use have not been established.

We are reminding the physician of this by placing an important note to this effect at the beginning of the package circular, a copy of which is enclosed. There are a few other changes in the circular and for easy recognition these have been put in boldface print.

Sincerely yours,

FREDERICK K. HEATH, M.D.
Vice President, Professional Communications.

THE UPJOHN CO.,
Kalamazoo, Mich., November 9, 1966.

DEAR DOCTOR: Recently you probably learned that a token quantity of one of our products had been seized by order of a U.S. District Court at the request of

the Food and Drug Administration because of an advertisement in the Journal of the American Medical Association. Because of confusion which has resulted from this action, we are enclosing for your information a public statement which we have made concerning it.

At issue here is the clarity of the regulations concerning medical advertising.

Our product Lincocin, the effectiveness and safety of which has *not* been questioned, has *not* been removed from the market.

We invite you to continue to prescribe Upjohn products. They are fine products based on Upjohn research and presented to the medical profession by an organization which does identify itself with the best principles and practices of American science and medicine.

Very truly yours,

J. C. GAUNTLETT,
Vice President for Pharmaceutical Marketing.

MERCK SHARP & DOHME,
DIVISION OF MERCK & CO., INC.,
West Point, Pa., October 1966.

DEAR DOCTOR: It is only natural that with over 144,000,000 patient days of therapy in 99 countries, we have added to our cumulative knowledge of Indocin ® (Indomethacin) in the treatment of arthritic disorders. This greater experience is reflected in the revisions contained in the enclosed package circular. These revisions will be made in all promotional material and package inserts as rapidly as possible.

While we urge you to acquaint yourself with the entire package circular as revised, we want to call your attention to one change in particular:

"In common with other drugs which have anti-inflammatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in intiating appropriate treatment of the infection. Indomethacin should be used with caution in patients with existing, but controlled, infections."

This and other important changes in the package circular have been set in boldface type so that you may find them easily. They should assist you in the more effective use of Indocin—which has become, next to aspirin, the most frequently prescribed antirheumatic drug.

Sincerely yours,

FREDERICK K. HEATH, M.D.,
Vice President, Professional Communications.
E. R. SQUIBB & SONS, INC.,
New York, N.Y., July 8, 1966.

IMPORTANT DRUG RECALL—STREPTOMYCIN SULFATE INJECTION

DEAR DOCTOR: Since February of this year we have been distributing Streptomycin Sulfate Injection U.S.P. of a slightly modified formulation for improved color stability. Although this formulation still meets all legally required standards, data recently accumulated with the more stringent Squibb standard for mouse acute toxicity lead our scientific staff to suspect that this formulation, at a future date, may not continue to meet the regulatory standard. It should be noted that to date, we have received no reports of unusual human toxicity related to this formulation; however, it is our opinion that its use should be discontinued.

In keeping with the traditional Squibb policy for quality, we have decided to recall this formulation from the market.

If you have material in your possession bearing the following control numbers, we *urgently* request that you *promptly* return it to the source from which you obtained it. Appropriate credit will be arranged.

List No.	Product description	Control No.
84221	Streptomycin sulfate injection 0.5 gm/cc. 2 cc. vial	5M811 6C672
84231	Streptomycin sulfate injection 0.5 gm/cc. 10 cc. vial	5M908 5M835 6D999
84826	Streptomycin sulfate injection 0.4 gm/cc. 2.5 cc vial	5W748

These control numbers are the only ones involved.

The above action has been discussed with and agreed to by the scientific staff of the Food and Drug Administration.

We sincerely regret this incident and request your cooperation by promptly returning the material.

NEISLER UNION CARBIDE,
June 7, 1966.

DEAR DOCTOR: This is a drug recall notice.

Please immediately stop using all stocks of *Unitensen Aqueous.* Return to us by insured parcel post your complete inventory of *Unitensen Aqueous.* Do not include any other merchandise with this shipment.

Neisler Laboratories, Inc. will issue full credit to you and also reimburse you for the parcel post expenses.

This recall notice is being sent you because our current laboratory tests indicate that the potency of some batches of *Unitensen Aqueous* may sometimes diminish during storage under some conditions. Pending further work we are recalling this product. The Food and Drug Administration has been advised of our action.

We have *not* received any reports indicating a lack of safety or efficacy for *Unitensen Aqueous.* Our decision to withdraw the product is solely based on the fact that it appears to have inadequate shelf stability.

Sincerely,

GERAAD G. HUNT,
Executive Vice President.

CHAS. PFIZER & CO., INC.,
New York, N.Y., May 18, 1966.

Re Buclizine-containing drugs.

DEAR DOCTOR: The Food and Drug Administration has requested that the package inserts for buclizine-containing products be revised to contain the following statement:

"Contraindication: Buclizine, when administered to the pregnant rat, induced fetal abnormalities at doses above the human therapeutic range. Clinical data are not adequate to establish nonteratogenicity in early pregnancy. Until such data are available, buclizine is contraindicated for use in early pregnancy."

Buclizine is contained in Pfizer Laboratories' Terracydin Capsules, and in J. B. Roerig's Tetracydin Capsules and Tao AC Capsules.

We have obtained F.D.A. approval to remove buclizine from each of these products in order to eliminate this contraindication to use in pregnancy. All new production of these products will omit buclizine from the formulations.

However, we have on hand a sizable inventory of each of these drugs containing buclizine not yet finally packaged and which will not be exhausted for several months. This inventory will contain a package insert which includes the contraindication quoted above.

Sincerely yours,

J. RALPH FOWLER, M.D.,
Medical Director,
J. B. Roerig & Co.

JOHN L. WATTERS, M.D.,
Medical Director,
Pfizer Laboratories.

CHAS. PFIZER & CO., INC.,
New York, N.Y., May 18, 1966.

DEAR DOCTOR: The purpose of this letter is to call to your attention in the contraindication and precaution sections of the package inserts for our drugs which contain hydroxyzine or meclizine, revisions which pertain to use during pregnancy. These revisions have been requested by the Food and Drug Administration.

The package inserts for products containing hydroxyzine have been revised to include the following statement:

"Contraindication: Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy."

The clinical use of hydroxyzine as an adjunct to the management of labor has been extensively reported in the literature without evidence of harm to the mother or fetus.

PRODUCTS CONTAINING HYDROXYZINE

Pfizer Laboratories
Vistaril Capsules
Vistaril Oral Suspension
Vistaril Parenteral
Ataraxoid Tablets

J. B. Roerig
Atarax Tablets and Syrup
Atarax Parenteral Solution
Cartrax Tablets
Marax Tablets and Syrup
Enarax Tablets
Amplus Capsules

The package inserts for products containing meclizine have been revised to include the following statement:

"Use in Pregnancy: The following information should be taken into account in determining whether the potential benefits of meclizine outweigh the risks of its use in women of childbearing age and particularly during pregnancy. A review of available animal data reveals that this drug exerts a tertogenic response in the rat. While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human fetus. Consequently, consideration should be given to initial use of a nonphenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum."

PRODUCTS CONTAINING MECLIZINE

Pfizer Laboratories
Bonine Tablets

J. B. Roerig
Bonadoxin Tablets and Drops
Antivert Tablets and Syrup

Meclizine when administered to the pregnant rat, mouse and rabbit induced fetal abnormalities in the rat only at doses substantially above the human therapeutic range. (For details of animal studies please see enclosed package insert.)

An estimated billion doses of meclizine-containing drugs have been consumed in this country alone since 1953, including an estimated one million prescriptions annually for pregnant women in recent years. While there have been a number of malformations associated with the use of meclizine, the evidence is inconclusive as to causation since malformations also occur among the offspring of mothers who take other drugs or no drugs at all.

As you no doubt are aware, as increasing scientific attention is being focused on the subject of teratology, studies are demonstrating that a fairly impressive number of drugs, when administered to laboratory animals, generally at doses substantially exceeding the comparable human dose, produce malformations among the offspring. Regrettably, the end point of scientific knowledge in the field of teratology is not at hand.

In conclusion, we fully endorse the well established medical principle that care should be exercised in the use of any drug during pregnancy.

Sincerely yours,

J. RALPH FOWLER, M.D.
Medical Director,
J. B. Roerig & Co.
JOHN L. WATTERS, M.D.
Medical Director,
Pfizer Laboratories.

THE STUART CO.,
DIVISION OF ATLAS CHEMICAL INDUSTRIES, INC.,
Pasadena, Calif., May 10, 1966.

DEAR DOCTOR: We have just been advised by the Food and Drug Administration of conclusions reached by that agency concerning the teratogenicity of buclizine in rats. FDA has decided that buclizine should be contraindicated for use in early pregnancy. Recent data, including animal experiments still in progress in our Bio-Medical Research Laboratories, indicate that buclizine (an active ingredient in Bucladin and Softran) induces a teratogenic response in rats when administered at dosage levels substantially higher than the maximum recommended dose for humans. These findings are at variance with earlier experiments in mice and rats performed by others which disclosed no indication of teratogenicity at high dosage levels. We accept the FDA decision in this matter even though our own animal experiments are still inconclusive and we have not had an opportunity to examine the data or reports upon which the agency's decision is based.

We have been requested to add the following caution to the labeling for Bucladin and Softran:

CONTRAINDICATIONS

Buclizine, when administered to the pregnant rat, induced fetal abnormalities at doses above the human therapeutic range. Clinical data are not adequate to establish non-teratogenicity in early pregnancy. Until such data are available, buclizine is contraindicated for use in early pregnancy.

Since the nausea and vomiting of pregnancy (an indication for Bucladin) are not usually of a critical nature and can generally be controlled by other means, it does not seem feasible to conduct extensive clinical experimentation in women in early pregnancy to establish beyond doubt the non-teratogenicity of buclizine.

Bucladin was introduced in 1957. In this period of almost nine years, there have been no reports received by Stuart of human malformations in which it could be established that buclizine was the causative agent. Because of this extensive history of use in pregnancy without demonstrated teratogenic effect, there does not appear to be reasonable cause for concern among your pregnant patients who have taken Bucladin or Softran.

The Stuart Company will continue to make Bucladin and Softran available on prescription for use by your patients when indicated at any time except during early pregnancy.

Sincerely yours,

R. J. KROENERT, *General Manager.*

CHAS. PFIZER & CO., INC.,
New York, N.Y., April 27, 1966.

DEAR DOCTOR: The purpose of this letter is to request that you promptly destroy all samples of our Pfizer Laboratories and J. B. Roerig divisions, which are in your possession. We make this request because we have detected some instances of mislabeling of drug samples which were packaged and labeled for us by outside suppliers.

This request is made because we fully share with you the high degree of importance attaching to the integrity of any drug sample given to a patient. We have every confidence that our request will meet with your sympathetic understanding, and your aquiescence to our request.

It is important to emphasize that the instances of sample mix-ups that we have discovered all involve samples packaged by outside suppliers which we and other pharmaceutical manufacturers use from time to time for this purpose. We realize that you have no way of knowing which of the samples you have were

packaged and labeled internally by us, so in the interest of expediency we are asking you to destroy all Pfizer Laboratories and J. B. Roerig samples.

As to trade packages of Pfizer Laboratories and J. B. Roerig drugs, you can have every confidence that when the pharmacist fills your prescriptions for these products they will continue to meet every applicable standard of identity, quality, purity and labeling.

Needless to say, we regret this situation and any inconvenience it causes you and we assure you that every step is being taken to prevent its recurrence. We will expend every effort to replenish your supply of Pfizer drug samples as rapidly as possible but if at any time you are faced with a need for samples, in the interim, may we suggest that you contact your Pfizer Laboratories or J. B. Roerig professional service representative.

Sincerely yours,

J. PHILIP SMITH,
Group Vice President.

MERCK SHARP & DOHME RESEARCH LABORATORIES,
DIVISION OF MERCK & CO., INC.,
West Point, Pa., April 13, 1966.

Subject: Association of positive Coombs test with Aldomet® therapy.

I should like to call your attention to a recent addition we have made in the enclosed package circular for our product Aldomet (methyldopa). You will find the new reference encircled in the Side Effects section of the circular. The same change will be made in the Aldoril® package circular.

As background, there has been a recent report in the British literature by Carstairs, Worlledge, Dollery and Breckenridge. They noted two patients in whom hemolytic anemia with a direct positive Coombs test developed after more than one year of treatment with Aldomet. They have reported also observations of a positive antiglobulin (Coombs) reaction in six patients receiving Aldomet in whom there was no evidence of hemolysis, reticulocytosis, or anemia. A copy of their paper is attached.

Further observations during the past few weeks both in England and the United States have confirmed the fact that some patients receiving Aldomet may develop a positive direct Coombs test without demonstrating any evidence of anemia, reticulocytosis or hemolysis. Several studies are now under way to determine the mechanism of these reactions, and whether they are the result of an altered immunologic process or a chemical interference with the Coombs reaction by Aldomet or any of its metabolites.

These observations suggest that if unexplained direct positive Coombs reactions are found in the course of crossmatching studies for transfusions, the possibility should be taken into account that Aldomet is being administered to such patients and might elicit such reactions.

If you have noted this occurrence in your own experience, I would appreciate learning of your observations.

Sincerely yours,

ELMER ALPERT, M.D.

PFIZER LABORATORIES,
DIVISION OF CHAS. PFIZER & CO., INC.,
New York, N.Y., April 1, 1966.

IMPORTANT SAMPLE RECALL

DEAR DOCTOR: In reviewing our inventory of physician samples, we have found a small number of 100 mg. Dibinese (chlorpropamide) tablet samples, lot 46460, incorrectly identified by the card enclosed with them as 250 mg. Diabinese tablets. Because the possibility exists that this incorrect card may have been employed in other samples in lot 46460, we are recalling this entire lot of 100 mg. samples. No other lots are involved, nor are any 250 mg. sample tablets involved.

The sample in question is a unit consisting of a seven-tablet circular plastic dispenser, a large printed card with a brochure in its pocket, and a booklet entitled "If You Have Diabetes," all enclosed in a clear acetate wrapper. Please inspect your total inventory of Diabinese samples of this type. If you have any, remove the booklet and the card containing the brochure. The lot number is em-

bossed in the upper left-hand corner of the foil backing. If the number 46460 appears on any of your samples, please return them to us as indicated below.

We also ask that you contact any patients to whom you may have given Diabinese samples recently. If by chance you received and gave to a patient a sample from this lot identifying the contents as 250 mg. Diabinese, when in fact the contents were 100 mg. tablets, the patient would obviously be taking less medication than you prescribed. Our professional Sales Representatives would have distributed samples from this lot to physicians no earlier than December 15, 1965, so it will be necessary for you to contact only those patients to whom you may have given these samples between December 15th and the date of this letter.

If you find any Diabinese samples from lot 46460, even if they bear the correct card identifying them as 100 mg. tablets, please promptly mail them to: Mr. John Mayreis, Chas. Pfizer & Co., Inc., 630 Flushing Avenue, Brooklyn, N.Y. 11206.

We wish to thank you for your cooperation in this matter, and to express our regrets for any inconvenience it may cause you or your patients. Please let us know if there is anything we can do to assist you.

Very truly yours,

JOHN L. WATTERS, M.D.,
Medical Director

PFIZER LABORATORIES,
DIVISION, CHAS. PFIZER & CO., INC.,
New York, N.Y., March 15, 1966.

IMPORTANT DRUG ALERT

DEAR DOCTOR: During the course of distribution to our Professional Sales Representatives of one lot of professional sample packages of *4 mg.* Renese tablets, we found that some of the white shipping cartons containing 18 sample packages (6 tablets per package) were incorrectly labeled as *2 mg.* Renese tablets, lot 51425. The sample packages themselves are properly labeled as *4 mg.* Renese tablets.

Normally in supplying your needs for professional samples, our Professional Sales Representatives would not have supplied this shipping carton to you. Since we cannot rule this out as a possibility in every case, however, we are taking this opportunity of writing to you.

We therefore ask that you inspect all the Renese tablet professional samples that you have on hand. Please immediately destroy any white shipping cartons you may have in your possession which bear the following information on the flap:

Renese 2 Mg. (6 Tablets), Lot No. 51425, 18 Detail Samples

Whether these white shipping cartons contained 2 mg. tablets (yellow) or 4 mg. tablets (white), the individual sample packages bear the correct identification. Neither the labeling of the sample packages nor the potency of the medication are at all in question.

Should you find as a result of this review of your samples that you require clarification or additional drug, please call upon your Pfizer Laboratories representative. Thank you for your cooperation in this matter.

Sincerely,

JOHN L. WATTERS, M.D.,
Medical Director.

ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LA ROCHE, INC.,
Nutley, N.J., March 9, 1966.

IMPORTANT: DRUG RECALL

DEAR DOCTOR: On February 28, we received a letter from FDA Commissioner James L. Goddard advising us of his intention to remove Madricidin from the market by regulatory means unless we chose immediately to withdraw the product.

Despite our belief that this should not be done, we have no practical alternative but to accede to the demand of the Food and Drug Administration to

immediately suspend sale of this product and to withdraw existing stocks from the market.

It is the contention of the Food and Drug Administration that present evidence for Madricidin does not establish its safety and effectiveness in the treatment of the conditions for which it is recommended and that "hazards" accompanying its use outweigh potential benefits.

However, we should like to make you aware that ever since this preparation was marketed with the accord of the Food and Drug Administration in January 1959, it has been prescribed by physicians for more than two million patients. The Government's position apparently discounts the experience accumulated by thousands of physicians and the hundreds of thousands of patients that have benefited from its use. During the seven years that this product has been available, we have received reports of only five cases of side effects and no reports of Stevens-Johnson syndrome in patients treated with it.

While we believe firmly that the demands of the Food and Drug Administration are inconsistent with this outstanding record, we have no choice but to comply. This is preferable to exposing the physician, his patients, and our company to the possible detrimental effect of the only alternative, government legal action to remove the product from the market.

Recall of Madricidin from patients is not deemed necessary. However, your patients will not be able to refill their present supplies once they have been exhausted, and all samples of Madricidin in your possession should be destroyed.

We regret any inconvenience that this announcement or newspaper stories prior to this letter may have caused you and your patients, and pledge our continuing efforts to safeguard and constructively advance traditional manufacturer-physician-patient relationships.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

WARNER-CHILCOTT LABORATORIES,
Morris Plains, N.J., March 7, 1966.

DEAR DOCTOR: You may be aware of recent publicity concerning legal action taken by the Food and Drug Administration on February 28, 1966 with regard to Peritrate SA, the sustained action dosage form of Peritrate. In connection with this action we believe it is important to bring to your attention the following statement issued on March 4, 1966 by the Commissioner of the Food and Drug Administration:

"It has come to my attention that physicians are receiving calls from their patients asking whether or not they should continue to take Peritrate SA.

"The FDA has never indicated that this drug is unsafe for use for the treatment of angina pectoris and wishes to reassure both patients and physicians that the recent action by FDA against the product was related solely to advertising and other promotional claims made by the manufacturer."

We are gratified that the Food and Drug Administration has made clear that its action has nothing to do with the safety of Peritrate. This prompt action not only represents a fine example of cooperative working relations between industry and government but will serve to allay the fears of those of your patients who may have been calling you.

Peritrate® in all its dosage forms remains available for your prescription.

Sincerely,

FRANK DITRAGLIA, M.D.,
Medical Director.

CIBA PHARMACEUTICAL CO.,
DIVISION OF CIBA CORP.,
Summit, N.J., February 16, 1966.

IMPORTANT DRUG RECALL

DEAR DOCTOR: CIBA Pharmaceutical Company has agreed, at the request of the Food and Drug Administration, to suspend sales of Elipten tablets and withdraw all existing stocks from the market. The Food and Drug Administration considers that there is a lack of substantial evidence that Elipten tablets are effective in the treatment of epilepsy; that it causes adverse reactions including

sexual precocity and masculinization of young females and that labeling with respect to Elipten does not cover all claimed adverse reactions. We are studying these questions raised by the Food and Drug Administration and have agreed to their request that we immediately withdraw all supplies of Elipten from the market.

Because all Elipten stock is being withdrawn, your patients will not be able to refill their present supplies. However, the Food and Drug Administration has agreed that we furnish physicians who request it sufficient supplies to permit patients now on Elipten to be tapered off and transferred to other anticonvulsant therapy. In this connection we draw to your attention the following precaution stated in our Elipten labeling:

"At no time should anticonvulsant drugs be abruptly withdrawn, as this may precipitate a marked increase in frequency of seizures or even status epilepticus."

On the basis of your own experience and in the light of this recall, we trust that you will be able to make whatever adjustments in your patients' therapeutic regimen you deem advisable.

Any stock of Elipten in your possession should be returned to CIBA Pharmaceutical Company, 556 Morris Avenue, Summit, New Jersey, Attention: Return Goods Department.

Sincerely,

C. H. SULLIVAN, M.D.,
Director, Drug Regulatory Affairs.

EATON LABORATORIES,
DIVISION OF THE NORWICH PHARMACAL CO.
Norwich, N.Y., January 18, 1966.

URGENT: DRUG RECALL, FURACIN OPHTHALMIC LIQUID

DEAR DOCTOR: Several recently manufactured lots of Furacin Ophthalmic Liquid have had a significant decrease in potency since the date of manufacture.

Please destroy any samples in your possession.

We have temporarily suspended all sales of this product and have withdrawn all existing stock from the market. We have resolved the difficulty and will resume distribution shortly. In the meantime, prescriptions for this product will not be filled and its use should be discontinued.

This notice pertains to Furacin Ophthalmic Liquid only, not to Furacin Ophthalmic Ointment.

We regret that this is necessary. We shall continue to expend our best efforts to assure you of safe and effective products, always resolving any doubts in favor of your patient's safety and better treatment.

EATON LABORATORIES.

LEDERLE LABORATORIES,
DIVISION, AMERICAN CYANAMID CO.,
PEARL RIVER, N.Y.,
PARKE, DAVIS & CO.,
DETROIT, MICH.,
ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LA ROCHE INC.,
NUTLEY, N.J.,
January 11, 1966.

DRUG WARNING

DEAR DOCTOR: Since 1957 to date, reports in the medical literature have been accumulating concerning the occurrence of Stevens-Johnson syndrome (erythema multiforme exudativum) associated with the use of long-acting sulfonamides.

This is a serious complication since it carries a mortality rate of approximately 25 per cent. To date, 116 cases of Stevens-Johnson syndrome (including 81 cases from the United States) have been reported in association with the use of long-acting sulfonamides. Almost two-thirds of the reported cases were children. In addition to the Stevens-Johnson syndrome, it is also known that serious blood dyscrasias, including aplastic anemia, agranulocytosis, pancytopenia and thrombocytopenia can occur. We are, therefore, taking this opportunity to bring

to your attention the fact that the package inserts of the products listed below are being revised to contain the following prominently displayed warning:

Warning: Fatalities have occurred due to the development of Stevens-Johnson syndrome (erythema multiforme exudativum) following the use of (drugs listed below). Therefore, the patient must be closely observed and should a rash develop during therapy with (drugs listed below), the drug should be discontinued immediately.

(Drugs listed below) is a sulfonamide which maintains a long-lasting blood level due to slow excretion. Because of the long-lasting blood levels, a smaller dosage than is normally employed with shorter-acting sulfonamides should be administered. Since the short-acting sulfonamides are effective for most of the same conditions, their use should be considered before the long-acting sulfonamides are employed.

Serious reactions associated with the use of long-acting sulfonamides should be reported promptly to the manufacturer or to the Food and Drug Administration.

Lederle Laboratories Division

KYNEX® (sulfamethoxypyridazine) Tablets.
KYNEX® ACETYL (n' acetyl sulfamethoxypyridazine) Pediatric Suspension.
AZO KYNEX® (phenylazodiamino-pyridine HCI sulfamethoxypyridazine) Tablets.

Parke, Davis & Co.

MIDICEL® (sulfamethoxypyridazine) Tablets.
MIDICEL® ACETYL SUSPENSION (n' acetylsulfamethoxypyridazine).

Roche Laboratories

MADRIBON® (sulfadimethoxine), Tablets, Chewable Tablets, Suspension, Pediatric Drops.
MADRICIDIN® Capsules: Each capsule contains: sulfadimethoxine, phenindamine tartrate, acetaminophen, caffeine.

ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LA ROCHE, INC.,
Nutley, N.J., December 30, 1965.

IMPORTANT: DRUG RECALL

DEAR DOCTOR: Hoffmann-La Roche, has agreed at the request of the Food and Drug Administration, to suspend sales of Librax® Capsules and withdraw all existing stocks from the market. In view of the widespread use of this product since 1961, we feel that an explanation of the circumstances leading to this withdrawal is in order.

In November, we advised you that we had received isolated reports of enhanced atropine?like side effects in patients on Librax therapy and had determined by the use of new analytical procedures that certain specific batches of Librax contained a trace amount of an analog of the clidinium bromide component which accounted for these effects. At that time, we voluntarily withdrew the involved lots and replaced pharmacists' stocks with capsules which had passed our new analytical procedure. Up to this time we have received no reports of adverse reactions involving this new material.

Because all Librax stock is being withdrawn, your patients will not be able to refill their present supplies once they have been exhausted.

As you know, all new drugs must be the subject of an approved New Drug Application in order to be marketed. We have been advised by the Food and Drug Administration that it was not willing to approve a supplement we had filed to our New Drug Application on Librax, concerning the clidinium bromide component. This supplement contained revised analytical procedures, data on the supplier of clidinium bromide and other technical information. The Librax on the market was produced in accordance with these revisions. As a result, on December 28th the Food and Drug Administration requested us to withdraw all supplies of Librax or the necessary legal steps would be initiated to have it removed since the Librax currently on the market was not produced in accord-

ance with the provisions of the original New Drug Application. Under these circumstances we elected to withdraw the stocks of Librax.

Since clinical experience has shown that Librax can be a valuable therapeutic aid for many patients, and we continue to be convinced that Librax is a safe and effective drug, we shall continue to explore with the Food and Drug Administration means for marketing Librax again as soon as possible. Meanwhile, we regret any inconvenience this may cause you and your patients and pledge our continuing efforts to make available drugs assuring patient benefits in efficacy, safety and practicality.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

ROCHE LABORATORIES,
Nutley, N.J., November 19, 1965.

DEAR DOCTOR: Over the last two weeks we have received isolated reports from widely scattered communities to the effect that a few patients were experiencing enhanced atropine-like side effects in response to Librax therapy, such as blurring of vision, dryness of mouth, urinary hesitancy and constipation.

Assays of the clidinium bromide component of certain of the offending capsules indicated their conformance to the normal rigid quality control standards. Not content with these assays we submitted the capsules to a more critical test—a newly developed thin-layer chromatographic procedure that is far more sensitive than the method heretofore employed. This new procedure will be used in all future assays of the anticholinergic agent in Librax.

The presence of a trace amount of an analog of clidinium bromide at approximately the level of one two-millionths of an ounce per capsule was revealed in certain recently distributed batches of Librax—infinitesimal but sufficient to account for the enhanced atropine-like effects reported.

Therefore, we are voluntarily replacing all involved lots of Librax presently in distribution. Librax is the only Roche product containing clidinium bromide. Your pharmacist will have new stocks within ten days.

Physicians should be alert to the possibility of increased reports of these atropine-like side effects in patients receiving Librax, particularly the elderly and those receiving higher dosages. Therapy should be discontinued in patients who exhibit these symptoms until they can purchase new supplies.

Any Librax samples or trade packages with lot numbers beginning 143—through lot numbers beginning 172—which you presently have on hand should be destroyed. You will receive fresh clinical supplies from your Roche representative or through the mail within the next three weeks by sending the enclosed business reply card.

We want you to know that you can continue to prescribe Librax with confidence based not only on your clinical experience with the drug but also on this further proof of Roche's continuing effort to improve and sustain precise quality control.

A Librax package circular is enclosed for your reference.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

MCNEIL LABORATORIES, INC.,
Fort Washington, Pa., November 12, 1965.

IMPORTANT: SAMPLE LABEL PRINTING ERROR BUTISERPAZIDE®–50, BATCH 8948, DATED 8/10/65

DEAR DOCTOR: During the period October 13 to October 15, 1965, you may have received two folding catch-cover samples of tablets BUTISERPAZIDE–50, which we mailed to physicians in your area. Each such sample folder was labeled correctly on the outside and inside "BUTISERPAZIDE®–50" and contained four, orange BUTISERPAZIDE–50 tablets in transparent film jackets. However, due to incorrect printing, as you will note on the facsimile provided below, the quantitative formula information lists the hydrochlorothiazide content in each tablet as 25 milligrams (⅜ grain) when in fact they contain 50 milligrams (¾ grain); also, immedidately below the formula information, it is stated the tablets are "Colored Green" when in fact they are colored orange. These incorrect sam-

ple folders are all dated *8/10/65*, which is shown on the outside of the folder.

Because of this incorrect quantitative statement of hydrochlorothiazide, it is respectfully requested that you destroy these two sample folders that are in your possession. At the same time, we ask that you sign and return the enclosed postpaid card for our records.

The two sample folders of BUTISERPAZIDE–50 were mailed in a small box together with two similar folding catch-cover sample folders of BUTISERPAZIDE–25, which are correct in every respect and need not be destroyed.

We regret any inconvenience caused you, and will appreciate your prompt attention to this matter.

R. R. SMITH, M.D.,
Medical Director.

PFIZER LABORATORIES,
New York, N.Y., 19, 1965.

DEAR DOCTOR: Subsequent to the market introduction of Tyzine® (tetrahydrozoline HCl) in 1954, infrequent instances of drowsiness have occurred when the drug has been administered to children under two years of age. Marked somnolence or even shock, especially after ingestion of the solution, has been encountered rarely. In every instance the effect has been reversible and without sequelae. A caution regarding the possible occurrence of this syndrome in cases of overdosage has appeared in the Tyzine package circular. Nevertheless, infrequent instance of this effect in children under two have continued to be reported.

Therefore, in consultation with the Food & Drug Administration the Tyzine labelling has been revised to contraindicate its use in children under two years of age.

Tyzine has been successfully employed as a topical nasal decongestant throughout the country for the last 10 years. It continues to be a most valuable therapeutic agent for the relief of inflammatory hyperemia and edema of the nasal mucosa and congestive obstruction of sinus and Eustachian ostia, as may occur in the common cold, hay fever, and other related disorders, in patients over two years of age. Tyzine 0.1% (Spray or Drops) may be used in patients over 6 years of age. Tyzine Pediatria .05% (Drops) should be used in patients from 2 to 6 years of age. For complete dosage and prescription information, please consult the accompanying package circular.

Sincerely,

JOHN L. WATERS, M.D.,
Medical Director, Pfizer Laboratories.

MARCH 1, 1965.

To: All Physicians

From: CIBA Pharmaceutical Company, Division of CIBA Corporation; Merck Sharp & Dohme, Division of Merck & Co., Inc.

We should like to call your attention to the attached reprint entitled "Ulcerative-Obstructive Lesions of the Small Intestine," which appeared in the J.A.M.A. *191*:116–119, Feb. 22, 1965. This article contains the most comprehensive information on this subject to date. You will also be interested in an editorial concerning this subject in the same issue of the Journal.

The available information based on the results of the hospital survey and other reports has implicated coated potassium salts in about half the known patients who have developed the obstructive-ulcerative lesion. Therefore, coated potassium-containing formulations should be administered only when indicated and when adequate dietary supplementation is not practical. Such preparations should be discontinued if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs.

As a result of these findings, Merck Sharp & Dohme, CIBA and the FDA concluded that an informative statement be incorporated in the labeling of appropriate products. Subsequently the FDA has requested *all* manufacturers of thiazide and certain other oral diuretics as well as coated potassium salt preparations to add the following statement to the labeling of all such products:

Warning:

There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration associated with the administration of enteric-coated thiazides with potassium

salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with non enteric-coated thiazides or certain other oral diuretics.

These small bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred.

Based on a large survey of physicians and hospitals, both American and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established.

Available information tends to implicate enteric-coated potassium salts, although lesions also occurred spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs.

Coated potassium tablets should be used only when adequate dietary supplementation is not practical.

ENDO LABORATORIES, INC.,
Garden City, N.Y., October 1964.

DEAR DOCTOR: Since the introduction of Numorphan (oxymorphone) some five years ago, clinical experience has shown that it is a very useful drug in the relief of severe pain. We enclose a file card, brought up-to-date, giving full product information, including precautions, side effects, indications and dose recommendations.

We call your special attention to the fact that the safe use of Numorphan (oxymorphone) in children under 12 years of age has not been established.

Among the advantages of Numorphan for pain relief are the following:

1. Prompt onset of action (10 to 15 minutes).
2. Prolonged duration of effect.
3. Ten times as effective as morphine and 100 times as effective as meperidine, weight for weight.
4. Broad therapeutic index.
5. Tranquility with only slight soporific effect—patients remain alert, capable of cooperation and self care.
6. Infrequency of side effects with recommended therapeutic doses.

Please do not hestitate to write us should you wish to obtain reprints of published articles on the use of Numorphan.

Very truly yours,

ROSS SAYERS, M.D.,
Medical Director.

E. FOUGERA & CO., INC.,
Hicksville, N.Y., April 1964.

IMPORTANT—DRUG RECALL—ORABILEX

Because of reports that Oliguria, renal insufficiency, and death may be associated with repeat doses of Orabilex, this product was withdrawn from the market in January. However, the Food and Drug Administration has advised us that some physicians have failed to return their supplies of Orabilex. In the event that you or your referring physicians have Orabilex on hand, please immediately return all supplies to your vendor for return to us for credit.

DEAR DOCTOR: In 1958, after several years of chemical, pharmacologic and clinical investigation, we introduced the new gallbladder contrast medium, Orabilex. Since that date this product has been employed by physicians throughout the world in several million patients. More than thirty papers have appeared in the medical press of this country alone, attesting to its excellence in providing accurate gallbladder studies.

As you are aware, there have been reports alleging that in rare instances the use of Orabilex has been associated with the development of renal insufficiency. In many of these cases recommended dosage was exceeded or Orabilex was used when cholecystography was contraindicated. In other instances Orabilex was administered concomitantly with other preparations. Also, past extensive toxicity studies under various conditions and at different dose levels failed to reveal any evidence of a nephrotoxic property of Orabilex.

Whereas medical opinion has failed to establish a cause-and-effect relationship, we nevertheless deemed it advisable to withdraw Orabilex from the market pend-

ing further investigation. All channels of supply have been notified of this decision.

We feel we would be remiss if we failed to express in this letter, our sincere thanks for your acceptance of Orabilex, and for your confidence in us as expressed in the many letters we have received. We consider ourselves to be dedicated to the research and investigation of products of service in radiology.

With renewed assurances of our desire to be of service to you, we remain

Sincerely yours,

C. H. BRADNEY,
Executive Vice President.

ABBOTT LABORATORIES,
North Chicago, Ill., April 24, 1967.

DEAR DOCTOR: Attached is a duplicate of a letter we recently sent you on Eutonyl™ (pargyline hydrochloride). Because of the importance of the subject matter, we urge you to read it, if you happened to miss the original.

It places in perspective recent medical information on Eutonyl—and may answer any questions you may have regarding the current status of Eutonyl in treatment of hypertension.

Many thanks in advance for your interest.

Sincerely,

W. D. PRATT,
Professional Services.

P.S.—Also please note the reply card. It will bring a generous supply of samples. Simply sign and mail.

ABBOTT LABORATORIES,
NORTH CHICAGO, ILL.

DEAR DOCTOR: We hope in this letter to clear up any confusion you may have had regarding our recent precautionary letter on Eutonyl™ (pargyline hydrochloride).

Recently, we asked the F.D.A. for permission to include in our literature new precautions relating to ingestion of cheese and also certain statements reemphasizing the need for caution in use of sympathomimetic drugs in patients taking Eutonyl. We also asked to be permitted to send physicians a letter outlining our recommended changes. This permission was granted on Wednesday, February 26, and our letter went into the mail two days later.

That same week, however, doctors were receiving a letter from another manufacturer announcing *withdrawal* (under protest) of another drug from the market. That drug, of course, was Parnate® (tranylcypromine).

We've learned now that the near simultaneous release of the letters has caused some confusion. In fact, quite a few reports have come to us that some physicians have concluded that *Eutonyl* was taken off the market.

Please be assured that Eutonyl is very much in the market.

The other drug, Parnate, was used for treatment of mental depression. Eutonyl is a drug for *hypertension.*

Below, we've summarized the *important changes* in the literature. The Comment in each case will help put this material in perspective.

1. We have added a contraindication against cheese. This is a result of hypertensive reactions in some patients on Eutonyl who have eaten aged or nonprocessed cheese.

Comment: We have received only 12 such reports. There may have been a few other cheese reactions, of course, which have not been reported to Abbott. The reactions are due to the presence of tyramine in certain types of cheese. Until more information is known about these cheese reactions, we can not recommend any "exceptions" to the rule of not eating cheese.

2. We are reemphasizing the possibility of *hypertensive* reactions in patients on Eutonyl who are given a centrally or peripherally acting sympathomimetic drug (e.g. amphetamine or ephedrine). Included are certain over-the-counter drugs—cold preparations, reducing pills, etc.—products that might contain amphetamine, ephedrine, or their derivatives.

Comment: The number of such reports is quite small—less than 15 out of *an estimated 1,700,000 drug uses in some 400,000 different patients.* (A "drug use" is any occasion in which the drug is prescribed or dispensed.) The important point is that these hypertensive reactions are avoidable. With the

exception of a single patient who had undiagnosed pheochromocytoma, *every report of hypertensive reaction received to date has involved either the eating of cheese or the taking of a drug containing a sympathomimetic amine.* (Pheochromocytoma is a basic contraindication to the use of Eutonyl).

3. Our new literature contraindicates the use of other MAOI or methyldopa (non-MAOI) in patients taking Eutonyl.

Comment: The use of MAO inhibitors is contraindicated simply because of the possibility of augmented side reactions. Similarly, with methyldopa. Keep in mind, however, that Eutonyl may be used very successfully with the triazides, and most other oral antihypertensives. In such cases, the dosage of Eutonyl can and should be reduced in order to obtain the benefits of combined drug action with fewer side effects.

Finally, doctor, we'll ask you to consider these background facts on Eutonyl. Keep in mind that Eutonyl has been in widespread clinical use or more than a year.

1. *There have been no reports of organ system toxicity from use of Eutonyl.* This includes blood dyscrasias, kidney damage, liver impairment, or optic changes which have occurred with other antihypertensive drugs or other MAOI.

2. *There have been no deaths reported from use of Eutonyl.*

3. There have been no reports of hypertensive reactions resulting from use of Eutonyl *alone.*

In closing, we would like to emphasize that Eutonyl has been thoroughly reviewed by the F.D.A. * * * that it is still very much in the market * * * that it is one of the major and most effective drugs available for treatment of hypertension.

In case you missed it, a copy of the revised Eutonyl literature is enclosed. All of the new information is clearly presented.

Thank you for your interest—and your time.

LAKESIDE LABORATORIES, INC.,
Milwaukee ,Wis., March 30, 1964.

IMPORTANT : DRUG WARNING

Dear DOCTOR: We have received two reports regarding fatalities due to anaphylactic shock following injections of Imferon® (iron dextran injection). In cooperation with the Food and Drug Administration, we are informing you and all other physicians of these reports. One of these cases was called to your attention in our 1964 PDR monograph and also has been noted in our journal advertising.

Since 1954, when iron dextran injection was introduced to physicians, a total of three such fatalities, including the two above ,have been reported. One report, published in the Pharmaceutical Journal (Pharmaceutical Society of Great Britain) May, 1960, is included in its entirety in our enclosed revised package insert, under ADVERSE REACTIONS. Please note also the new WARNING section.

In regard to the reactions reported to us, one of the patients was a sixty-six year old female with no history of allergy. The reporting physician ascribed the cause of death to anaphylactic shock following ten to fifteen minutes after the first dose of iron dextran injection. The other fatality occurred approximately one hour after the fourth injection of the drug. The patient was an eighty-one year old female being treated for hypertension, heart disease, diabetes and anemia secondary to gastritis. The injection caused intense pain and slight urticaria which had not been evident previously. On the day of the injection the patient did not appear to be feeling as well as usual. Death was thought by the physician to be due to natural causes but was reported to us as a possible anaphylacic shock because of the pain, urticaria and suddenness of death.

Although the incidence of reported fatal reactions is very low—one is well over four million—we wish to make certain that members of the medical profession are fully aware of possible reactions as well as the usefulness of the drug, when its use is indicated.

We respectfully request that you submit to Lakeside Laboratories and the Food and Drug Administration reports of all side effects and adverse reactions,

particularly of the anaphylactic type, that you have encountered in your patients during or subsequent to the administration of Imferon (iron dextran injection).

Sincerely,

WILLIAM C. JANSSEN, M.D.,
Director, Clinical Research.

SMITH KLINE & FRENCH LABORATORIES,
Philadelphia, Pa., February 24, 1964.

IMPORTANT—DRUG WITHDRAWAL NOTICE

DEAR DOCTOR: Late last fall we notified you of certain hypertensive reactions that had occurred during 'Parnate' (tranylcypromine, SK&F) therapy. We pointed out that these hypertensive reactions sometimes resulted in cerebrovascular accidents, occasionally fatal in outcome. And we revised our Prescribing Information to include this material.

We also requested physicians to send us additional information as to any similar cases encountered in their practice, and as a result, we have received a number of additional reports.

After reviewing with the Food and Drug Administration the data from this country and abroad, we believe that of the hypertensive reactions reported, approximately 50 cases of cerebrovascular accidents, including 15 fatalities, may be attributable to the use of 'Parnate' (tranylcypromine, SK&F), among the more than 3½ million patients who have received the drug.

We are now informed by the FDA that because of these reactions they believed that 'Parnate' (tranylcypromine, SK&F) should be taken off the market.

With all due respect for the FDA, it is the opinion of the SK&F medical staff and the opinion of many eminent physicians whom they have consulted that the benefits of 'Parnate' tranylcypromine, SK&F) outweight the risks; that it is a useful and valuable drug for the treatment of a serious illness and should remain available to the medical profession. This view is supported by the recent findings of the British Safety of Drugs Committee.

Nevertheless, under protest, we are withdrawing 'Parnate' (tranylcypromine, SK&F) from the U.S. market. We are taking this step because under the present law and regulations, where there is an honest difference of medical opinion on scientific matters, there is no effective appeal to an impartial body of medical experts by whom the matter can be considered in a calm, scientific manner. Such a procedure has been strongly advocated by leading medical authorities.

In view of the withdrawal of the product, would you therefore please instruct your patients who are taking 'Parnate' (tranylcypromine, SK&F) to discontinue and to destroy whatever remaining tablets they may have. In transferring patients from 'Parnate' (tranylcypromine, SK&F) to another antidepressant, allow a medication-free interval of at least a week.

We will continue to present our views to the Food and Drug Administration and to explore with them the possibilities and procedures for having 'Parnate' (tranylcypromine, SK&F) made again available to the physician.

Very sincerely,

WALTER A. MUNNS,
President.

SMITH KLINE & FRENCH LABORATORIES,
Philadelphia, Pa., December 1963.

IMPORTANT—DRUG WARNING

DEAR DOCTOR: Although paradoxical hypertension and severe headache have always been listed among the possible side effect of Parnate (tranylcypromine, SK&F), instances of an unusually severe reaction of this type have come to our attention. The reaction is described in detail below. Reports of serious sequelae from this reaction have appeared in the foreign literature, but no reports have been published in this country. Accordingly, in our continuing effort to keep you fully informed about our products, we are passing this information on to you.

In cooperation with the Food and Drug Administration, we have revised our Parnate (tranylcypromine, SK&F) Prescribing Information, a copy of which is enclosed. Following are sections from it that have been revised either wholly or in part:

CONTRAINDICATIONS

A. The following contraindications should be carefully observed because hypertensive episodes associated with a distinctive reaction have been reported. *Such reactions are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea and vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin) and photophobia. Either tachycardia or bradycardia may be present, and associated constricting chest pain and dilated pupils may occur. In rare instances, intracranial bleeding, sometimes fatal in outcome, has been reported in association with this paradoxical increase in blood pressure.*

1. IN PATIENTS WITH CEREBROVASCULAR DEFECTS OR SEVERE CARDIOVASCULAR DISORDERS

Parnate (tranylcypromine, SK&F) should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with severe cardiovascular disease.

2. IN COMBINATION WITH 'TOFRĀNIL'*, 'ELAVIL'*, OR MAO INHIBITORS

Under no circumstances should Parnate (tranylcypromine, SK&F) and 'Tofrānil' be administered together or in rapid succession. In addition to the possibility of a hypertensive reaction, severe seizures have been known to occur in patients receiving such combinations. Likewise, Parnate (tranylcypromine, SK&F) should not be used with other MAO inhibitors or with 'Elavil'.

In patients being transferred to Parnate (tranylcypromine, SK&F) from another MAO inhibitor or from 'Tofrānil' or 'Elavil', allow a medication-free interval of at least a week, then initiate Parnate (tranylcypromine, SK&F) using half the normal dosage for at least the first week of therapy. Similarly, at least a week should elapse between the discontinuance of Parnate (tranylcypromine, SK&F) and the administration of another monoamine oxidase inhibitor or of 'Tofrānil' or 'Elavil'.

3. IN COMBINATION WITH SYMPATHOMIMETICS

Based on reactions seen in a few patients who have received sympathomimetics or other stimulants, particularly methamphetamine by injection, during Parnate (tranylcypromine, SK&F) therapy, it appears that certain patients are particularly vulnerable to the effects of these drugs when the activity of certain enzymes is inhibited. Use of these drugs with Parnate (tranylcypromine, SK&F) may precipitate hypertension, headache and related symptoms. Methyldopa and research compounds such as dopamine and tryptophan, and according to a recent speculation, the ingestion of cheese, may also contribute to the possibility of a hypertensive reaction. Parnate (tranylcypromine, SK&F) should not be used in the presence of pheochromocytoma since such tumors secrete pressor substances.

Important: Recommended treatment in hypertensive reactions—If a hypertensive reaction occurs, Parnate (tranylcypromine, SK&F) should be discontinued and therapy to lower blood pressure should be instituted immediately. Headache tends to abate as blood pressure is lowered. On the basis of present evidence, phentolamine (available as 'Regitine'†) or pentolinium (available as 'Ansolysen'†) is recommended. (The dosage reported for phentolamine is 5 mg. i.v., and for pentolinium, 3 mg. s.c.) Care should be taken to administer these drugs slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling. Other symptomatic and supportive measures may be desirable in particular cases.

WARNINGS

The occurrence of palpitation or unusually frequent headaches during Parnate (tranylcypromine, SK&F) therapy may indicate intolerance to the drug. Therapy should be discontinued when these signs are seen.

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*Trade Marks Reg. U.S. Pat. Off.: 'Tofranil' for imipramine, Geigy, and 'Elavil' for amitriptyline, Merck & Co., Inc.

†Trade Marks Reg. U.S. Pat. Off.: 'Regitine' for phentolamine and methanesulfonnate, U.S.P., CIBA; and 'Ansolysen' for pentolinium bitartrate, Wyeth.

We are investigating all possible aspects of this problem. If you have any direct knowledge of a hypertensive episode, a cerebrovascular accident or other untoward reaction associated with Parnate (tranylcypromine, SK&F) therapy, we would appreciate your sending a complete description to our Medical Department or to the FDA. If possible, case reports should include a detailed statement of the patient's medical history and a listing of the foods and other drugs ingested immediately preceding the onset of acute symptoms. We will provide all physicians with a further report on this subject as soon as definitive information is available.

Very sincerely,

WALTER A. MUNNS,
President.

PFIZER LABORATORIES,
New York, N.Y., August 21, 1963.

IMPORTANT DRUG WARNING PLEASE READ

DEAR DOCTOR: It has come to our attention recently that Diabinese® (chlorpropamide) is being used in some instances for the treatment of diabetes during pregnancy. Sulfonylurea therapy of diabetes during pregnancy is contrary to the advice and recommendations of the general consensus of expert opinion on the subject, and there is, therefore, insufficient data supportng its efficacy and safety in this condition.

Pregnancy, along with infection, surgery, trauma and other stressful situations has always been considered to be a complication of diabetes and an indication for insulin therapy. It is almost axiomatic that diabetic control becomes more complicated and insulin requirements increase under such conditions.

The primary indication for sulfonylurea therapy is uncomplicated diabetes mellitus of the stable, mild or moderately severe, non-ketotic, maturity-onset type. Accordingly, the use of this drug in pregnancy is not indicated. In addition, diabetes in the majority of women capable of bearing children is not of the stable, maturity-onset type.

We are unaware of significant reliable data on the use of chlorpropamide during pregnancy, and therefore, its use is contraindicated in this condition. Indeed, caution is urged in prescribing this drug to any woman capable of bearing children because of the potential danger to the mother and to the embryo or fetus in an unsuspected pregnancy.

Accordingly in cooperation with the Food and Drug Administration, we have revised our Diabinese (chlorpropamide) package insert to include the following caution:

"Diabinese (chlorpropamide) is contraindicated in pregnancy. In view of the question of safety in this condition, serious consideration should be given to the potential hazard of its use in women of the childbearing age who may become pregnant."

In closing, we urge that any reports of your past experience with Diabinese (chlorpropamide) during pregnancy, either adverse or favorable, be forwarded in detail to us and to the Food and Drug Administration. We shall hold such reports in strict confidence.

Very truly yours,

ROBERTS M. REES, M.D.,
Medical Director.

LLOYD BROTHERS, INC.,
Cincinnati, Ohio., August 6, 1963.

DEAR DOCTOR: We would like to call to your attention a mystery and possible problem which has been encountered with our new product Copoietin Ferrous Tablets. Copoietin Ferrous was introduced eight weeks ago after several years of clinical research. The results convinced us that we had a quality product to offer for the treatment of anemia.

During the past week, we have discovered that some tablets of Copoietin Ferrous do not disintegrate properly in the body although every batch has passed the rigid table disintegration tests as established by U.S.P. For some as yet unexplained reason, the accepted standard disintegration tests do not enable us to assure Lloyd Brothers' standards of quality. Until this mystery can be solved, Lloyd Brothers has elected to withdraw from distribution all stocks of the drug presently available for sale. We ask that you destroy any samples

of Copoietin Ferrous that may be in your possession in order to ensure against any therapeutic failure in your patients.

We have elected to take this course of action voluntarily in order to ensure the highest quality of drugs consistent with our standards.

We hope that this apparent mystery can be resolved with scientific facts in the near future. When this takes place, we will again offer Copoietin Ferrous for your consideration. In the meanwhile, we beg your indulgence. We sincerely appreciate your interest in Lloyd Brothers' products and assure you of our interest in supplying only the best products possible for your patients.

Sincerely,

H. R. REAMES, Ph. D., M.D.

WALLACE LABORATORIES,
Cranbury, N.J., July 30, 1963.

DEAR DOCTOR: As you know, we have periodically revised and issued copies to you of the Physicians' Reference Manual on "*Miltown*" (*meprobamate*) in order to keep you up-to-date on all information on meprobamate available in the world's literature. As part of our medical information program, also, we have periodically sent to you copies of the current package insert. Accordingly, we wish to call your attention to a revision of the package insert, and especially to the sections on "Important Precautions" and "Side Effects" of the enclosed.

The choice of any drug—any therapy—as you well know, must always involve acceptance of the drawbacks with the advantages. The continued use of meprobamate over the years is largely due, we feel, to its unusually favorable balance between high efficacy and low toxicity. In most cases of anxiety and tension, this balance has made meprobamate the drug of choice over other tranquilizers.

This favorable balance between efficacy and toxicity was reflected at the Annual Meeting of the American Medical Association in Atlantic City last month, where three physicians, practicing independently and in totally different settings, reported their work with tranquilizers and sedatives.

One physician treated psychiatric outpatients at a clinic in a large eastern city; the second reported work with hospitalized psychotics and neurotics in a southern state institution; the third, in private practice, treated anxiety and tension in professional and skilled workers.

All these physicians have been using 'Miltown' (meprobamate) for nearly a decade and were thus able to make evaluations based on long experience. All of them found meprobamate to have a favorable balance between efficacy and toxicity as compared with other tranquilizers studied.

Our facilities are available to you for summaries of the above reports, and for abstracts or complete papers on any aspect of meprobamate therapy. If you contact me directly, I will see that your request receives immediate attention.

Cordially,

MARTIN C. SAMPSON, M.D.,
Medical Director.

ROCHE LABORATORIES,
Nutley, N.J., July 3, 1963.

DRUG WARNING LETTER

Re: Intravenous use of KONAKION® (phytonadione) vitamin K_1 activity.

DEAR DOCTOR: Konakion Injectable has been in general use in the United States since early 1959. It has recently come to our attention that five patients receiving Konakion (phytonadione) by intravenous administration experienced serious reactions including one fatality.

We are therefore advocating the elimination of the intravenous use of the product. In an emergency situation, such as actual hemorrhage, the treatment of first choice is the administration of whole blood or plasma. Konakion (phytonadione) may then be administered intramuscularly.

You are requested to submit to the Company or the Food and Drug Administration reports of all side effects and all adverse reactions that you have encountered in your patients during or subsequent to the administration of Konakion (phytonadione) Injectable.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

WINTHROP LABORATORIES,
NEW YORK, N.Y.

IMPORTANT DRUG PRECAUTIONS

DEAR DOCTOR: The recent experience of various investigators has shown that Aralen® (brand of chloroquine), used alone or as an adjunct to other drugs and therapeutic measures, may be very helpful in the management of patients with lupus erythematosus or rheumatoid arthritis. Although many physicians have found that the incidence of serious side effects is lower than that encountered with other potent agents that are often employed in such patients, certain ocular complications have sometimes been reported during prolonged daily administration of chloroquine. Therefore, when chloroquine or any other antimalarial compound is to be given for long periods, it is essential that measures be taken to avoid or minimize these complications.

Thus initial and periodic (trimonthly) ophthalmologic examinations (including expert slit-lamp, fundus and visual field studies) should be performed. The initial examination will reveal if any visual abnormalities, either coincidental or due to the disease, are present and will establish a base line for further assessment of the patient's vision. Should corneal changes occur (which are thought to be reversible and which sometimes even fade on continuance of treatment), the advantages of withdrawing the drug must be weighed in each case against the therapeutic benefits that may accrue from continuation of treatment (sometimes a severe relapse follows withdrawal). If visual disturbances occur—which are not fully explainable by difficulties of accommodation or corneal opacities—and particularly if there is any suggestion of visual field restriction or retinal change, administration of the drug should be stopped immediately and the patient closely observed for possible progression.

We should like to request your cooperation in reporting to Winthrop Laboratories or to the Food and Drug Administration any patients in your own practice who have developed impairment of vision or retinal change during or subsequent to the administration of chloroquine.

A reference card of a convenient size for filing is enclosed. It contains information on the various indications for Aralen (including lupus erythematosus, rheumatoid arthritis, malaria and amebiasis), dosage, side effects and precautions.

Very truly yours,

E. J. FOLEY, M.D.,
Vice President, Medical Director.

PARKE, DAVIS & CO.,
DETROIT, MICH.

DRUG WARNING—ZARONTIN

DEAR DOCTOR: In conformance with our policy to inform physicians promptly of adverse or unusual effects from our products, and in co-operation with the Food and Drug Administration, we are calling attention to several reports received recently Zarontin® (ethosuximide).

Several cases of agranulocytosis and severe pancytopenia have been reported. Recently two cases (one fatal) of bone marrow depression have been received. These reports came from Europe; and even though many details are not known, the following information was supplied to our representatives.

Case I. Patient was a 15-year-old female with a history of having received Zarontin for four years in a dosage range from 7 to 10 capsules daily. The diagnosis was agranulocytosis and marrow transplants were not successful.

Case II. Patient was a 15-year-old male who developed increasing pallor and bleeding from the nose during the autumn of 1961 while receiving Zarontin and phenobarbital. A severe anemia (hemoglobin 5.1 Gm.), leukopenia (2480) with a pronounced granulocytopenia, and a severe thrombocytopenia were found. Zarontin was discontinued. The patient received a blood transfusion, and a bone marrow aspiration on October 20, showed hyperplasia with increased erythropoiesis and many immature red cells. During the next two months he received seven blood transfusions and 25 mg. of prednisone daily and penicillin prophylactically. The thrombocytopenia and granulocytopenia persisted and on February 2, 1962, a splenectomy was performed. During the following four months transfusions were not necessary, but the platelets and granulocytes remained low.After two transfusions the hemoglobin began to increase, reticulocy-

tosis developed, and there was a steady increase in the number of platelets and granulocytes. On February 11, 1963, the hemoglobin was 84 per cent, white blood cell count—5800 with 30 per cent granulocytes, platelet count—208,000 and reticulocytes—5 per cent. He is still receiving steroid therapy and phenobarbital.

The enclosed copy is a revised package insert which will accompany the market package of Zarontin. The insert provides the latest essential information regarding precautions, side effects, pharmacology, indications, and dosage for the recommended use of this anticonvulsant. We would appreciate the submission of any report, at your earliest convenience, to the Company, of side effects or adverse reactions following the use of Zarontin.

Sincerely yours,

P. F. R. DE CAIRES, M.D.,
Director.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., May 28, 1963.

IMPORTANT—DRUG WARNING

DEAR DOCTOR: New warnings are being required in the labeling of topical cortico-steroid preparations for ophthalmic use.

The warnings are shown in the attached memorandum prepared by our Bureau of Medicine.

We have requested all manufacturers of Topical Corticosteroid Preparations and Steroid Antimicrobial Combinations intended for Ophthalmic use to include the warnings in labeling and advertising of these preparations.

From time to time, the Food and Drug Administration, individually or in cooperation with professional or industry groups, will issue statements of important drug developments from the standpoint of new and serious adverse reactions, warnings, and contraindications.

The envelopes and letters in such cases will generally be marked to show that they transmit such information; for example, with a statement such as Drug Warning.

We will be glad to have you report to us any adverse reactions associated with the use of any drug. These reports will be given the most careful consideration.

Sincerely yours,

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

MAY 28, 1963.

MEMORANDUM

To: Geo. P. Larrick, Commissioner of Food and Drugs.
From: Ralph G. Smith, M.D., Acting Director, Bureau of Medicine.
Subject: Contraindications and Side Effects of Certain Opthalmic Preparations.

Recent information gathered by the medical staff of the Food and Drug Administration with the assistance of a number of outside medical experts shows a need to warn physicians of certain contraindications to and side effects in the ophthalmic use of topical corticosteroid preparations, including their combinations with antimicrobial drugs.

1. The following are the "*contraindications*":

a. acute herpes simplex, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva;

b. tuberculosis of the eye;

c. fungal diseases of the eye;

d. acute purulent untreated infections of the eye, which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid. Purulent conjunctivitis and purulent blepharitis are not indications, but contraindications for topical steroid or steroid-antibiotic combinations. If conjunctivitis and blepharitis are listed as indications, they should be qualified as non-purulent, not purulent.

2. The following are two *important "side effects":*

a. extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently;

b. in those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

All manufacturers of Topical Corticosteroid preparations and steroid antimicrobial combinations intended for ophthalmic use have been requested to revise the labeling and advertising of these preparations to include warnings concerning the above contraindications and side effects.

AYERST LABORATORIES,
New York, N.Y., May 3, 1963.

IMPORANT—DRUG WARNING

DEAR DOCTOR: During the past several years, there have appeared reports totalling approximately 12 cases of fatal liver necrosis following surgical procedures performed under anesthesia technics of which "Fluothane" (Halothane) was a major component. It is interesting that a considerable proportion of these cases are accounted for by cholecystectomies.

It has thus far not been possible to establish a clear cause and effect relationship between the liver necrosis and the anesthetic although studies are under way. Results from these studies will be presented as soon as they become available. Meanwhile the administration of "Fluothane" (Halothane) to patients with known liver or biliary tract disease is not recommended.

Enclosed with this letter is a copy of the revised package insert and attention is drawn to the following statements:

Adverse Reactions

Fatal massive hepatic necrosis or cholestatic jaundice may occur following surgery performed under anesthesia of which Halothane in its usually safe concentration is a major component.

Contraindications

The administration of Halothane to patients with known liver biliary tract disease is not recommended.

Halothane is not recommended for obstetrical anesthesia except when uterine relaxation is needed. Halothane is rarely indicated in operations for the removal of retained products of conception. The uterine relaxation obtained, unless carefully controlled, may fail to respond to orgot derivatives and oxytocic posterior pituitary extract. Halothane is primarily a uterine muscle relaxant, and its employment should be reserved for cases of external cephalic version and for those phases of operation during which intrauterine manipulation or the removal of the placonta demand greater ease of accessibilty to the uterine cavity.

Precautions

Halothane may increase cerebrospinal fluid pressure. Thus, in patients with markedly raised intracranial pressure. Halothane administration must be preceded by measures which will effect a reduction in cerebrospinal fluid pressure.

We will appreciate the submission to us or the Food and Drug Administration of any reports of adverse effects associated with the use of "Fluothane" (Halothane) in your own practice.

Assuring you that we shall keep you fully informed regarding future developments,

I am sincerely,

JOHN B. JEWELL, M.D.

DRUG WARNING

IMPORTANT—FOR IMMEDIATE READING

DOSAGE—PRECAUTIONS AND CONTRAINDICATIONS IN CHOLECYSTOGRAPHY

E-FOUGERA & CO., INC.,
Hicksville, N.Y., March 1963.

DEAR DOCTOR: Recent reports have described the occurrence of certain severe side effects following the administration of more than 4.5 gm. of Orabilex (bunamiodyl sodium). Dosage recommendations and precautions have been revised as follows:

1. Repeat doses (that is, more than 4.5 gram) of Orabilex may be associated with the development of oliguria, renal tubular necrosis, and death. Use of other cholecystographic agents within one week after Orabilex ingestion may be dangerous and even fatal.

2. Orabilex is contraindicated in patients with a history of renal disease, or in the presence of any symptoms or signs suggestive of renal disease or dysfunction. Evaluation of renal function should be performed preparatory to the use of Orabilex.

A revised package brochure is enclosed for your review.

The mechanism by which multiple doses of cholecystographic media may contribute to renal embarrassment is not known.

Continuing clinical and laboratory investigations bearing on this problem are in progress. We would appreciate the submission of reports of side effects or adverse reactions following the use of Orabilex or other cholecystographic media at your earliest convenience.

Sincerely yours,

F. J. SANEN, M.D.,
Medical Director.

DRUG WARNING LETTER

SANDOZ PHARMACEUTICALS,
Hanover, N.J., March 8, 1963.

DEAR DOCTOR: In accordance with our desire to keep you up-to-date with the latest information on all our products, complete product information on Torecan is enclosed. The purpose of this letter is to draw your attention to certain modifications in indications and precautions which under FDA regulations are considered "changes in labeling." *Torecan* (*thiethylperazine*) has been on the market as an antiemetic and antinauseant since September, 1961. In the course of its broader therapeutic application, some aspects associated with its clinical use have emerged with greater clarity.

In common with other phenothiazines, Torecan may produce extrapyramidal stimulation (pseudo-parkinsonism) with the varied symptom complex characteristic of this complication. As this is more likely to occur in children and young women, Torecan is contraindicated in children under twelve years of age and in pregnancy.

Extrapyramidal effects may be manifested as a dystonic reaction (e.g. torticollis, dysphagia, oculogyric crisis, convulsion), akathisia or as pseudo-parkinson syndrome. When seen for the first time, such reactions may be mistakenly diagnosed as tetanus, hysteria, encephalitis, etc. While the syndrome is self-limiting if therapy is stopped, the clinical course may be curtailed by the administration of sedatives, anti-parkinson agents or intravenous injection of caffeine and sodium benzoate. Diphenhydramine hydrochloride intravenously has also been reported to bring relief of these symptoms.

When used as an antiemetic against vomiting induced by anesthesia, occasional instances of moderate hypotension have occurred within one-half hour of administration. This has also been reported with other phenothiazine-type antiemetics, but unlike other phenothiazines, no case of delayed hypotension has been reported with Torecan.

Restlessness and postoperative depression have not been a serious problem, but the possible development of other known reactions to the phenothiazine-antiemetics must be borne in mind.

We will be most happy to answer any questions or comments that you may have on Torecan or any other of our drugs.

Sincerely,

CRAIG D. BURRELL, M.D.,
Director Medical Services.

GEIGY PHARMACEUTICALS,
Yonkers, N.Y., November 27, 1962.

DEAR DOCTOR: The November 17, 1962 issue of the British Medical Journal carried a letter to the editor concerning a woman who had taken Preludin®, brand of phenmetrazine hydrochloride and who had been delivered of two children with severe congential defects of the left diaphragm. Although this internal defect bears no relation to phocomelia, the authors reviewed the patient's history of drug therapy during early pregnancy, and reported that she had taken Preludin between the fourth and twelfth weeks of pregnancy.

We enclose a reproduction of the full publication. Apparently, the history of drug ingestion "on the advice of a friend" was obtained in retrospect years after the event. There is also no information concerning the nature of two earlier miscarriages in the same patient.

The recurrence of congential defects in repeated pregnancies of the same woman is well recognized. Butler and Claireaux (Lancet, March 31, 1962, pp. 659–663, "Congential Diaphragmatic Hernia as a Cause of Perinatal Mortality") described this phenomenon and cite inherited factors and several common complications of pregnancy as possibly etiologic. Their description of pathologic findings closely parallels that reported in the British Medical Journal, and includes an instance of two infants with diaphragmatic hernia born to the same mother eight years apart.

It is estimated that there have been over ten million patient months of therapy with Preludin in the United States. Approximately 85% of these patients were females, and about 5 to 10% of them had obtained their prescriptions from obstetricians. We estimate that about 500,000 pregnant women received Preludin in the United States. There has been no evidence of a change in incidence of fatal diaphragmatic hernia as compared to the pre-Preludin era and we know of no other reports suggesting any type of congential problems in relation to Preludin.

Accordingly, we believe that the position of Preludin in the treatment of obesity has not been altered by the recent publication in England.

In general, we can understand the view expressed in some medical circles that no drug should be employed during early pregnancy unless the physician feels there is a clear need for it. However, we see no reason why Preludin differs from literally hundreds of other commonly used drugs in this respect.

Only the physician can evaluate the dangers of obesity to the health of each individual patient, and match this with the therapeutic measures he deems advisable.

Sincerely yours,

HART E. VAN RIPER, M.D.,
Medical Director.

G. D. SEARLE & CO.,
Chicago, Ill., August 7, 1962.

IMPORTANT—DRUG CAUTION

DEAR DOCTOR: We are addressing this letter to you in keeping with our policy of bringing to you all of the pertinent facts concerning our products and as a response to recent publicity dealing with the occurrence of thrombo-embolic phenomena coincident with women receiving Enovid.

Since its introduction there have been reported to us as of this date 28 cases of thrombo-embolic disease in the more than one million users of Enovid in the United States. Among these were 10 cases of pulmonary embolism, 5 of which were fatal. In addition, there are press reports of 4 cases, including 1 death from the United Kingdom.

In some of these one or more of the usually accepted inciting causes of thrombophlebitis were evident; in some they were not.

Reports to the manufacturer do not reflect the accurate incidence of reactions and the available statistics are not adequate to determine whether or not there is a causal relationship, but caution requires consideration of this possibility.

It must be remembered that pulmonary embolism can occur without discernible inciting cause and without preceding peripheral thrombophlebitis. Nevertheless, careful studies by investigators experienced in the measurement of the extremely complex factors involved in the clotting mechanism are continuing, including an evaluation of the role of fluid accumulation sometimes seen after Enovid administration. This will be reported in a technical bulletin at an early date. At the present time the available laboratory data neither prove nor disprove a causal relationship between Enovid administration and the occurrence of thrombophlebitis.

The cases of thromphlebitis reported to us have usually occurred early in the course of Enovid administration and at the lower dosage level. Experience based on patients taking Enovid at higher doses has not demonstrated any dose response relationship.

Physicians should be as alert to the possible occurrence of thrombophlebitis in patients to whom Enovid is prescribed as they are in patients taking other medication.

The above facts should be given particular attention if Enovid is considered for administration to patients with thrombotic disease or a history of thromphlebitis.

We request that any thrombo-embolic occurrence in women receiving Envoid be reported to us and to the Food and Drug Administration.

Sincerely yours,

IRWIN C. WINTER, Ph. D., M.D.,
Vice President, Medical Affairs.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, April 17, 1962.

DEAR DOCTOR: This letter is to inform you of the Merrell decision to withdraw MER/29 (triparanol) from the market. We are today, with the cooperation of the Federal Food & Drug Administration, asking all hospital and retail pharmacies, as well as other possible outlets, to return immediately their total stock of this drug.

This decision is based on additional reports of side effects of the kind reported to you in our letter of December 1, 1961, some of which have occurred at the usual dosage. It is recommended that you have your patients discontinue use of MER/29.

As you probably know, Merrell has had and will continue to have an extensive research program in cardiovascular disease. MER/29 has been one important phase of this effort. The work on this compound by us and many others has made contributions to basic knowledge in this field.

We would appreciate any data you may be able to furnish us concerning your own past experience with this drug. Such data are most useful when supplied in case history form.

Sincerely yours,

FRANK N. GETMAN.

PFIZER LABORATORIES,
New York, N.Y., March 1962.

DEAR DOCTOR: Enclosed you will find a copy of the new Product Brochure for our multi-spectrum antibiotic, Signemycin.

In October 1961, we informed you that studies were in progress to investigate reports of changes in tests of liver function in some patients treated with triacetyloleandomycin.

Confirmatory studies have been concluded and the results have led to revisions which have been incorporated in the new Product Brochure.

Sincerely yours,

ROBERTS M. REES, M.D.,
Medical Director.

THE UPJOHN CO.,
Kalamazoo, Mich., March 15, 1962.

DRUG WITHDRAWAL—MONASE

DEAR DOCTOR: In spite of extensive pre-marketing clinical and animal studies which indicated a wide margin of safety, an occasional patient has developed

agranulocytosis in association with the administration of Monase. Because of this unforeseen and nonpredictable occurrence, The Upjohn Company in cooperation with the Federal Food and Drug Administration is withdrawing Monase from the market.

It has not been possible to establish definitely that Monase was the sole causative agent in every case since other drugs were sometimes administered concurrently. However, in each instance, Monase was the common factor.

We request that you instruct your patients to discontinue Monase. Refund for returned tablets will be arranged through the dispensing pharmacist.

Very sincerely yours,

EARL L. BURBIDGE, M.D.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, February 21, 1962.

DEAR DOCTOR: On December 5th, 1961 we advised you of the possible relationship of congenital malformations observed abroad in offsprings of certain patients who had taken thalidomide (Kevadon in Canada) early in pregnancy. This letter is to summarize the current status.

There still is no positive proof of a causal relationship between the use of thalidomide during pregnancy and malformations in the newborn. Reports are now appearing in the medical literature indicating only that thalidomide was employed in certain cases where malformation developed. The research necessary to determine whether or not such malformation may indeed be related to the drug is continuing and because of the complexity of the problem will require considerable time.

It is encouraging to note that studies in pregnant rats have not shown a single malformation in more than 1,100 offsprings of thalidomide-treated animals.

Additional surveys are under way to determine if there has been an increase in the incidence of malformations both in countries where thalidomide has been extensively employed as a sedative/hypnotic and in certain other countries where it is not marketed.

In view of the complexity of the problem and the time required to delineate the facts, the contraindication stated in our December 5th letter is still necessary. A new and fully descriptive brochure containing the contraindication to the use of Kevadon in women of child-bearing age will reach you shortly.

Sincerely yours,

JOHN N. PREMI, M.D.,
Medical Director.

WYETH LABORATORIES,
Philadelphia, Pa., January 23, 1962.

NEW INFORMATION—TRIACETYLOLEANDOMYCIN

DEAR DOCTOR: In October 1961, I informed you of the occurrence of jaundice and hepatic biochemical abnormalities resulting from the administration of triacetyloleandomycin administered in doses of one gram (1 Gm.) per day for periods of two weeks and longer.

These observations have been confirmed by further studies and appropriate changes have now been incorporated in our directions for use of triacetyloleandomycin, Wyeth, Cyclamycin®. A copy of the revised directions for use is enclosed for your study and reference.

Additional studies of triacetyloleandomycin, Cyclamycin, administered in doses of one gram (1 Gm.) per day for one week reveal no significant hepatic abnormality and that the drug is safe for use by the recommended dosage schedule.

The effectiveness of triacetyloleandomycin, Cyclamycin, is such that prolonged therapy is seldom required in the treatment of most common susceptible infections for which it is recommended.

Sincerely yours,

GEORGE E. FARRAR, Jr., M.D.,
Medical Director.

J. B. ROERIG & CO.,
New York, N.Y., January 1962.

DEAR DOCTOR: We are pleased to report to you in the enclosed new prescription information the current status of our antibiotic products TAO, and TAOMID. These revised brochures are based on extensive, carefully controlled clinical

studies and provide you with complete prescription information for your guidance in the use of our TAO products in your practice

As you may recall, in October 1961, we advised the medical profession of two preliminary studies in which abnormal changes in liver function tests had been observed following the administration of TAO for 14 days or longer. These observations have been confirmed by further studies and appropriate changes have now been incorporated in our directions for use of our TAO product.

The effectiveness of TAO is such that prolonged therapy is seldom required in the treatment of most common susceptible infections for which it is recommended. It is therefore concluded that you may continue to employ TAO in your practice with full confidence in the treatment of acute bacterial infection including cases due to staphylococci resistant to other antibiotics, in accordance with the enclosed prescription information.

Sincerely yours,

JOHN L. WATTERS, M.D.,
Medical Director.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, December 5, 1961.

DRUG WARNING—KEVADON

DEAR DOCTOR: We have received information from abroad on the occurrence of congenital malformations in the offspring of a few mothers who had taken thalidomide (marketed in Canada as Kevadon) early in their pregnancies It is impossible at this time to determine whether, in fact, there is any causal relationship.

However, until definitive information is available to us, as a precaution we are adding the following contraindication to the use of Kevadon:

Kevadon should not be administered to pregnant women nor to premenopausal women who may become pregnant.

We are actively following this matter and you will be advised when it is finally determined whether or not this precautionary step was necessary

Sincerely yours,

JOHN N. PREMI, M.D.,
Medical Director.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, December 1, 1961.

DRUG WARNING—MER/29 (TRIPARANOL)

DEAR DOCTOR: In cooperation with the United States Food and Drug Administration, we are writing to inform and caution you concerning adverse effects, including some unpublished reports, associated with the use of MER/29 (triparanol). Although comparatively few serious clinical injuries have been reported to date, their possible significance is emphasized by findings from animal studies.

Cataracts. Four cases of cataracts in humans are reported in patients who have received MER/29. One of these cases occurred in a patient receiving the recommended dosage of 250 mg. of MER/29 daily. Cataracts and corneal opacities have also been produced with MER/29 in animals. Slit lamp examinations are necessary for early detection of developing cataracts. For this reason such examinations are indicated prior to and periodically during therapy. Before this problem came to our attention, approximately one thousand persons being treated with MER/29 were patients of ophthalmologists. Most of them have had careful eye examinations, including use of the slit lamp, before and during drug therapy. Results on these patients will be reported to you as soon as they are available.

Hair Changes. There have been many cases of hair loss, either baldness or thinning of hair, changes in hair color and texture, and loss of body hair. Such hair changes may be related to the skin change discussed below as well as to the eye changes discussed above. It is recommended that MER/29 therapy be discontinued promptly at the first evidence of hair or skin changes to minimize progressive effects possible including eye injury.

Ichthyosis and other skin changes. There are reports of skin reactions ranging from dryness, itching, and scaling to severe exfoliation, and ichthyosis. Some of these changes were also associated with hair loss and cataracts. It is recommended that MER/29 therapy be stopped immediately if such skin changes occur.

Depression of Adrenocortical Function. Adrenocortical function depression as shown by reduced output of adrenal steroids has been produced by MER/29 in animals, and in man at high dosage levels. This effect has not been ruled out in humans at recommended dosage levels. Appropriate precautions should be observed if MER/29 is employed in patients with suspected borderline adrenocortical function or in patients who are subjected to stress.

Other Adverse Effects. Other adverse clinical effects reported include 4 possible cases of leukopenia and scattered cases of abnormal liver function tests, impotence, diminished libido, veginal smear alterations, nausea, vomiting and urine test changes simulating proteinuria. At a level of 25 mg/kg per day of MER/29 deaths have occurred in some dogs within 35 days, with liver damage in some animals. It has caused abortion and prevented conception in rodents, diminished spermatogenesis in dogs, stopped egg laying in chickens, and was assumed to cause acute intravascular hemolytic episodes in some dogs in one study.

The side effects of all types reported to us to date total substantially less than one percent of the patients treated. This includes a number of patients who have been treated with MER/29 in clinical research studies for continuous periods of more than a year, including a few in excess of three years.

In view of all reports concerning adverse effects, it is recommended that MER/29 be used only in patients who can be maintained under very close supervision and frequent observation. Dosage should never exceed 250 mg. per day.

Further studies are under way to assess more fully the incidence and seriousness of adverse effects, with a view to a re-evaluation of the conditions and indications for use of MER/29. We will appreciate any information you may contribute from your clinical experience with MER/29.

Sincerely,

CARL A. BUNDE, PH. D., M.D.,
Director of Medical Research.

(Whereupon, at 4:20 p.m. the subcommittee was adjourned to reconvene at 10 a.m., Tuesday, November 28, 1967.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, NOVEMBER 28, 1967

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:15 a.m. in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The hearing of the Subcommittee on Monopoly will come to order.

Our witness this morning is Dr. Helen B. Taussig. Dr. Taussig, the committee is very pleased that you have been willing to take the time to come here and testify this morning. You have a most distinguished record and I have here your biographical background, which I will ask be printed in the record.

(The biographical data referred to follows:)

BIOGRAPHICAL DATA—DR. HELEN BROOKE TAUSSIG

Born in Cambridge, Massachusetts: May 24, 1898.

EDUCATION

Radcliffe College, 1917–1919.
University of California, 1919–1921: A.B.
Special Course at Harvard, Fall of 1921.
Boston University School of Medicine, 1922–1924 (One year research).
Johns Hopkins University, School of Medicine, 1924–1927: M.D.
Archibald Fellow in Medicine, 1927–1928.
Interne in Pediatrics, 1928–1930.

APPOINTMENTS

Physician-in-Charge, Harriet Lane Home, Cardiac Clinic, Johns Hopkins Hospital, 1930–1963.
Instructor, Pediatric Cardiology, Harriet Lane Home, Cardiac Clinic, Johns Hopkins Hospital, 1930–1946.
Associate Professor of Pediatrics, Johns Hopkins University, July 1, 1946–June 30, 1959.
Professor of Pediatrics, Johns Hopkins University, July 1, 1959–July 1, 1963.
Professor Emeritus of Pediatrics, Johns Hopkins University, July 1, 1963.
Appointment to President Lyndon B. Johnson's Commission on Heart Disease, Cancer and Stroke, March 9, 1964.
President-Elect, American Heart Association, October 1964–October 1965.
Alternate United States Delegate to the XX Internation Conference of the Red Cross Meetings, Vienna, Austria, October 1–10, 1965.
President of the American Heart Association, October 1965–October 1966.
Chairman, Central Committee of the American Heart Association 1966–

Member of the Board of the International Cardiology Foundation, representing the American Heart Association 1967–
Honorary Chairman—Committee of Responsibility, 1967 (January) Concerning the war-burned, war-injured children of Vietnam.
Member Emeritus of the Board—Sub-Board of Pediatric Cardiology, April 25, 1967–
Director-at-Large: American Heart Association, 1967–1970.
Member of the United States Delegation—20th World Health Assembly, Conference—Geneva, Switzerland, May, 1967.

MEDICAL SOCIETIES

Pediatric Research Society
American Pediatric Society
American Heart Association:
Member of the Editorial Board of "Circulation".
Vice-President, October 1960–1963.
President Elect, October 1964–1965.
President, October 1965–1966.
Council Representative, Editoral Board of Supplements, American Heart Association, July 1, 1963–1966.
Maryland Rheumatic Fever Association
Association of American Physicians
Heart Association of Maryland: President, 1952–1954; Secretary, 1959
American College of Physicians, 1957
International Academy of Pathology
Tetratological Society
British Cardiac Society—Honorary Member
Medical International Cooperation:
Medical Advisory Board
Board of Trustees
American College of Cardiology: Awarded Honorary Fellowship 5/27/60.
American Board of Pediatrics: Membership on the Sub-Board of Pediatric Cardiology.
New York Academy of Sciences, Member, April 1962.
New York Academy of Sciences, Fellowship, 1966.
National Association of Standard Medical Vocabulary, March 1962.

AWARDS

Women's National Press Club Award, 1947.
Chevalier Legion d'Honneur, 1947.
Mead-Johnson Award, 1948.
Passano Award, 1948.
Feltrinelli Prize Awarded in Rome, Italy, 1954.
Albert Lasker Award, October, 1954.
Elizabeth Blackwell Citation, New York Infirmary, January, 1954.
Award of Merit, American Heart Association, June, 1957.
Eleanor Roosevelt Achievement Award, September, 1957.
Award of Merit, Gairdner Foundation, Toronto, Canada, May–1959.
Woman of Achievement Award, American Association of University Women, Denver, Colorado, June 24, 1963.
Thomas River Memorial Research Fellowship Award, 1963–1968. First Award, National Foundation, Baltimore, Maryland, (June 26, 1963)
Gold Heart Award: American Heart Association, October 27, 1963, Los Angeles, California.
Medal of Freedom: Presented by—President of the United States of America—Lyndon B. Johnson, Monday, September 14, 1964.
The Theodore and Susan Cummings Humanitarian Award, February 20, 1965, American College of Cardiology, "For generous sharing of knowledge with your Colleagues overseas, which created goodwill for our country".
Spirit of Achievement Award: The Women's Division of the Albert Einstein College of Medicine, New York City, April 20, 1966.
John Phillips Memorial Award: (Bronze Medal). American College of Physicians, April 21, 1966.
Founders Award: Radcliffe College, Cambridge Massachusetts, June, 1966.

Myrtle Wreath Award: Hadassah, Women's Zionist Organization of America, Inc. New York Hilton Hotel, December 14, 1966.
Carl Ludwig—Medal of Honor—1967. Deutsche Gesellschaft Für Kreislaufforschung, Received April 1967. William G. Kerckhoff-Institut, Bad Nauheim, Germany.
Medal and Plaque: Visiting Professor; "In Recognition of her outstanding contributions to the Field of Heart Disease. Presented at the Georgetown University Hospital. October 4, 1967. Washington, D.C.

HONORARY SOCIETIES

Pi Beta Kappa—University of California, 1921.
Alpha Omega Alpha—Johns Hopkins University, School of Medicine, 1927.
American Academy of Arts and Sciences.

HONORARY DEGREES

D. Sc., Boston University, School of Medicine, 1948
D. Sc., Goucher College, 1949.
D. Sc., Woman's College of the University of North Carolina, 1950.
LL. D., Hood College, 1950.
D. Sc., Northwestern University, 1951.
D. Sc., Columbia University, 1951.
D. Sc., Women's Medical College of Pennsylvania, 1951.
D. Sc., Middlebury College, Middlebury, Vermont, 1952.
D. Sc., Western College for Women, Oxford, Ohio, 153.
D. Sc., University of Athens, Athens, Greece, 1956.
D. Sc., Harvard University, 1959.
D. Sc., Göttingen University, Göttingen, Germany 1960.
Dr. Med.: University of Wien, Austria, 1965: Ceremonies of the 600th Anniversary of the University of Wien.
D. Sc., Randolph-Macon Woman's College, Lynchburg, Virginia, March 12, 1966.
D. Sc., Cedar Crest College, Allentown, Pennsylvania, May 1966.
Dr. Humanity: Colby College, Waterville, Maine, June 1966.
D. Sc., University of Massachusetts, Amherst, June 1966.
D. Sc.: Jefferson Medical College and Medical Center, Philadelphia, Pennsylvania. Presented at the 143rd Commencement Exercises—June 2, 1967.
Honorary Degree—Professor Emeritus and Doctor of Medicine, University of Athens, Athens, Greece, November 1956.
Honorary Medal: American College of Chest Physicians, May, 1953.
Honorary Member: Sociedad Venezolana De Cardiologia, 1957.
President-Elect: American Heart Association, October 1964–1965.
President of the American Heart Association (First Woman President) October 1965–1966.
Chairman of the Central Committee, American Heart Association, Oct. 1966–67.
Director at Large, American Heart Association, October 24, 1967–1970.

CONSULTANT

Pediatrician and Pediatrician OPD—Johns Hopkins University, School of Medicine.
Consultant in Pediatric Cardiology to the Marine Hospital.
Pediatric Consultant Staff of the Baltimore City Hospitals.
Visiting Consultant in Medicine, Sinai Hospital.
Consultant in Pediatric Cardiology—Greater Baltimore Medical Center.

Senator NELSON. We note you were physician in charge of the Harriett Lane Cardiac Clinic, Johns Hopkins Hospital, from 1930 to 1963; that you were appointed by President Johnson to the Commission on Heart Disease, Cancer, and Stroke in March 1964; that you were president of the American Heart Association from October 1965 to October 1966; that you are a member of the Board of International Cardiology Foundation, representing the American Heart Association in 1967; and that you are director at large of the American Heart Association, 1967 to 1970.

I note a long list of very distinguished awards that you have received, as well as a long list of honorary degrees. This biography will be printed in the record.

I think everybody knowledgeable about medicine and health matters is familiar with your great and distinguished contribution to health and medicine in this country, and I suppose the contributions of which the public is most aware of are that you were the codeveloper of the blue baby operation, and that you are the one who alerted the medical profession in this country to the dangers of thalidomide.

The committee appreciates very much your taking the time to come here to make your contribution to the hearings which this committee has been conducting now for several months. I would ask you if it is satisfactory with you that you proceed to read your statement, and if you have no objection, from time to time I would like to interject some questions, so that you may develop in greater detail some of the points you have made. Thank you, Doctor.

STATEMENT OF DR. HELEN B. TAUSSIG, PROFESSOR EMERITUS OF PEDIATRICS, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD.

Dr. TAUSSIG. Thank you, Senator Nelson. It is a pleasure to be here today, and I am glad to be of any help and service I can. You have already explained to the people here who I am, so I don't believe that I need to repeat that.

By way of introduction may I explain to you how I first heard about thalidomide. One of my former fellows, Dr. Alois Beuren of West Germany had studied with Dr. Bing and Dr. Andrus and then studied with me for a year in the days when Congress permitted postdoctoral trainee fellowships of the National Institutes of Health to be granted to foreign doctors. I emphasize this because although some foreign fellowships have been abused, some have brought us rich returns.

In a very real sense the same is true about trainee fellowships as is true of research fellowships. Just a small percentage of research really pays off but that which pays off, pays off so well with such high dividends that it justifies all the other money which goes into research. And I feel in a sense so it is in traineeships. Only a few pay off with high returns both to their own country and to ours.

The only difference between the two is, virtually every doctor is a better doctor for having had an additional period of training. So I think there is no lost money there.

Dr. Beuren's training brought rich returns in Germany and here. Thanks to an evening he spent at my house when he returned for a brief visit that I heard about thalidomide. That evening he told me that the doctors in West Germany were seeing a great number of children born with gross malformations of the extremities, little flippers instead of arms or legs, or no arms or no legs; and what was more, that Dr. Lenz thought the malformation was caused by a sleeping tablet.

I brought over with me some slides only hoping to remind you of how miserable the malformation is. Here is a picture of my reprints. I also have some pictures of these unfortunate children.

Senator NELSON. We will accept those for the record, Dr. Taussig.[1]

Dr. TAUSSIG. Thank you. I would like to add right here that when you see a picture of a child with a little flipper of a hand arising from the shoulder, it may seem bad but when you see the child in life, it is infinitely worse because you have got a child that can't do anything, and that wants to do something and it can't.

It was the next morning, after Dr. Beuren had been talking to me that I realized the full implication of the situation, namely, the danger which might lurk in drugs if indeed it were true that a sleeping tablet did cause such a malformation. By then Dr. Beuren had left for Germany so I wrote, airmail, asking if I would be welcome to investigate the situation. Dr. Beuren telephoned transatlantic "Yes" and 3 weeks later I landed in Hamburg and Dr. Beuren's chief, Dr. Joppish, loaned me their best resident to help with my travels.

Two points must be clearly held in mind. I went to Germany because I realized that if true, the phenomenon had a deep, wide, and serious implication. Nevertheless, Dr. Frances Kelsey in the Food and Drug Administration was the person who refused to release thalidomide for sale in this country.

Senator NELSON. Let me ask you, if I may at this point, Doctor, a couple of questions for the record.

Clinical tests were conducted in this country in any event, weren't they?

Dr. TAUSSIG. Clinical test were conducted in this country and I think was the tremendous effort to obtain a rapid clinical test and wide distribution of the drug that inflamed the country. It was then the law of the land that clinical tests were allowed without the control of the FDA at all. It was only when the drug was released for sale that it came under the surveillance of the FDA.

Senator NELSON. And there were some proven cases of deformities in this country as a consequence of the clinical testing, is that correct?

Dr. TAUSSIG. Yes, I think so. I believe that lawsuit is still coming up in this country.

There were some cases where it certainly was strongly indicated or known that the mother had taken Kevadon and had a malformed baby. There were other drugs which have been brought into this country which resulted in malformed babies.

Senator NELSON. Who discovered this drug?

Dr. TAUSSIG. The drug was developed by Chemie-Grünenthal. I heard stories that it had been developed by another company, and then thought it was not worth producing, and then that company denied doing it. Certainly Chemie-Grünenthal in Germany developed and manufactured the drug and put it on sale in Germany in large quantities.

Senator NELSON. I don't recall that you state this in your testimony, but do you know the date on which the drug was first used anywhere in the world?

Dr. TAUSSIG. Well, let's not say anywhere, but first used widely in the world. I believe it was 1958. I have it in the article here and can check it in a moment, but it was either 1958 or 1959, and it was fairly widely sold by 1961, and the country was in trouble by 1961. I think 1958 was the first time they marketed the drug.

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[1] See supplemental information beginning at p. 1522, infra.

Senator NELSON. What was the date that you went over to Germany to make your own investigation?

Dr. TAUSSIG. February 1962.

Senator NELSON. Had there been publicity in Germany about the adverse effects of the drug as of that time?

Dr. TAUSSIG. Yes, there had. I am coming to it again in my testimony, Senator. One of the striking things to me was that they had a serious epidemic. They had had very widespread publicity in Germany in November 1961, and scarcely a word of it reached our press over here.

Senator NELSON. In November of 1961 there was widespread publicity?

Dr. TAUSSIG. In Germany. Yes.

Senator NELSON. Specifically naming this drug as the probable cause?

Dr. TAUSSIG. Yes. This was 2 days after the drug was withdrawn from the market in Germany, and 4 days after it was publicly announced at a pediatric meeting. First Dr. Lenz announced that he suspected a specific drug and he didn't mention the name. A number of doctors that evening said to him, "Just confidentially, will you tell me was it Contergan"—as it was known in Germany—"I asked because we had such a child and my wife took such a drug."

And he said "Yes," and 2 days later at the meeting it was generally known that Contergan was suspected to cause the malformation. The drug was then withdrawn from the market, and the health department put on a tremendously wide newspaper, television, and radio publicity throughout Germany. It was barely picked up by the press over here.

Senator NELSON. Then it was November 1961 when there was widespread publicity in Germany?

Dr. TAUSSIG. Yes.

Senator NELSON. When did the first widespread publicity occur in this country? It was after your trip, I take it?

Dr. TAUSSIG. Yes, it was well after my trip. I suppose that really Mr. Morton Mintz' article had given widespread publicity to it in July. I had spoken at medical meetings when I came back, and it was known in the medical profession by then, and I testified in Congress in May. I don't think the entire country was inflamed until the summer.

Senator NELSON. And when was the article written by Mr. Morton Mintz printed in this country?

Dr. TAUSSIG. Mr. Mintz is right here and I can assure you, I have the date as July 15, 1962, in the Washington Post. Is that correct?

Senator NELSON. About July 15, 1962?

Dr. TAUSSIG. Yes.

Senator NELSON. This is almost nine months after the widespread publicity in Germany; is that correct?

Dr. TAUSSIG. Yes, that is right. Could I just read you a few dates here that I have?

Senator NELSON. Yes, go ahead.

Dr. TAUSSIG. My own investigation clinched the matter in my mind, and in Dr. Kelsey's mind. It is important to emphasize that the public ordinarily never hears about drugs which are not passed by the FDA. There isn't widespread publicity. It is just silently refused. Hence I

think the country might not have realized the potential danger of drugs, had I not gone to Germany.

Now, this was in spite of the fact that 3,000 to 5,000 children were injured in West Germany. West Germany was wrought with anxiety and fear but we knew nothing about it.

As I told you, Dr. Lenz first announced that he thought that thalidomide might be the cause, and the drug was withdrawn from the market, and this was at the end of November 1961, and I was told that the publicity in Germany was tremendous. It was carried on the radio, the television, and the front page of virtually every newspaper in that country, and yet scarcely a word of it reached the American press.

Senator NELSON. What about the professional journals in this country? Were articles carried at that time?

Dr. TAUSSIG. At that time, no. Time magazine was the only journal that I know that picked it up; they sent a man over to investigate and published a brief column on "The Nightmare of a Sleeping Tablet." That was in February 1962. I know people read it but I don't think the true significance of it made any impression on them.

Senator NELSON. Do you have any explanation for the reason that the professional journals in this country didn't even carry articles about it?

Dr. TAUSSIG. No, I don't. I believe they didn't realize what was going on in West Germany. I think the first professional report was the one I gave to the American College of Physicians in April 1962. I did give a report at the Johns Hopkins Hospital and at the University of Maryland, when I first came back, immediately after my trip. I got back on the 1st of April, and I think it was about the 15th of April that I spoke in Philadelphia at the American College of Physicians, and that was carried in the press.

Senator NELSON. I take it, then, that even after the widespread publicity in Germany in 1961, the experimental clinical testing continued in this country for quite some time?

Dr. TAUSSIG. Yes. I believe application for the sale of the drug in this country was not withdrawn until April 1962.

Mr. GORDON. Was this before Mr. Mintz' article was printed or after the article?

Dr. TAUSSIG. I believe that the company had tried to withdraw the drug distributed for clinical trial, but not a very tremendous effort to recall the samples, before Mr. Mintz' article.

Senator NELSON. It was only being used in this country at that time in clinical tests?

Dr. TAUSSIG. In clinical tests, and I am sure no more was given out, but the percentage of recall was not great. It wasn't recalled in Canada until the middle of the summer. It wasn't recalled in other countries until after the outbreak of phocomelia had come to an end in Germany; that is, 8 months after the drug had been withdrawn and women had been warned not to take the drug.

Senator NELSON. I had thought that in the scientific community there was a fairly rapid exchange of information around the world on matters such as this. Is there any reason to account for this situation?

Dr. TAUSSIG. Well, as I say, I came back on the 1st of April. I talked to the American College of Physicians in the middle of April.

I talked to the American Pediatric Society in the first week of May, and then I reported here to the Antitrust Subcommittee of the Judiciary Committee on Food and Drug Regulations on May 24, 1962.

Senator NELSON. That was the Kefauver committee at that time?

Dr. TAUSSIG. Yes, that was the Kefauver committee or subcommittee. I must say when I first published or reported it, I was criticized by some of the people, saying that I was not a pharmacologist, I was a physiologist, and my response was I might not be either a physiologist or a pharmacologist, but if any of you had had a child with as severe malformation as that, you would be trying to prevent it happening here.

I don't think you had to be anything great but a humanitarian, perhaps, to be convinced of what was right in the situation. I published, or at least I sent in a short editorial, and was not very warmly received, and finally published my longer article on June 30, 1962, reporting my findings in Germany.

Mr. GORDON. Dr. Taussig, which American company was seeking to market thalidomide in this country?

Dr. TAUSSIG. William S. Merrell.

Senator NELSON. I see. Now, a New Drug Application was apparently filed. Was it filed under the name of thalidomide or under a trade name of Kevadon?

Dr. TAUSSIG. I believe it was filed under the trade name of Kevadon. It was, and I believe is, so far as I know, in countries the accepted procedure, that if a product is produced by one pharmaceutical company, and they license another company to sell it, they give that company the permission to select their own name, and have an independent name, and that means that every company that makes a drug puts it out under a different name. This makes it extremely difficult to trace the drug.

Senator NELSON. Go ahead. Where are you, exactly?

Dr. TAUSSIG. I was saying that my scientific article was published on June 30, 1962, and I published one in the Scientific American in August 1962, but I do think it was Mr. Morton Mintz' article in the Washington Post in July 1962 that did more to inflame the country than any other single article, and I think that I can get the copy, I hoped to have a copy of his original article, to have it incorporated into the record.[2]

My purpose today is to reemphasize the danger that might lurk in drugs, and the difficulty that the lay people have in identifying drugs. As our drugs become more specific and more useful, they become more potent, and consequently there is greater danger of side effects.

Furthermore, the late side effects are the hardest of all to detect. For example, if you take a pill and you immediately develop hives or you shortly thereafter develop nausea or vomiting or diarrhea, you readily connect the reaction you are having with the drug you have taken. If so, you certainly not only don't want to take it again, you want to know the name of the drug, but you also want to know what other preparations contain the same substance.

In contrast to this, when you take a drug and everything is lovely afterwards, you take a sleeping tablet, and if you get the best sleep

[2] See supplemental information beginning at p. 1522, infra.

you have had for a long time, you have slept well and awake refreshed, it is fine. You may like to know what you have taken, but you are satisfied with that particular pill, and as long as you can purchase it, all is well and good, and moreover, if you really get relief, you care very little about the price. And I think that is an important point also.

You continue to take the drug and other drugs, and then after a year or two you develop numbness and tingling in your hands and legs, which we call polyneuritis. You can't sleep and you take more sleeping tablets. You take the best sleeping tablet you have had before, namely, the one you took some years ago, and it is quite a long time before you or your doctor realize that the nervous trouble you are suffering from is caused by the long continued use of this sleeping tablet, as other sleeping tablets have not been known to cause such trouble.

Then the problem arises to know what other medicines contain that ingredient. It is particularly bad when you get a bad ingredient in something like a sleeping tablet, because sleep brings relief to many ills, and a great many conditions, perhaps a majority of illnesses, are helped by sleep.

Thus, if you have a headache or arthritis, a pill which relieves the pain, and when combined with one which will give you sleep, is very beneficial. The same is true of a gastrointestinal upset, or an attack of asthma, or a migrane headache.

Alas, even the morning nausea of early pregnancy is relieved by a tranquilizer. Most sleeping tablets, when given in small doses act as tranquilizers. Hence thalidomide was combined with many other drugs, and each combination was given a new name.

The drug was so good that the pharmaceutical rights for manufacture were sold to many other drug firms in many other countries, and as I told you, the accepted practice is that each firm which manufactures the drug has the permission to use a brand name of its own choosing.

And so when the danger of thalidomide was recognized, it was found that the drug was masquerading under at least 50, if not 100 or more different names. I have given you a list in the appendix of the different names I verified as containing thalidomide.[3]

Mr. GORDON. Dr. Taussig, did any of these have the generic name on them?

Dr. TAUSSIG. Not that I know of. I looked up most of these and I had to struggle to find out what company produced them, and then I had to write to the company and I asked them whether the drug contained thalidomide, if so how much, when was it marketed and when was it withdrawn, and it was only when I got a definite statement from the company yes, it did contain thalidomide that I put them on this list.

Senator NELSON. Did all the companies respond to your inquiry?

Dr. TAUSSIG. These that I listed here did. Some others I didn't get any response from. A few of them responded late. The preparations at the bottom which came from South America, I didn't check. Earlier I had been told that the drug was not sold in South America, and then in August 1962, after the last, or virtually the last case had been seen in Germany—because it was 8 months from the time the woman took

[3] See p. 1521, infra.

the drug in the sensitive period, to the time the infant was born—a month after that, the end of the epidemic in Germany, they found that the drug was sold in South America under the seven different names listed here.

Senator NELSON. And none of those drugs contained on the label the generic name of the drug?

Dr. TAUSSIG. So far as I know, none. I did not see the bottle myself, but I understood that the health department went in and made a search for them and the amount of Thalidomide they found in Sao Paulo was almost beyond belief, something like 96,000 kilograms of the pure substance.

Senator NELSON. Go ahead, Doctor.

Dr. TAUSSIG. I gave the list of these. I have been told that this list is not complete at all, but it was as far as I was able to check on the amount, and it is enough certainly to illustrate the number of names under which it passed.

It seemed incredible at first, to the medical profession, but it certainly became evident that one tablet of 50 milligrams, which was less than one-half of what had been considered a full normal strength dose if taken at the critical time during pregnancy, could severely injure the fetus.

The usual dose was 100 milligrams. The medicine was considered safe, so safe that man could not commit suicide by an overdose, and yet a dose of 50 milligrams could seriously injure the unborn child. Indeed nine doses of 30 milligrams have been found to injure the fetus.

Moreover, I believe it is only one of the degradation products of Thalidomide that injures the fetus, and that product is only in the bloodstream for a short period of an hour or two and hence it doesn't seem probable that it has a cumulative effect, but rather that each successive dose injures the embryo at a particular stage in fetal development.

Thus the evidence is overwhelming that a single very minute dose, but certainly a very small dose of a toxic substance can be highly injurious. Of course, the embryo is tiny and only a minute amount of toxic material is required to injure it at a specific point.

Another thing, of course, we learned from thalidomide was that a chemical could have an entirely different effect on an embryo or a fetus than on a person after birth. Thalidomide reacted on the nervous tissue of the adult giving sleep, and it reacted on the mesenthymal tissue, the forerunner of bone and muscle, in the embryo.

In addition, it is important to appreciate that the medical profession now recognizes that a number of conditions are late effects of earlier insults. When a late effect becomes manifest, that is the starting point for the investigation. In the case of thalidomide the starting point was the malformed infant, and the natural supposition was that something had injured the fetus during pregnancy.

Drugs are not the only thing which could cause such an injury. Some element in some detergents might, something you inhaled might, food preservatives might. Indeed, such possible sources were investigated in Germany, but today we are discussing drugs.

The problem is how to detect injurious reactions or side effects to the drugs, when they do occur. Clearly the more names the offending agent is distributed under, the more difficult is the problem of detection. It is

obvious that if you have an epidemic that is nationwide and an epidemic is produced by a drug that is sold or distributed under a hundred different names, its detection becomes much more difficult.

I shudder to think that if a drug were ever produced as a tranquilizer or as a good tonic or a drug claimed to increase virility, and it affected the sperm in such a manner as to injure the brain or even the reproductive organs of the fetus, how difficult it would ever be to trace that drug, and how virtually impossible if the drug masqueraded under 500 different names.

I don't think this is an impossibility, in truth I don't believe it is more improbable than landing a man on the moon seemed 30 years ago. Therefore, one of the helpful things we can certainly do, is to see that the generic name is on the label.

Senator NELSON. In your article published July 11, 1963, in the New England Journal of Medicine, on page 93, you address yourself directly to this point. I want to read from that, and ask you a couple of questions, because I think you have addressed yourself specifically and clearly to the issue that you raise here, as to the manufacture and distribution of drugs, the same drug under a multiplicity of trade names, and the danger involved. In that article you said:

> The difficulty in detection of the production and sale of drugs containing thalidomide is illustrated by a report in the Brazilian magazine, Ocruziero of September 6, 1962. The investigation was precipitated by the birth of a child with phocomelia. The magazine writer was told that thalidomide was not on sale in Brazil, but through his own inquiries he learned of 50 other infants born with phocomelia. Thereupon, he visited a pharmacy and purchased the drug under the name of Sedin. Later he found that Sedalis and Slip were also manufactured in Sao Paulo and distributed in Brazil.
>
> Thereupon, the health authorities instituted an investigation. They found that thalidomide was sold under five different names, Sedin, Sedalis, Slip, Ondasil, and Verdil. Moreover, in a ten-day surprise search, they confiscated nearly 2,500,000 pills—or boxes of pills—46,000 flasks containing thalidomide and 96,000 kilograms of the pure substance in the pharmacies and pharmaceutical firms in Sao Paulo.

This was in the summer of 1962.

Dr. TAUSSIG. Yes.

Senator NELSON (reading):

> Such events illustrate the importance of an international office of drug information that would notify the health authorities in all countries of the world when a drug was suspected of being dangerous.
>
> Although the drug has been withdrawn from the market, the danger is real that thalidomide, which has masqueraded under so many different names in so many parts of the world, will turn up again and again. Some pills, which were prescribed in good faith by physicians are now tucked away in many a medicine closet, with only a prescription number and no name. The serious consequence of this well established custom of filling prescriptions by number is illustrated by one unfortunate woman who, because the bottle was unlabeled, unwittingly took Distaval during two successive pregnancies and has two children with phocomelia. There is a movement in England to change the law so that the pharmacist would be required to put the name of the drug on a prescription unless specifically requested by the physician to withhold it. Although there is no law in the United States regarding withholding the name of a medicine given by prescription the custom is firmly established that prescriptions are filled by number and the name of the drug is withheld. This is a dangerous custom since it means that a large amount of unlabeled medicine is accumulated by everyone. There is danger not only that a medicine that has been withdrawn from the market may remain available but also that, when medicines are taken by mistake, especially by children, the doctor may be at a loss to know what has been taken. Although

common sense calls for a change in this custom a concerted effort by the medical profession will be necessary to effect such a change.

What method or organization would you suggest be established to provide this type information internationally?

Dr. TAUSSIG. I am very happy to say that last May at the World Health Assembly they said they were attempting to set up some form of international, not necessarily monitoring but advisory system for reporting drugs and for distributing the information, especially warning of dangerous effects. I think the most one would hope to do would be to have an international authority notify health authorities in the various countries that such and such a drug had been found dangerous and had been withdrawn.

It is true of other drugs that have far less serious complications and I have heard from a number of my friends in India that they don't know of these until they are finally published in journals, and the journals reach them, which is quite a lot later, or until travel and exchange of knowledge occurs. I think World Health is working on that particular problem, and I was very happy to hear that they were.

Senator NELSON. On the question of putting the generic name on the prescription, as you state in your testimony, it is not the practice to do so in this country. We have had testimony by distinguished physicians and pharmacologists that it is very important that the generic name be put on the label of the bottle that the paient gets, so that a doctor can check and will know at a subsequent date what is in the bottle.

You said that it will require a concerted effort, as you put it, by the medical profession, to effect such a change. Do you have any opinion as to why the medical profession, through its major organizations, has not already done this, since it is so obviously in the public interest?

Dr. TAUSSIG. No, I don't; except that they are busy with many other things. It has been such a firmly established practice.

I think that I said it will require concentrated effort of the medical society only because of the feeling that it might be impossible to get a law through Congress, and there are so many more important aspects to get into the actual law of the land. Probably it stems from deficiency in the teaching in pharmacology and medical schools and lack of appreciation. Today if an M.D. writes the name of the drug and does not state specifically to have it written on the bottle, it does not appear on the label.

In former days, I think two generations ago, people were not taken into the confidence of the doctors quite as much, and the doctor thought the patients shouldn't know what they were taking. But certainly in our country today we are dealing with a sophisticated public, and in most instances the patients want to know what they are taking, and they have a right to know what they are taking.

It is only occasionally that there is some psychiatric reason why you don't want to put a name on, and it could certainly be allowed, but if it were more generally accepted, I think it still would be a very wise thing. I would be very strongly in favor of feeling that the generic name should be on every bottle of medicine that goes out.

Senator NELSON. As I understand your testimony, you feel that the generic name should appear on every bottle except in a specific case

where a physician may have a special reason for requesting that it not be done?

Dr. TAUSSIG. Yes. I feel that if there really is good reason, he should have that right, and I think unless you were granted that there would be tremendous opposition, because of the few conditions where it is undesirable for the patient to know the name of the drug.

Senator NELSON. This has been precisely the same testimony that we have had from other distinguished authorities who have appeared before the committee. It still puzzles me why the AMA, the Academy of General Practice, or various professional organizations, have not taken a stand on this and advocated this kind of a practice, which is obviously in the public interest. Thus far we have heard no testimony to indicate that it would be contrary to the public interest.

Dr. TAUSSIG. I think it is in the public interest, and I think in fairness there are some physicians who specifically request it, but unless it is specifically requested when they write it, custom and tradition is such that it does not get on, and occasionally it doesn't get on then.

Senator NELSON. I might say we intend to take further testimony on this issue and hear all viewpoints.

Dr. TAUSSIG. I would back you strongly in saying that we should have the generic name on the bottle, and I say the generic name, because if it is produced under 50 different names, it is very hard to know whether you may not be changing to exactly the very same product you have had before.

Senator NELSON. After we hear further testimony, I intend to have legislation drafted which will require what your testimony and the testimony of other witnesses advocates. I hope that at that time you and many other experts in the field appear in behalf of this kind of legislation.

Dr. TAUSSIG. If I am here and able to, I certainly shall.

Senator NELSON. Now, if there had been this legal requirement that the generic name of the drug be included on the label in the case of thalidomide, is it your judgment that some of these cases of phocomelia would have been avoided?

Dr. TAUSSIG. I would hope so. I think widespread use—I say I would hope so, because we can't dictate what other countries are going to do. That is one of the difficulties, and a widespread variety of names occur in the sale of drugs in other countries as well as here.

Now, I don't know much here—they actually take the others—or they try to produce a better or a somewhat better and slightly different product in the various drug companies here, but it would then still have the basic principles on it, with the generic name on the bottle, so that you would know what it is.

Senator NELSON. As you recite in your testimony, there were 50 to 100 different brand names of thalidomide on the market.

Dr. TAUSSIG. Yes.

Senator NELSON. In South America there were five when they didn't think there were any. My question is, if the practice all over the world was to include the generic name might we have avoided tragedy?

Dr. TAUSSIG. If the practice was all over the world, yes; and even also if the people got suspicious and wished to know what they were taking when they bought drugs in other countres that they bring

into our country or if even they knew in our country it would have helped with the people who brought in the drug, had they known that the drug was thalidomide.

Senator NELSON. I notice you said in your article in the New England Journal and/or in your testimony that thalidomide was used in combination with a number of other drugs, and that these probably are sitting on somebody's shelves around the world now.

Dr. TAUSSIG. I wouldn't be a bit surprised.

Senator NELSON. And may still be used without any knowledge on the part of the individual that this dangerous drug thalidomide is in the preparation?

Dr. TAUSSIG. Yes.

Senator NELSON. I ask that this very fine article by Dr. Taussig be printed in the record at the conclusion of her testimony.[4]

Mr. GORDON. Dr. Taussig, I would like to clarify one point here. The chairman asked you in regard to the 50 infants, who were born with phocomelia in Brazil, whether some of these cases could have been avoided if the drug had been known by the generic name of thalidomide. I am not sure I understood the answer to his question.

Dr. TAUSSIG. Yes. I think they definitely would, for the simple reason that a number of physicians, I don't say how many, but certainly the physicians that I talked with from South America were well aware that thalidomide was a dangerous drug, and that they were telling me that they were fortunate they did not have thalidomide in South America. Therefore, I think if they had known that they did have it, they would have warned people against taking it. But they didn't recognize that there was any relation to thalidomide in the drugs they had. The names on the labels meant nothing to them.

Senator NELSON. As a matter of fact, you note in your article in the New England Journal, on page 93, that the Brazilian magazine Ocruziero had investigated the problem and the magazine writer was told that thalidomide was not on sale in Brazil, when in fact it was on sale, under five different trade names.

Dr. TAUSSIG. Absolutely. I think if they had known that it was on sale, they would have taken action, and I am quite sure the health department acted extremely promptly there when they found it out, but it just escaped them entirely.

Mr. GORDON. Given the potent drugs which are now being developed, is it your judgment that this type of a situation could occur again?

Dr. TAUSSIG. Yes, it is. As I have said, I don't think we can get absolute safety, it can't be guaranteed for any new product or drug, but certainly major risks can be detected by careful testing.

I think we have to know to prevent as much as possible, and furthermore testing in primates was required to demonstrate clearly that thalidomide did produce phocomelia. It is a question whether every drug can be so tested, but nevertheless elementary precautions must be taken.

Drugs can and should be tested in a variety of animals and a variety of ages, for instance, for pregnant mothers, and the aged people who are known to react differently to different drugs.

Although a drug may be tested and tried for a specific disease in a specific age group, and recommended for such, if the drug is effective,

[4] See supplemental information beginning at p. 1522, infra.

almost invariably the use of the drug will be extended beyond its original purpose both by the medical profession and by the lay people who so glibly recommend drugs to their friends. They think they know a great deal better than doctors know what is good for their friends to take.

Senator NELSON. In your article and/or your testimony, you refer to the fact that phocomelia did appear in tests using thalidomide at some stage in rabbits and in some other animals. From your checking in Germany, was there a failure here of proper testing of the drug to find this out? What kind of testing was done?

Dr. TAUSSIG. Well, the German laws are very much more lax than ours. There is extremely little animal testing done. Of course, at that time it was not the type of reaction they were looking for. They had not thought of considering this.

Really they felt it was a sleeping tablet, and when at first they tried it in animals and the drug didn't make any animals sleep, and so the company thought it must be something that will be good for epilepsy, and they sold it first as an anticonvulsant and word came back it was no good as an anticonvulsant, but it is a beautiful sleeping tablet for man, so then they sold it for that.

Subsequently after the drug was suspected of causing phocomelia, it was massive doses in rabbits that finally produced the malformation. I think we learned a great deal about testing since then, and since then it has also been found that nonhuman primates do react very similarly to man, and that you can produce phocomelia in the rhesus monkey with doses relatively comparable to man, with extraordinary regularity if the drug is given at the right time.

Of course, there remains the possibility that other drugs may cause other types of injury. Now we are beginning to recognize that as the organs are developing is the time that a drug will injure the organ. Once you have a good arm, you are not going to get a medicine that is going to injure the development of that arm.

We haven't in the least answered the question of whether you can alter the metabolism of an organ, whether you can change the function of the liver or the pancreas by a drug given later in pregnancy or whether you can hurt the brain later in pregnancy, so that you can't say the only time you should test for drugs is during the first or early portion of pregnancy; it is only during early pregnancy that a drug is going to produce organ difficulties.

It is a very, very complicated question. But a lot can be done by careful testing, to have indication of whether it is safe or not, and I am sure we will learn more.

But with it all, we ought to have very careful records kept when it is first tried in man, because you can't ever say that man always reacts even like the rhesus monkey. But you can keep very careful records and not have the widespread disaster.

The later the untoward the reaction comes out, the more difficult it is to trace it to the drug. If you see it immediately after it is relatively easy; if you see it 9 months after pregnancy it is harder; if you saw it as the child reaches maturity, it would be very hard to trace back what had been taken. But if we can keep careful monitoring of this, it is going to help us a lot, and it ought to go a long way to prevent a widespread disaster.

Senator HATFIELD. Dr. Taussig, according to my understanding, the USP standards are more physical than biological. Do I understand from your statement here about drugs that they can and should be tested on a variety of animals before use for the infants, the pregnant mother, and so forth? Does this recommendation of yours go beyond what are present USP standards?

Dr. TAUSSIG. I don't know how specific the regulations are. I think a number of doctors are working on the problem, and I think the various standards would follow very quickly when the best methods and the best animals for trial are known.

There is a great deal of keen interest in trying to determine it today, which we have learned from sad experience is necessary, and until one really appreciated it, one hadn't started to study which was best.

I think with our present experience, a few preliminary things are clear. If a drug is obviously bad for a variety of animals, it is probably bad for man. If it doesn't hurt those, it should be tested more carefully.

Senator HATFIELD. Do you feel then that there should be a more extensive and comprehensive testing than is presently used to establish USP minimum standards?

Dr. TAUSSIG. I think they are trying to do a pretty good job right now. I think that the ideal, perhaps even the best, is really not known. As I say, I think you have got to be fair to both sides, and to realize that drugs are tremendously valuable, and that you don't want to discourage all production of new drugs, but you certainly want to get all known dangers eliminated.

Senator HATFIELD. Let me ask you another question. When you say that the drugs react differently upon different people, how do we get then to the so-called equivalency tests and other such problems in dealing with the generic or brand names?

Dr. TAUSSIG. As to age groups, I think there is a general understanding today in testing various drugs that are going to be used for children, on very young animals, and on newborn animals, that older people react differently, and it is only really after this that we have seriously taken into consideration what is the effect on the fetus, and testing that.

Of course, the danger may be something quite unexpected. For example, if it is so good as a sleeping tablet for older people, why is it not equally good for a younger person or for a pregnant woman?

Senator HATFIELD. Will drugs act differently on different people within the same age group?

Dr. TAUSSIG. Well, some drugs. Of course, the sensitivity varies, some drugs people find more effective than others. This is an individual variation.

Senator HATFIELD. But doesn't this then raise a problem as to determining equivalency, efficacy, and all these other measurements of drugs?

Dr. TAUSSIG. I think it raises a problem. I don't believe it raises insurmountable problems, to know what is its reasonable probability. One difficulty lay in the lack of regulation for a clinical test. The doctor just gave a sample and the patient responds, yes, he had a good night's sleep; or, no, it didn't give him a good night's sleep, and that was considered as a trial and virtually no records were kept.

Senator HATFIELD. Do you think the USP should use more biological testing than what it does now to determine standards for these drugs? Do you feel that there is sufficient biological tests, as you advocate here, in using both animals and people to determine these minimum standards?

Dr. TAUSSIG. Well, I think they are doing a good job now in the face of a difficult problem. I believe, that the recent evidence that has been brought forth by James Wilson that you can produce phocomelia in Rhesus monkeys is going to encourage testing in these higher animals.

That is an expensive way of doing it, but, if it is going to save untold lives, it is going to be less expensive in seeing that a dangerous drug gets on the market. It will be expensive for the drug companies, but, if that is going to be the means of safety, the public will want it.

Gradually, I think, we are going to realize which drugs are likely to have more severe reactions than we have today. In other words, I wouldn't like to put more in the Bureau of Standards until we are perfectly sure we are giving the right lead and the right line.

Senator NELSON. Earlier in your testimony you referred to an article by Mr. Morton Mintz which appeared in the Washington Post on July 15, 1962, regarding thalidomide. You said you would furnish us with a copy. We have a copy of that article.

Dr. TAUSSIG. Oh, fine.

Senator NELSON. And I would request that at the end of your testimony the article by Mr. Mintz be printed in the record. Go ahead, Doctor.[5]

Dr. TAUSSIG. Thank you.

Senator NELSON. I think you were on page 6.

Dr. TAUSSIG. Yes, at the top. One of the basic simple elementary precautions is to have the generic name on every drug, and when the drug is a compound with the various preparations, each of the substances should be clearly listed so that the lay person and the physician may have the opportunity to know what the preparation contains.

The question has been raised as to inactive ingredients. These too, might be listed, so that people who are allergic to an inactive substance could know it. It is a very difficult thing of how much to list. You don't want to get so much on the label that nobody is going to read it.

The most important thing is to know, I think, if they are allergic to some inactive ingredient, that that person probably knows it and would try to find out whether it was in all the pills that come in.

Senator NELSON. But you do advocate that the generic name of the active ingredients of any drug or drug combination be placed on the label of the prescription bottle that the patient himself gets?

Dr. TAUSSIG. Yes. Let's be fair to the drug companies because they have produced many valuable drugs. The wonder drugs of today have altered the face of medicine. Private enterprise and the competition which results therefrom has been and is a tremendous stimulus, and we want this to continue. Quite rightly if a pharmaceutical manufacturer produces a superior product, they wish their name on the product. It could be either the name that catches the imagination or the name of the company.

[5] See p. 1525, infra.

Some drugs are chemicals which are manufactured by the ton. It seems doubtful that such drugs, for example, as aspirin, doriden or thalidomides vary in potency, but in these drugs competition keeps the price down.

Senator Nelson. The competition keeps the price down?

Dr. TAUSSIG. Yes.

On the other hand, potency can vary in the preparation of antibiotics, and probably in hormonal drugs and other synthetic preparations. Minor variations in manufacture may make a major difference. I believe in a very real sense the Food and Drug Administration can only demand certain standards.

Under most circumstances where standards are set, I think most persons or most manufacturers try to produce a superior product. It matters not whether it is minimal standards for a nursing home, for the care of laboratory animals or for drugs. By and large the persons involved in working with them try to do a superior job, especially when superiority brings profits.

It is highly desirable, and should be encouraged; therefore, together with the generic name the company's name should appear on the product.

The medical profession in turn should be encouraged to try the various products and try to determine which is most effective. There is no fear that the drug companies will not encourage them to try the various products. We need put no effort on that.

The doctors should know which preparation he is using, but above all he should know the various ingredients in the preparation he is giving. It is for that reason I firmly believe that the generic name of the drug or a simplified generic name should be on the name of the bottle as well as the manufacturer's name.

Senator HATFIELD. On the bottom of page 6, when you mention that the medical profession in turn should be encouraged to try the various products and try to determine which is most effective, are you speaking now within generic compounds and generic drugs?

Dr. TAUSSIG. Yes.

Senator HATFIELD. Or as between brand names or what?

Dr. TAUSSIG. I was speaking that if two companies produce products, for example, in antibiotics that are basically similar. There is variation in each. Of course, each drug firm is trying to produce the best one.

Senator HATFIELD. Yes.

Dr. TAUSSIG. That is true and we want them to try to produce it. There is no question about that. This is where we do get improvement in combination.

Senator HATFIELD. So there may be differences here even within a generic compound; is that right?

Dr. TAUSSIG. Yes; I believe so.

Senator HATFIELD. As to the efficacy and potency?

Dr. TAUSSIG. As to how it is finally produced. I think today we must meet basic minimum standards.

Senator HATFIELD. So in the competitive world of brand names of various manufacturers, there is this goal that they are seeking?

Dr. TAUSSIG. Yes.

Senator HATFIELD. To be better than their competitor?

Dr. TAUSSIG. I think so.

Senator HATFIELD. Even though they are dealing within the same generic relationship?

Dr. TAUSSIG. Either seeking to be better than their competitor or equally good and be able to price it lower. I think that is more like it, either one, but both of which——

Senator HATFIELD. And there may be therapeutic differences here in the generic——

Dr. TAUSSIG. Yes, I think there may. It is very hard to say.

I also believe that the pharmaceutical firms would derive certain benefits in having the generic name of the drug on the bottles. For example, if the generic name was on the bottle, it would prevent a less scrupulous company from marketing a product which did not contain the essential ingredient and giving the product such a closely similar name that people believe it is the same product.

This again is more outside the country than in the country. For example, Softenon was the trade name given to thalidomide sold in Spain. I was totally unable to find out whether Softenil contained thalidomide. It was a question of which company and then getting them to answer. But they are so close that anyone might perhaps think they were taking the same product.

In the same way the drug companies would derive another protection by having the generic name on the label. Were such a procedure common, it would prevent the less scrupulous company from studying the formula, manufacturing the drug, and selling it under a different name. Although such a procedure is illegal, nevertheless this certainly occurred in the case of thalidomide. It was outside this country of course. Moreover, when this occurs it is only if the sale is of sufficient magnitude does it pay the original manufacturer of the drug to sue the other company.

Our Food and Drug Administration I believe prevents the stealing of formulas on any wide scale in the United States, and of course the FDA has no control over what happens within a State, and it has no control of what happens outside the country. The FDA is concerned with interstate commerce.

We cannot control drug manufacturers throughout the world, nor should we attempt to do so, but I do think we should keep our own house in order. And I think it helps to set a standard of what you hope others will follow suit in doing.

Are there any further questions here before I turn to another subject?

Senator NELSON. No, go ahead.

Dr. TAUSSIG. This brings me to another problem which I hope will be of vital concern to your committee; namely, the quality control of the drugs which are exported from the United States. My interest and concern in this problem was aroused last May in 1967 when President Johnson gave me the privilege to attend the World Health Organization Assembly in Geneva as an alternate delegate.

One of the major subjects of discussion was the quality control of drugs. This subject had been under study by the World Health Organization for several years, but little had been achieved.

The official record of the World Health Organization, volume 157, the Executive Board of the 39th Session in Geneva, January 1967, on the quality control of pharmaceutical preparations:

Having considered the report of the Director General on the quality control of pharmaceutical preparations, noting that this matter has been the subject of repeated discussion at previous sessions of the Executive Board and the World Health Assembly;

Bearing in mind resolution WHA 18.36, which invited governments to take the necessary measures to subject pharmaceutical preparations, imported or locally manufactured, to adequate quality control;

Recalling particularly resolution WHA 19.47, requesting the Director-General to continue his assistance to member states for the improvement of the quality control of pharmaceutical preparations, and for the establishment of quality control laboratories for national or regional purposes, as well as the establishment of general principles for the quality control of products entering into international commerce;

Noting with concern that the requests of member states that drugs should not be exported without having been subject to the same quality control as those issued to the home market in the country of origin are not yet generally applied, and that in many cases pharmaceutical preparations are continuing to circulate without such control;

Noting, however, with appreciation, that certain member states are prepared—

And we are, too—

to place their facilities for quality control at the disposal of other countries, upon request to W.H.O. or direct to the member states.

1. Considers that the formulation of generally accepted principles for quality control of pharmaceutical preparations entering international commerce and their adoption by all member states are desirable; and

2. Requests the Director-General:

(i) to proceed with the formulation of such principles;

(ii) to continue to assist member states in developing facilities for quality control of drugs they may have to import, or in securing access to facilities elsewhere; and

(iii) to report to the Twentieth World Health Assembly.

Professor Geric opened the discussion saying—

that the head of his delegation had referred, in the general discussion to quality control of pharmaceutical preparations as a question to which his delegation attached particular importance. The subject had been considered by the Health Assembly for many years. There was still inadequate control of preparations exported to the developing countries and on occasion out-of-date preparations were exported.

Senator NELSON. I note from the Food and Drug Act that the only requirement that exists for the exportation of drugs from this country to foreign countries is that—

A food, drug, device or cosmetic intended for export shall not be deemed to be adulterated or misbranded under this Act if it, (1) accords to the specifications of the foreign purchaser, (2) is not in conflict with the laws of the country to which it is intended for export, and (3) is labeled on the outside with the shipping package to show that it is intended for export, but if such article is sold or offered for sale in domestic commerce, this subsection shall not exempt it from any of the provisions of this Act.

Now my question is this: If the requirement is that a drug exported from this country "accords to the specifications of the foreign purchaser and is not in conflict with the laws of that country," it seems to me that your criticism is well directed, since there probably are no underdeveloped countries in the world which have laws on the matter or have the expertise or competence to develop the laws. Further, they

do not have the scientific personnel to set the standards and enforce the law in any way; is that not correct?

Dr. TAUSSIG. I think that is the great thing. The drug importing nations are on the whole the developing nations. The small nations do not begin to have the facilities to inspect the drugs to see what they are getting or to set the standards for what they want.

Senator NELSON. I think I can guess from your testimony what you would say, but let me put the question specifically. Do you see any reason why the laws of our own country under the Food and Drug Act should not set standards as high for the exportation of drugs to other countries as for the distribution and consumption of drugs in this country?

Dr. TAUSSIG. I see no reason; I think it is a disgrace that we do not. I think we should not sell drugs to foreign countries that we would not permit to be sold in our own country. Now that is all the developing nations are asking, that they could be assured that they were of the same quality that is required in the exporting country.

Senator NELSON. I want to say to you that the Chair agrees with you 100 percent that it is a disgrace that our law will permit us to sell drugs in the international trade to foreign countries that are not equipped to protect themselves of a quality not considered to be adequate for consumption in this country. The committee certainly appreciates that you have called this to our attention and the committee will address itself to that problem with some appropriate legislation if that seems to be the best way to deal with it.

Dr. TAUSSIG. Thank you. I think that the rest of my testimony shows that the World Health Organization is not a police force, that they cannot dictate to our country what we can sell elsewhere. They can only hope to recommend, and it certainly has not come forcefully home to our country that we are selling drugs to foreign countries, not observing the same standards for export that we require in this country. There is some feeling that the smaller countries should set their own standards, but I think that practically it is impossible, and that the testimony at the World Health Assembly showed that most countries thought it was asking more than could reasonably be expected from a small emerging country.

Senator NELSON. The Chair would simply state that the Chair agrees with you that this country has a moral obligation to distribute in international trade drugs of equivalent quality to those we distribute in our own domestic market.

Dr. TAUSSIG. That is right.

Senator HATFIELD. Dr. Taussig, what kind of a position does this kind of situation put the American representative on the World Health Organization in?

Dr. TAUSSIG. Well, I think that everyone felt that it was an important thing. Dr. Blood said that the U.S. Government would be glad to help other countries in testing their drugs or to help in setting up an international committee and that they were glad to put their consultative technical assistance and their training facilities to use by the World Health Organization and to help any countries that they could. They did not feel that it was perhaps a problem to legislate.

Senator HATFIELD. Do you not think that puts us in a rather hypocritical posture though, if we are out trying to assist other countries

through the Peace Corps, through economic aid, and all these other things, and this kind of action is permitted?

Dr. TAUSSIG. And this kind of action comes in. Yes, I do. I think it is a very, very disgraceful thing.

Senator HATFIELD. It tends to undo all the other work we try to do.

Dr. TAUSSIG. The FDA undertakes—I believe the new drugs are regulated, but not the antibiotics, and technically I think that if the pharmaceutical firms say this drug is potent at the time they are selling it, and then take off the expiration date—they do not have to put on an expiration date—by the time the drug is shipped halfway around the world, and by the time it has been bought in quantity, and dispersed again it may be a good deal later.

The drug may have been potent at the time it left this country, but by the time it got distributed over there, it was no longer within the date.

Senator HATFIELD. Is there a way for the manufacturer to anticipate the time of use?

Dr. TAUSSIG. Well, all the antibiotics give you the date of expiration. Now the pharmaceutical firms will say, and I think it is true, that most of them are still potent quite a considerable period of time, but how long beyond is not known. The last thing the developing nations want is to get a drug which is not a potent drug, and no country likes to have it said "It is good enough for your country but it is not for ours. We do not know if it is potent, but you can use it."

Senator HATFIELD. According to your answer to the question of the chairman, we are in effect permitting the marketing of a lesser standard, lesser quality of drugs than we permit our own people in this country to use.

Dr. TAUSSIG. Yes, and that, I think, is wrong. And there is another point in that regard, that if you are considering legislation that I would like to bring to your attention, and it is the further problem, and I do not think it is in the least an insurmountable problem, that there are some pharmaceutical companies, and naturally we are in the group manufacturing and exporting, that manufacture some drugs for export that are not used in their own country, so that you do not have the same standard of quality control.

Sir George Godber of England expressed the opinion that for drugs which were manufactured but not used in the producing country, it would be possible to use standards that were used in another country that did both produce and use the drugs. And something to that effect or that some other regulations should come in is quite important.

For example, we have very little leprosy, it is practically unknown here. The parasitic infections are a tremendous problem in many of the other countries of the world but scarcely one of concern to us. Nevertheless our drug companies are interested.

Schistomiasis is a widely prevalent parasitic infection that is found in contaminated water and the drug firms are making a tremendous effort to find and sell some beneficial drug. The best product I was told has been developed by Ciba, which is partly a Swiss company, and of course we do not control that, it is a drug which is taken by mouth. It has been effective. They had a clinical trial in Africa, and they said this is a fine drug.

Japan and the Philippines reported very serious reactions of hallucinations and even convulsions from taking the drug.

There was a meeting of the New York Academy of Science discussing it and these facts were brought out, and in the end the feeling of our scientists here was that it was not a drug that should be distributed as mass distribution out in the country, because under such circumstance it could not be controlled. It was a good drug for use in the hospital.

The drug companies, as I understand it, said well, it does not cause liver damage and the untoward reaction is not irreversible if the drug is stopped, we think it is safe for mass distribution. Our scientist did not agree.

Now Parke-Davis has a drug that is a suppressant. I do not know that they will, but it is the natural thinking that the drug companies try and consider "Now can we produce a better drug that has this benefit but not this bad side effect?

Well now, if they do, certainly that drug ought not to be sold massively in that country, if we have not had some trial or supervision here, at least know that they have had a careful clinical trial there to know that it is safe before it is widely sold.

I think we ought to have some regulation. If the drug is never going to be used in this country, we should have some check of a controlled clinical trial before we give our approval for sale, or large scale, in foreign countries.

I think you will see that this is a little different question than that which we consume in our country and then export and that which is merely made for export, and yet I think we should be honorable there and as careful as we reasonably can be, and certainly I would feel very badly if I thought that we even could allow, permitted the drug company to export a drug that had not been carefully tested, or reasonably carefully tested. I suppose, nothing is perfect.

Senator NELSON. Do we allow a company to sell a drug overseas that has not been adequately tested to met the FDA standards in this country?

Dr. TAUSSIG. Well, I think that if the drug is not used in this country, it does not have to pass any FDA standards in this country, if it is not for sale in this country.

Senator NELSON. I did not realize that.

Dr. TAUSSIG. I think so. I think if it is not for sale in this country, just as much as within a State as I understand it, the company can produce anything. They cannot produce a great deal that is not interstate, and when it is interstate the FDA regulates and puts in its regulations.

I think that is straight, that any small pharmaceutical firm can produce anything for sale within its State that does not pass the FDA.

Senator HATFIELD. Mr. Chairman, Dr. Taussig, do we have any problems with imported drugs from other countries on this same basis?

Dr. TAUSSIG. Well, I think the imported drugs from other countries, major ones, are imported and sold through some pharmaceutical firm to which they sell the rights. I think the FDA does not allow drugs to be sold interstate that have not passed regulations. Of course, that is where they were able to hold up thalidomide. And they wanted

to know if it was safe. It has been a very bitter bone of contention between the pharmaceutical houses and the FDA. They say if it is all right in other countries why is it not sold in our country? Why is it not safe? Is that not a good enough clinical test?

I think thalidomide showed it was not a very good clinical test.

Senator HATFIELD. In other words, a drug manufactured in country S cannot be imported into this country for direct distribution to a consumer?

Dr. TAUSSIG. I do not know.

Senator HATFIELD. It has to be through a drug house, a pharmaceutical house, which in turn comes under the control of FDA; is that correct?

Dr. TAUSSIG. I would have to look up the law. I do not know whether drug manufacturers can sell directly over here. He must have some campany that represents him over here, and I think once he is represented here, I think so, but I would ask you to check that to be sure of the law in this problem.

Senator NELSON. You mentioned some time back the concern World Health Organization has expressed about the shipping of out-of-date drugs. Can you of your own knowledge give us any specific cases, and if not, does the World Health Organization have on file specific cases of drugs that were shipped out of our country which were out of date at the time of shipment, or because of the distance and the problem of distribution were out-of-date before they could be consumed in the receiving country?

Dr. TAUSSIG. I do not know what the World Health Assembly or Organization has on file. I do know that it was repeatedly emphasized that a lot of the countries were receiving outdated or poor medications, and I do know that we are not the worst offenders, but I dislike to think we are or even could be offenders at all.

As regards my own particular experience, I do know of a slightly different experience at the Hospital Amazonica Albert Schweitzer in Pucallpa, which is high in the Andes where Dr. Binder is taking care of a great many of the Indians. It is an extraordinary hospital, and again as most such hospitals is financed on extremely limited funds, and he requested his organization to help get some drugs.

When I was there they were trying to treat tuberculosis without any of the modern drugs at all. He told me that they had been sent a shipment of drugs which the drug houses had contributed, and that most of the antibiotics were out of date by the time they reached him. He said, he did not know whether the drugs were potent but they had a date but the expiration date had gone by, by the time that the drug actually reached him. When shipping drugs one should take into consideration the time required for the trip, plus clearing customs, let alone distributing it; in addition one does not use up all drug supplies in a couple of weeks or a month after it gets there, you hope that the drug supply is going to last some time. Dr. Binder could not possibly have offered the drug to other hospitals in the region, because he did not want to offer to other hospitals drugs that he thought were bad and that he knew were out of date.

Senator NELSON. How did he know they were out of date?

Dr. TAUSSIG. Those had an expiration date on them, and the expiration date had gone by, by the time it had reached them.

Senator NELSON. So this was a contribution from a drug house, but by the time he received it the expiration date had passed.

Dr. TAUSSIG. It really was not much of a contribution by the time they received it. Moreover, he would have been very much more suspicious had he got the next batch without any date on it.

Senator NELSON. It would be interesting to find out whether it was a deductible expense also.

Go ahead, Doctor.

Dr. TAUSSIG. I think that mainly the rest of my testimony here was emphasizing that they did feel very strongly that quality control of drugs was needed and I mention on page 13 that I did not know the law regarding the export of steel, but that the U.S. Government or a manufacturer in the United States, if it sold steel of inferior quality and the building collapsed, I am sure the repercussions would be great and terrible. But unfortunately, when we permit the sale of an antibiotic which is no longer potent and people die in a far-off country where disease is rife and the mortality rate is already high, nothing is heard therefrom. Nevertheless, such a thing is possible and it is a disgrace to the Nation. Not only is it morally wrong not to insure that the drugs that are exported are of the same quality that is required for home consumption, but I think our relations with other nations demand that disasters and deaths from the use of impotent and out-of-date preparations should not be permitted to occur and far less tolerated.

Furthermore, if the richest country in the world does not care whether it exports pharmaceutical products that are substandard in quality, how can we expect other countries not to do the same. I do not think it is a matter that the World Health Organization should try to control. I think the responsibility rests in each country. I feel that we have a moral obligation to do so.

Dr. Alan of Turkey said "only some of the producing countries and a minority of the importing countries are in a position to offer effective control. Accordingly, the majority of the population of the world are being treated by pharmaceutical preparations that have not been carefully controlled."

The Russian delegation expressed the importance of it, especially in the developing countries, against the flood of preparations, many of them of inferior quality which are released in the market.

One delegate said that the best solution would be for the countries exporting pharmaceutical preparations to apply the same strict control measures as they provided in preparations within their country, and I certainly hope that our national pride and our fundamental honesty demands that the Congress of the United States enacts such legislation to be the law of the land. Simply do unto others as we would be done by.

I am really ashamed that we permit and even foster the dispensing of pharmaceutical products to other lands that are not permitted to be sold in this country.

Senator NELSON. Let me say again that the committee certainly appreciates your calling this to our attention. I certainly agree with you that our national pride and fundamental honesty demands that the U.S. Congress should enact legislation which would make it the

law of the land that the drugs we export meet the same standards required of drugs to be distributed domestically.

Dr. TAUSSIG. I will be happy to come and testify again.

Senator NELSON. We will draft some legislation to that effect and perhaps invite you back, if you are willing to come, to testify specifically on this question.

Dr. TAUSSIG. I shall be happy to come.

Senator HATFIELD. Dr. Taussig, I wonder do you know whether or not the ability to control the quality of exported drugs would necessitate special or new legislation, or do you know whether the FDA could do this now under its present authority?

Dr. TAUSSIG. I understand that it did not have authority to do it.

Senator HATFIELD. It did not have authority. This would need specific legislation.

Dr. TAUSSIG. I think it would necessitate this. I think Mr. Gordon told me that they did not have the authority.

Mr. GORDON. Mr. Chairman, I ask that some statistics on thalidomide which were secured recently from the Food and Drug Administration be inserted in the record at the appropriate place.

Senator NELSON. They will be inserted in the record.

(The statistics referred to follow:)

(Excerpts—Hearings on Interagency Coordination in Drug Research and Regulation, Senate Subcommittee on Reorganization and International Organizations, Committee on Government Operations, August 1 and 9, 1962, 87th Cong., 2d Sess., Pt. 1, p. 249)

THALIDOMIDE

U.S. Statistics as of August 21, 1962:

1. Deformities caused by "Kevidon" in the U.S.: 9 children were born with deformities definitely attributable to the drug; 5 cases of deformity in addition were possibly related to the drug.
2. Approximately 1267 physicians had Thalidomide to give to their patients on an experimental basis.
3. Approximately 19,822 people were given Thalidomide by these clinical investigators.
4. Approximately 624 pregnant women were given Thalidomide.
5. Prior to FDA decision to confiscate the drug, no reports on its effects had appeared in U. D. medical literature.

Dr. TAUSSIG. That completes my testimony, thank you.

I believe you have the articles, at least two of them that are together, in the record.

Senator NELSON. Which two do you refer to?

Dr. TAUSSIG. The one in the New England Journal, and the editorial on lesson of the effects of thalidomide.

Senator NELSON. Yes; we have your article on the New England Journal and the editorial as well as Mr. Mintz's article.

Dr. TAUSSIG. I do not know whether you care to have my original article published in the AMA or not. If so, you are welcome to it.

Senator NELSON. Yes; do you have a copy of that?

Dr. TAUSSIG. I have a copy of that and I have a copy of the article that came out in the Scientific American only that it is written for lay consumption and is perhaps more comprehensible, but I do not think there is anything very technical in my article for the medical profession.

Senator NELSON. We would like to have each of those, and they will be inserted in the record in the appropriate place.

Dr. TAUSSIG. Thank you very much.

Senator NELSON. I want to thank you very much, Dr. Taussig. Your testimony has been very helpful to the committee, and we appreciate your taking the time to come here.

Dr. TAUSSIG. Thank you.

Senator NELSON. Senator Hatfield, did you have any questions?

Senator HATFIELD. I have no other questions.

I note that you have inserted Mr. Mintz' article in the record. There are a number of other articles that I have seen, and it seems to me that they might all be made at some point appropriately a part of this record.

Dr. TAUSSIG. If you would like, I would be glad to send you a list and you can select what you wish.

Senator NELSON. There have been some very fine articles on thalidomide that are appropriate at this point, and if the minority and majority counsel could call them to our attention, we will insert them at the proper place in the record. And, Dr. Taussig, if you have any additional articles relevant to the testimony you have given today that you think would be helpful to the committee, and valuable to the hearing record, we would appreciate your sending them to us.

Dr. TAUSSIG. Thank you very much. I will be glad to.

Senator NELSON. Thank you very much, Doctor.

Dr. TAUSSIG. Thank you.

(The prepared statement and supplemental information submitted by Dr. Taussig follow:)

STATEMENT OF DR. HELEN B. TAUSSIG, PROFESSOR EMERITUS OF PEDIATRICS, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

I am Dr. Helen Taussig, Professor Emeritus of Pediatrics at the Johns Hopkins University, and best known as co-developer with the late Dr. Alfred Blalock of the "Blue Baby" operation, and also known to this committee as the doctor who alerted the medical profession and the country to the dangers of thalidomide.

By way of introduction may I explain to you how I first heard about thalidomide. One of my former fellows, Dr. Alois Beuren of West Germany had studied with Dr. Bing and Dr. Andrus and then studied with me for a year in the days when Congress permitted post-doctoral trainee fellowships of the National Institutes of Health to be granted to foreign doctors. I emphasize this because although some foreign fellowships have been abused, others have brought rich returns. In a very real sense the same is true about trainee fellowships as is true of research fellowships. Just as only a small percentage of research pays off but that which pays off, pays off with such high dividends that it justifies all the other money which goes into research. So it is in traineeships. Only a few pay off with high returns both to their own country and to ours. The only difference between the two is that virtually every doctor is a better doctor for having had an additional period of training. Dr. Beuren's training brought rich returns in Germany and here. Thanks to his training in this country he was given the first Chair of Cardiology in Germany. Thanks to an evening he spent at my house when he returned for a brief visit that I heard about thalidomide. That evening he told me that the doctors in West Germany were seeing a great number of children born with gross malformations of the extremities, little flippers instead of arms or legs, or no arms or no legs; and what was more, that Dr. Lenz thought the malformation was caused by a sleeping tablet. It was the next morning before I realized the full implication of the situation, namely, the danger which might lurk in drugs if indeed it were true that a sleeping tablet did cause such a malformation. Dr. Beuren had left for Germany so I wrote, air mail, asking if I would be welcome to investigate the situation? Dr. Beuren telephoned transatlantic "yes" and three weeks later I landed in Hamburg and Dr. Beuren's Chief, Dr. Joppish, loaned me their best resident to help with my travels.

Two points must be clearly held in mind. I went to Germany because I realized that if true, the phenomenon had wide and serious implications. Nevertheless, Dr. Frances Kelsey in the Food and Drug Administration was the person who refused to release thalidomide for sale in this country. She saved this country from untold tragedy. My investigation not only clinched the matter in her mind but ordinarily the public never hears of the drugs which are *not* passed by the Food and Drug Administration; hence this country might never have realized the potential danger in drugs had I not gone to Germany. In spite of the fact that three to five thousand children were injured in West Germany and the country was wrought with anxiety and fear, we knew nothing of it. When Dr. Lenz first announced that he thought that thalidomide might be the cause and the drug was withdrawn from the market, I am told the publicity in West Germany was tremendous. News was carried on radio, television and the front page of virtually every newspaper in the country and yet the news scarcely reached the American press. Certainly our country was not disturbed. Time magazine picked it up, sent a man over to investigate and published one brief column on "the nightmare of a sleeping tablet." (February, 1962). Some persons read the report but the true significance was not appreciated at that time. After my trip to West Germany, I reported my findings to the American College of Physicians in April, 1962 and to the American Pediatric Society in May, 1962, and on May 24, 1962, I testified before the Antitrust Sub-Committee of the Judiciary Committee on H.R. 6245. The Journal of the American Medical Association, issue of June 30, 1962, carried my first medical article on the subject and the Scientific American published my lay article in August, 1962. Nevertheless, Morton Mintz' article in the Washington Post, on July 15, 1962, did more to inflame the country than any other single article. I have a copy of his article; will you kindly incorporate it into the record at the appropriate place?

The major purpose of my testimony today is to re-emphasize the danger that may lurk in drugs and the difficulty which the lay public has in identifying a drug.

As drugs become more specific and thus more useful, they become more potent and consequently the danger of side-effects increases. Furthermore, the late side-effects are the hardest of all to detect. If you take a pill and you immediately develop hives or you shortly thereafter develop nausea and vomiting, or diarrhea, you readily connect the reaction with the drug. If so, you certainly want *not only* to know the name of the drug but also what other preparations contain the same substance. In contrast to this, when you take a drug and everything is lovely afterwards, as with a sleeping tablet and you've slept well and awake refreshed, it is fine. You may well like to know what you have taken. Nevertheless, that particular pill satisfies you. As long as you can purchase it, all is well and good. Moreover, if you get the relief you need you care little about the price (a point to which I shall return).

You continue to take the drug and other drugs too, and after a year or two you develop polyneuritis, that is, numbness and tingling in your hands and feet. You cannot sleep and you take more sleeping tablets, and you take the best sleeping tablets you have ever had, namely, the same one you took a year or so ago. It is a long time before you or your doctor realize that the nervous trouble you are suffering from is caused by the long continued use of that sleeping tablet. Then the problem arises to know what other medicines contain that ingredient. Sleep brings relief to many ills. A great many conditions, perhaps the majority of illnesses, are helped by sleep. Thus, if you have a headache or arthritis, a pill which relieves the pain, and when combined with one which will give you sleep, is very beneficial. The same is true of a gastro-intestinal upset, of an asthmatic attack or a migraine headache. Alas, even the morning nausea of early pregnancy is relieved by a tranquilizer. Most sleeping tablets given in small doses act as tranquilizers. Hence, thalidomide was combined with many other drugs and each combination was given a new name! The drug was so good that the pharmaceutical rights for manufacture were sold to drug firms in many other countries and the accepted practice is that each firm which manufactures the drug has permission to use a brand name of its own choosing. So when the danger of thalidomide was recognized it was found that the drug was masquerading under at least 50, if not 100 or more, different names. Appendix I gives a list of names which I have verified as containing thalidomide. I was told by one of the leading European pediatricians that the list is far from complete.

Incredible though it initially seemed, it became evident that one pill of 50 mgm. which was less than one-half of what had been considered full strength and

entirely safe, if taken at the critical time during pregnancy could severely injure the fetus. The usual adult dose was 100 mgm. The medicine was considered safe, so safe that man could not commit suicide by overdose, yet one dose of 50 mgm. could cause a serious malformation in the unborn child. Indeed, nine doses of 30 mgm. have been known to injure the fetus seriously. Moreover, I believe that only one of the degredation products of thalidomide injures the fetus and that product is only in the blood stream for an hour or two. Hence it is not a cumulative effect but rather it would appear that each of the nine doses of 30 mgm. injured the embryo at a particular stage in fetal development and the result was a severely damaged child (no arms or legs). The evidence is overwhelming that a single minute dose of a toxic substance can be highly injurious. The embryo is tiny and only a minute amount of a toxic material is required to injure it at a specific point. Another thing learned from thalidomide was that a chemical may have an entirely different effect on an embryo or a fetus than on a person after birth. Thalidomide was found to react with mesenchymal tissue (the forerunner of muscle and bone) in the embryo and on nervous tissue of the adult.

In addition it is extremely important to appreciate that the medical profession now recognizes that a number of conditions are the late effects from an earlier insult. When the late result becomes manifest that is the starting point for the investigation. In the case of thalidomide the starting point was the malformed infant. The natural supposition was that something had injured the fetus during pregnancy. Drugs may not be the only thing which could cause injury, some element in detergents might, some food preservative might, air pollution might. Indeed such possible sources were investigated in Germany. Today we are discussing drugs and how best to have drugs both as potent as possible and as safe as possible. The problem is how to detect the injurious reaction or side effect to the drug when they do occur. Clearly the more names the offending agent is distributed under, the more difficult is the problem of detection. The difficulty in the detection of a drug sold under trade names is illustrated by the fact that not until August 1962 was it discovered that thalidomide was sold under five different names. Moreover, a surprise search by the health authorities resulted in the confiscation of two and one-half million pills (or boxes of pills), 46,000 flasks containing thalidomide, and 96,000 kilograms of the pure substance in Sao Paulo. Thus, it is obvious to everyone that if an epidemic is nationwide or worldwide and the casue of the epidemic lies in the product which is sold or distributed under 100 different names, the detection and recognition of that product is extremely difficult. I shudder to think that if a drug was ever produced which was a tranquilizer, a good tonic, or a drug claimed to increase virility and it affected the sperm in such a manner as to injure the brain or even the reproductive organs of the fetus, how difficult it would be to trace that drug and how virtually impossible if the drug masqueraded under 500 different names! This is not an impossibility nor in truth is it more improbable than landing a man on the moon seemed thirty years ago. Hence, the value of having the generic name on the label seems incontrovertible.

Absolute safety cannot be guaranteed for any new product or drug. The major risks can be detected by careful testing. Furthermore, testing in primates was required to demonstrate clearly that thalidomide produced phocomelia. Perhaps every drug cannot be so tested but, nevertheless, elementary precautions can be taken. Drugs can and should be tested on a variety of animals and a variety of ages, for infants, the pregnant mother, and the aged are known to react differently to drugs. Although a drug may be tested and tried for a specific disease in a specific age group, if the drug is effective, almost inevitably the use of the drug will be extended beyond its original purpose both by the medical profession and by lay people who so gibly take a drug recommended by a friend.

Again, one basic simple elementary precaution is to have the generic name on every drug and when the drug is a compound of various preparations it should have each of the substances *clearly* listed so that the lay person and the physician may have the opportunity to know what the preparation contains. The inactive ingredients, too, should be listed as some people may be allergic to the inactive ingredient, but they should not be listed as conspicuously as the active ingredients.

Now let us be fair to the drug companies for they have produced many valuable drugs. The wonder drugs of today have altered the face of medicine. Private enterprise and the competition which results therefrom has been and is a tremendous stimulus. We want progress to continue. Quite rightly, if a pharmaceutical manufacturer produces a superior product they wish their name on the product. It could be either a name that catches the imagination or it could be the

name of the company. Some drugs and chemicals are manufactured by the ton. It seems doubtful that such drugs, as for example—aspirin, doriden, or thalidomide, vary in potency but in these competition keeps the price down. On the other hand, potency can vary in the preparation of antibiotics and probably in hormonal drugs and other synthetic preparations. Minor variations on manufacture may make a major difference. I believe in a very real sense the Food and Drug Administration can only demand a certain standard. Under most circumstances where standards are set, most persons or manufacturers try to produce a superior product. It matters not whether it is minimal standards for a nursing home, for the care of laboratory animals, or for drugs. By and large the persons involved try to do a superior job, especially where superiority brings profits. In the competitive world the pharmaceutical firms try to produce superior products. This is highly desirable and should be encouraged and therefore together with the generic name, the company's name should appear on the product. The medical profession in turn should be encouraged to try the various products and try to determine which is most effective. The doctor should know which preparation he is using, but above all he should know the various ingredients of the preparation he is giving. Therefore I firmly believe that not only the generic name of the drug (or a simplified generic name) should appear on every bottle but also the manufacturer's name. The pharmaceutical firms would, I believe, derive certain benefits by having the generic name of the drug on the bottle. For example, if the generic name was on the bottle it would prevent a less scrupulous company from marketing a product which did not contain the essential ingredient and giving the product such a closely similar name that people believe it is the same product. For example, *Softenon* was the trade name under which thalidomide was sold in Spain. I was unable to find out whether or not *Softenil* contained thalidomide.

The pharmaceutical firms would also derive another protection by having the generic name on the label. Were such a procedure common practice, it would prevent the less scrupulous companies from studying the formula, manufacturing the drug and selling it under a different name. Although such a procedure is illegal, nevertheless, this occurred in the case of thalidomide. Moreover, only if the sale is of sufficient magnitude does it pay the original manufacturer of the drug to sue the other company. Our Food and Drug Administration regulations, I believe, prevent the stealing of a formula on any wide scale in the United States but the F.D.A. has no control over what happens within a state and "support your local product" is a common slogan.

We cannot control drug manufacturers throughout the world nor should we attempt to do so, but we can and should keep our own house in order.

This brings me to another problem which should be of vital concern to your committee, namely, the quality control of the drugs which are exported from the United States. My interest and concern in this problem was aroused last May (1967) when President Johnson gave me the privilege to attend the World Health Organization in Geneva as an Alternate Delegate. One of the major subjects of discussion was the quality control of drugs. This subject had been under study by the World Health Organization for several years but little had been achieved. The Official Record of the World Health Organization, Volume 157. Executive Board report of the 39th Session in Geneva 17–27, January, 1967, (EB.39.R8) on the Quality Control of Pharmaceutical Preparations:

"Having considered the report of the Director-General on the quality control of pharmaceutical preparations:

"Noting that this matter has been the *subject of repeated discussion at previous sessions of the Executive Board and the World Health Assembly;*

"Bearing in mind *resolution WHA 18.36, which invited governments to take the necessary measures to subject pharmaceutical preparations, imported or locally manufactured, to adequate quality control:*

"Recalling particularly resolution WHA 19.47, requesting the Director-General to continue his assistance to Member States for the improvement of the quality control of pharmaceutical preparations, and for the establishment of quality control laboratories for national or regional purposes, as well as the establishment of general *principles for the quality control of products entering into international commerce.*

"Noting with concern that the requests of Member States that drugs should not be exported without having been subject to the same quality control as those issued to the same market in the country of origin are not yet generally applied, and that in many cases pharmaceutical preparations are continuing to circulate without such control;

"Noting, however, with apprehension, that certain Member States are prepared to place their facilities for quality control at the disposal of other countries, upon request to W.H.O. or direct to the Member States.

"1. Considers that the formulation of generally accepted principles for quality control of pharmaceutical preparations entering international commerce and their adoption by all Member States are desirable: and

"2. Requests the Director-General:

"(i) to proceed with the formulation of such principles.

"(ii) to continue to assist Member States in developing facilities for quality control of drugs they may have to import, or in securing access to facilities elsewhere; and

"(iii) to report to the Twentieth World Health Assembly."

Professor Geric (Yugoslavia) opened the discussion (quoted from page 2—A20/P&B/SR/8. and recalled "that the head of his delegation had referred, in the general discussion to quality control of pharmaceutical preparations as a question to which his delegation attached particular importance. The subject had been considered by the Health Assembly for many years. There was still inadequate control of preparations *exported* to the developing countries and on occasion *out-of-date preparations were exported.* It was apparent, accordingly, that the problem was a grave and complex one. The time had come for energetic, albeit, cautious action by the international community with a view to arriving at some solution."

The problem is grave and complex as the quality control of drugs concerns the identification of the product, the purity, the sterility, and also the importance of the study of toxic effects, and in addition, the process of packaging and labelling. An ideal solution may be difficult to arrive at and virtually impossible for the World Health Organization to control the manufacturing process in the various nations. Nevertheless, a few broad facts emerged: First, that the nations of the world were divided into three groups, those who manufacture drugs but did not export them; second, those who manufacture and export drugs; and third, those who do not manufacture and only import drugs. Moreover, the repeated plea from the developing nations, which by and large are the drug importing nations, was that the same level of quality should be required for the drug which was exported as for those destined for home consumption.

Dr. Otolorin of Nigeria, stated that the countries importing pharmaceuticals required *something positive to be done to protect these countries from malpractice.* He said that he, like the Delegate from Norway, was taken aback by the statement: "At the 19th World Health Assembly a suggestion was discussed for a system of certification to be evolved for drugs to be exported in order to ensure that they were subjected to the same quality control as applied to drugs for consumption in the exporting country. It was concluded that such a system did *not* appear feasible". Such a regulation may not be feasible for the World Health Organization to enforce but surely no more reasonable request was ever voiced by importing nations than that the drugs which were *exported* to them should be subject to the same measures of control as these drugs were for home consumption. Not only the Delegate from Nigeria voiced this request but also the Delegates from Senegal and from Spain. This was the repeated plea from the developing nations of the world.

The World Health Organization is not a police force and therefore such a regulation does not appear feasible for W.H.O. to enforce. Therefore, W.H.O. turned its attention to trying to set up a mechanism to help the importing nations test for the quality of drugs they import.

Furthermore, our government has offered to aid the drug importing nations in testing the quality control of the drugs they import. I quote from Dr. Blood's report (of U.S.P.H.) in which he reiterated "that wider national and international control of pharmaceutical products continue to be a matter of very great concern to our country. His government (i.e., the United States Government) had been and would continue to be ready to provide consultative technical assistance and training facilities to W.H.O. or any of its Member States in developing international standards and national codes for control, manufacture, processing, packaging or marketing of drugs. It was also prepared to provide certain testing services if some practical international system could be developed under the aegis of W.H.O.".

I am glad that the United States Government, through the U.S.P.H.S. has offered to help the drug importing nations to test their drugs. This approach to the problem is, however, unrealistic. The plain truth is that the countries which are too small to manufacture drugs or which have so recently emerged

that they are unable to produce drugs, are not in a position to afford the elaborate laboratories necessary to test drugs.

Dr. Aujoulat of France stated "one of the most important difficulties facing the Organization in its aim to control the quality of pharmaceutical products was that of the creation of laboratories at the level of each country—it would be difficult for many countries. . . . He believed that countries with populations of less than two million should give up the idea, for the present, of having their own laboratories or industries".

Dr. Alan of Turkey stated that "the subject of quality control of pharmaceutical preparations had appeared on the agenda of the Health Assembly for many years and was likely to do so for many more. As the situation stood at the present, only some producing countries and the minority of importing countries were in a position to effect quality control. Accordingly, *the majority of the world population was being treated with pharmaceutical preparations which had not been full controlled*".

Dr. Commissiong (of Trinidad and Tobago) pointed out that "the Director-General's report was evidence that something was being done in a very vexed area." He thanked the delegate of Norway for his contribution and had some points to add, namely, "*The cost of adequate control procedures and laboratories was the same for small countries and large countries, and was outside the scope of small countries.* His country depended on aid from outside for supplies of drugs. Standards in his country were based on whether the product was suitable for use in the exporting country".

"To hear of the 'double standard' used by some manufacturers was very distressing. The establishment of regional laboratories would assist greatly. Countries producing drugs should be responsible for the standards of drugs they exported. *It was a moral obligation not to capitalize on the deficiencies of others*".

Dr. Commissiong is right, the drug exporting nations have a moral obligation not to capitalize on the weakness of other countries. Each nation should assume responsibility for the standard of the drugs they export.

Our present laws require that all *new* drugs which are exported meet the same standards as those which we consume in our country. I am ashamed that the United States belongs to the group of nations which may on occasion export out-of-date preparations. No law exists to require antibiotic preparations so urgently needed in so many countries to meet the standards required in our country. The consequence is that manufacturers are permitted to ship out-of-date antibiotics and, I believe, with no expiration date on the bottle. Many pharmaceutical manufacturers will maintain that these preparations are potent for a far longer time than the date of expiration. Be that as it may, shipments to the other side of the world take time and more time is required to dispense the drug. Moreover, the fact remains that the United States Government permits antibiotics to be sold or distributed to other countries which they would not permit to be sold in our country. This, in my opinion, is a disgrace. Antibiotics which have lost their potency are almost worse than useless.

I do not know the law regarding the export of steel but if the United States Government or a manufacturer in the United States sold steel of inferior quality and the building collapsed, I am sure the repercussion would be both tremendous and terrible. Unfortunately, when we permit the sale of antibiotics which are no longer potent and people die in a far off country where disease is rife and the mortality rate already high, nothing is heard therefrom. Nevertheless, that such a thing is possible is a disgrace to this nation. Not only is it morally wrong not to insure that drugs exported are of the same quality that is required for home consumption, but our relations with other nations demand that diasters and deaths from the use of impotent or out-dated preparations are not to be permitted to occur, far less are tolerated. Furthermore, if the richest country of the world does not care whether it exports pharmaceuical products of substandard quality how can we expect other countries not to do the same. This is not a matter for the World Health Organization to try to control. Each country should assume that responsibility. We have a moral obligation to do so.

As Dr. Alan from Turkey said "only some producing countries and the minority of importing countries were in a position to effect quality control. Accordingly the majority of the world population were being treated with pharmaceutical preparations which has not been fully controlled".

Dr. Novgorodcfv (U.S.S.R.) stressed the importance of control of pharmaceutical preparations in view of the defencelessness of the population, especially in developing countries, against the flood of preparations, many of them of inferior

quality, released on the market. One Delegate had said that the best solution would be for countries exporting pharmaceutical preparations to apply the same strict control measures as they applied to preparations used within the country. The World Health Organization should not have to make recommendations or try to set such standards for us. Our national pride and fundamental honesty demands that the United States Congress should enact legislation so that would be the law of the land. It is simply "do unto others as we are done by". I am ashamed that the United States Government permits or even possibly dipenses, through USAID, any pharmaceutical product to other lands which is not permitted to be sold in this country.

There is one further problem that should be taken into consideration when the new law is written, namely, some drug firms manufacture drugs for export which are not used in their own country. The export of such products should also be subject to quality control.

Sir George Godber of England expressed the opinion that for drugs that were manufactured but not used in the producing countries, it would be possible to use the standards used by one or another of the producing countries which did use the drug. This, too, is a sound and reasonable suggestion and should be the law of our land.

Other problems concerning the quality control of drugs and their possible toxic effects are difficult to solve. I am glad that the United States Government has offered to help the World Health Organization to aid the drug importing nations to test the drug they import. In addition, the U.S.P.H.S. has offered to assist W.H.O. to establish some form of system for reporting and warning nations of the untoward side effects, especially the late side toxic effects of drugs, as for example, the injury to the fetus from thalidomide.

Such measures are needed and I am proud and happy that the United States is ready to help on these different problems. These offers, however, do not lessen our obligation to respond to the repeated pleas from the drug importing nations that all pharmaceutical products which we export are subject to the same quality controls as are required for home consumption.

The enactment of legislation to eliminate the sale of inferior or out-of-date preparations to other countries is urgently needed. Such legislation would be a concrete step forward in the problem of the quality control of drugs and of great benefit to the world. I hope and pray that such may become the law of our land.

This concludes my testimony. Thank you.

APPENDIX

THALIDOMIDE PREPARATIONS

(50–100 mgm.)

Contergan
Distaval
Softenon
Kevadon
Talimol
Imidene Ipnotico
Quetimid
Quietoplex
Sedimide
Thalin
Sedoval K17
Isomin
Neurosedyn
Neurodyn
Neosedyn
Noxodyn (40 mgm)
Lulamin
Sleepan
Valgis
Talargan
Profamil
Sediserpil

(20–25 mgm.)

Algosediv
Bonbrain
Glutanon
New-Nibrol
Shin Nibrol
Noctosediv
Sanodormin
Talinette
Imidene
Sedatum
Ulcerfan

(In small amount)

Asmaval (Eng.)
Admadion (Italy)
Enterosediv
Grippex
Polygripan
Polygiron
Preni-Sedin
Gastrimide
Pro-Ban-M
Tensival
Valgrain
Peracon Expectoran

OTHER PREPARATIONS

(Amount unknown. Sold in South America)

Slip
Sedin
Sedalis
Ondasil
Verdil
Neurofatis
Noccus

[From the New England Journal of Medicine]

MEDICAL INTELLIGENCE

THE EVILS OF CAMOUFLAGE AS ILLUSTRATED BY THALIDOMIDE[1]

(By HELEN B. TAUSSIG, M.D.)[2]

The abrupt decline in the occurrence of phocomelia in West Germany eight months to the day after the public announcement that thalidomide (Contergan) was suspected as the cause offered conclusive evidence that Lenz (1) and McBride (2) were correct in their belief that the ingestion of this substance in early pregnancy caused phocomelia in the offspring. Indeed, the incidence of phocomelia dropped almost to zero. In September, 1962, I was advised that 1 case had been reported in August; this woman had not heard the warning and had taken thalidomide in early pregnancy. These events show how widespread the publicity was on November 28, 1961.

Lenz and Knapp (3) have emphasized the fact that injury to the fetus occurred only when the drug was taken during the "sensitive period," which was between the twenty-eighth and the forty-second day (inclusive) after conception or the thirtieth to the sixtieth day after the first day of the last menstrual period. In a subsequent careful analysis of his material Lenz (4) has correlated the time during which the mother took thalidomide with the type of abnormality found in the infant. In every case in which the infant was born with an abnormality of the arms the mother had taken thalidomide between the thirty-ninth and the forty-first day (inclusive), whereas when the legs were abnormal, the mother had taken the drug between the forty-first and the forty-fourth day after the last menstrual period. This observation is in line with the fact that arm buds appear slightly before the leg buds. When the infant was born with an abnormality of the external ear, however, the mother was found to have taken thalidomide between the thirty-fifth and the thirty-seventh day after the last menstrual period. This is in striking contrast to the fact that the exernal ear is not discernible until after the arms and legs are readily apparent. The early date at which injury occurs to the anlage of embryonic cells destined to form the ear is similar to the effect of the rubella virus on the heart. The commonest cardiac abnormality resulting from an infection with the rubella virus in early pregnancy is persistent patency of the ductus arteriosus, whereas the cells destined to be concerned in the closure of the ductus arteriosus are among the last cells in the heart to be discernible.

The incidence of cardiac abnormalities caused by thalidomide is relatively high. In Lenz's 4 series 17 per cent of the living infants and 50 per cent of those who had died had cardiac abnormalities. Nevertheless, no specific type or types were apparent.

A wide variety of other malformations have been observed from thalidomide poisoning, but, as yet, the relation of these abnormalities to the time of ingestion of the drug has not been determined.

The problem remains whether thalidomide alone is responsible for the outbreak of phocomelia or whether other drugs may cause a similar deformity. This question is raised because a history of the ingestion of thalidomide has been obtained only in approximately 50 per cent of the cases. If, however, thalidomide was responsible for only half the cases, the incidence should have declined markedly, but the outbreak of phocomela would scarcely have come to an abrupt end. In a recent letter Dr. Lenz 5 advised me that during the first six months of 1962 the incidence of phocomelia in Hamburg was 1 or 2 per 1000 births, whereas after August 1, 1962, among the first 5000 births in the city of Ham-

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[1] From the Cardiac Clinic of the Harriet Lane Home, the Johns Hopkins Hospital, and the Department of Pediatrics, Johns Hopkins University School of Medicine.

[2] Professor of pediatrics, Johns Hopkins University School of Medicine.

burg, 2 infants had been born with phocomelia. In both, the mothers had failed to hear the warning, and both had taken thalidomide in early pregnancy.

Amnesia is a great factor. Few people, if any, could swear whether or not they have taken any pill eight months ago, far less two or three years ago. The small amount of thalidomide that can injure the fetus renders it difficult to trace the drug. One tablet of 100 mg. taken during the "sensitive period" can severely injure the fetus. Possibly, 1 tablet of 50 mg. is sufficient. Nine tablets each containing 30 mg., taken over a period of a week, have been known to injure the fetus severely. The pill need not have been a tranquilizer or sleeping pill, for thalidomide was added to a number of other drugs that were used for headache, migraine, asthma, ulcers, enteritis and arthritis.

The many different names (Table 1) under which the drug has been marketed make it difficult to determine whether the woman has taken thalidomide. Indeed, almost every firm that makes or is licensed to sell the drug sells it under a different name. Such a policy is in all probability financially advantageous to the firm, but it presents a real difficulty to the doctor and the patient. Moreover, the drug has been sold or distributed as samples in many, many countries. The names Contergan, Distaval, Softenon, Kevadon and Talimol are familiar. Softenon was the trade name used for export. Softenon was distributed to Austria, Belgium, Holland, Finland, Switzerland, Spain, Portugal and Sweden. France refused to grant a license merely because of technical difficulties, not because of any suspicion of late untoward effects. In Sweden, Norway and Denmark firms were licensed to sell the drug under the respective names of Neurosedyn, Neurodyn and Neosedyn. In addition Sweden had Noxodyn; Denmark had Lulamin. Finland had a number of drugs containing thalidomide; thus, in addition to Softenon, Polygrion, Preni-Sediv, Noctosediv and Enterosediv were available. Polygripan, although containing only a small amount of thalidomide, was exported to Iraq, Iran, Palestine, Turkey and Greece, Pakistan, India, and Hong Kong. In Israel thalidomide was licensed for sale as Thalin and Thalinette. Fortunately, the firm was late in obtaining its license, and the sale of the drug was permitted for only a few weeks.

TABLE 1. *Trade names under which thalidomide was marketed*

(50–100–mg. amount)	Shin-Nibrol
Contergan	Noctosediv
Distaval	Sanodormin
Softenon	Thalinette
Kevadon	Imidene
Talimol	Sedatum
Imidenc Ipnotico	Ulcerfan
Quetimid	(Amount not known)
Quietoplex	Slip
Sedimide	Sedalis
Thalin	Ondasil
Sedoval K17	Verdil
Isomin	Neurofatis
Neurosedyn	Noccus
Neurodyn	Imidan
Neosedyn	(Small amount)
Noxodyn (40 mg.)	Asmaval
Lulamin	Admadion
Sleepan	Enterosediv
Valgis	Grippex
Talargan	Polygripan
Profamil	Polygiron
Sediserpil	Preni-Sediv
Sedin	Gastrinide
(20–25-mg. amount)	Pro-Ban M
Algosediv	Tensival
Bonbrain	Valgraine
Glutanon	Peracon Expectorans
New-Nibrol	

Other countries were more progressive and consequently less fortunate. Although Grunenthal withdrew the drug for export at the same time as the firm withdrew it from the West Germany market, and also notified the pharmaceutical

firms whose sale of thalidomide it had licensed, the countries in which the drug was manufactured independently from Grunenthal continued to sell it for varying periods. One large firm in Japan, which started to manufacture thalidomide shortly after Grunenthal first marketed it, was sued by Grunenthal for priority, and the suit was won. Thereafter, the Japanese firm sold "Isomin" under license for Grunenthal and withdrew it in December, 1961. At least seven other small pharmaceutical houses in Japan manufactured the drug and sold it under various names: Bonbrain, Neo-Nibrol, Shin Nibrol, Glutanon and Sanodormin. These sales were independent of West German regulations, and the drug was not withdrawn from the market until the end of May, 1962, when 700 cases of phocomelia had been reported in Japan.

A similar thing happened in a number of other countries. Various pharmaceutical firms studied the formula, manufactured the drug and sold it under a variety of trade names. Thus, in Italy thalidomide was sold under the names of Imidene, Imidene Ipnotico, Profamil, Quetimid, Quietoplex, Sedimide, Sediserpil, Sedoval K17 and Ulcerfan. In spite of an outbreak of phocomelia in Turin in June, 1962, some of these products were not withdrawn in Italy until September, 1962.

The difficulty in detection of the production and sale of drugs containing thalidomide is illustrated by a report in the Brazilian magazine *Ocruziero* of September 6, 1962. The investigation was precipitated by the birth of a child with phocomelia. The magazine writer was told that thalidomide was not on sale in Brazil, but through his own inquiries he learned of 50 other infants born with phocomelia. Thereupon, he visited a parmacy and purchased the drug under the name of Sedin. Later, he found that Sedalis and Slip were also manufactured in São Paulo and distributed in Brazil. Thereupon, the health authorities instituted an investigation. They found that thalidomide was sold under five different names, Sedin, Sedalis, Slip, Ondasil and Verdil. Moreover, in a ten-day surprise search, they confiscated nearly 2,500,000 pills (or boxes of pills), 46,000 flasks containing thalidomide and 96,000 kg. of the pure substance in the pharmacies and pharmaceutical firms in São Paulo. This was in the summer of 1962.

Such events illustrate the importance of an international office of drug information that would notify the health authorities in all countries of the world when a drug was suspected of being dangerous.

Although the drug has been withdrawn from the market, the danger is real that thalidomide, which has masqueraded under so many different names in so many parts of the world, will turn up again and again. Some pills, which were prescribed in good faith by physicians, are now tucked away in many a medicine closet, with only a prescription number and no name. The serious consequences of this well established custom of filling prescriptions by number is illustrated by 1 unfortunate woman who, because the bottle was unlabeled, unwittingly took Distaval during two successive pregnancies and has two children with phocomelia. There is a movement in England to change the law so that the pharmacist would be required to put the name of the drug on a prescription unless specifically requested by the physician to withhold it. Although there is no law in the United States regarding withholding the name of a medicine given by prescription the custom is firmly established that prescriptions are filled by number and the name of the drug is withheld. This is a dangerous custom since it means that a large amount of unlabeled medicine is accumulated by everyone. There is danger not only that a medicine that has been withdrawn from the market may remain available but also that, when medicines are taken by mistake, especially by children, the doctor may be at a loss to know what has been taken. Although common sense calls for a change in this custom a concerted effort by the medical profession will be necessary to effect such a change.

Experimental work with thalidomide has been initiated in many places. Somer's (6) experimental production of phocomelia in the offspring of New Zealand white rabbits, fed enormous doses of thalidomide from the eighth to the sixteenth day of gestation, has been repeatedly confirmed by him and in other laboratories. The Himalayan white rabbits (7) appear to be susceptible to the effect of thalidomide on the fetus. Furthermore, Somers (8) has reported that although the does is seventy-five time that given to man, the blood levels (9) in rabbits are only three times that normally obtained in man after a full therapeutic dose. Nevertheless, the production of phocomelia in other animals and even in other breeds of rabbits has not met with the same degree of success.

Much remains to be learned. Clearly, all animals do not react alike. What is safe for one is not necessarily safe for another. Even after all known safeguards

are taken, new drugs must be tested on man with the greatest caution. A central computing office for the evaluation of these reports is essential. Such an office must be impartial and must have no financial interest in the product.

Absolute safety is impossible. The final test of any drug used by man is how it affects man. Nevertheless, the medical profession must make a concentrated effort to give the public the greatest possible protection. Therefore, extremely careful records must be kept when drugs are first given to various groups of persons. Furthermore, these records must be filed in such a manner that possible untoward late complications can be correlated with the various drugs. Although this is especially important for drugs used during pregnancy it is by no means limited to such drugs. Other drugs may have late untoward effects on man; consequently, all new drugs require careful scrutiny. Therefore, it should be reemphasized that drugs should be prescribed with the greatest of caution to women in the childbearing age.

The list of drugs in Table 1 that I have been able to verify is not a complete one since Dr. Fanconi (10) told me that he had seen a list in Switzerland containing more nearly 100 than 50 names. Nevertheless this list illustrates the many names under which a single drug may be marketed, and thereby shows the wisdom of the recent change in the laws requiring that official names be printed on the label in letters half the size of the trade name.

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[From the Washington Post, July 15, 1962]

"HEROINE" OF FDA KEEPS BAD DRUG OFF MARKET

(By Morton Mintz)

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophesies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable—even, she said, stupid. That such attributes could have been ascribed to her is, by her own acknowledgement, not surprising, considering all of the circumstances.

What she did was refuse to be hurried into approving an application for marketing a new drug. She regarded its safety as unproved, despite considerable data arguing that it was ultra safe.

It was not until last April, 19 months after the application was filed with the FDA, that the terrible effects of the drug abroad were widely reported in this country. What remains to be told is how and why Dr. Kelsey blocked the introduction of the drug before those effects were suspected by anyone.

Dr. Kelsey invoked her high standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1510 offspring, none was delivered with "evidence of malformation."

In a separate study, one rat did deliver a malformed offspring, but the dosage had been 1200 times the usual one. Rabbits that were injected with six times the comparable human dose also were reported to have produced no malformed births.

Recently, the FDA publicly decried the "excessive contacts" made with its personnel by pharmaceutical manufacturers who are anxious to speed the agency's handling of new-drug applications.

MANY REQUESTS

So it was not at all surprising that dozens of contacts were made with Dr. Kelsey by representatives of the American licensee for thalidomide, the chemical name for the sedative. They had what they strongly believed was a clear and overwhelming case—but Dr. Kelsey delayed, and delayed, and delayed.

They visited her in her drably furnished, bare-floor office in an eyesore Tempo on Jefferson dr. sw. They phoned. They submitted a flow of reports and studies. It was apparent that substantial investments and substantial profits were at stake. And all of this was routine.

The application had come to Dr. Kelsey—simply because it was her turn to take the next one—in September, 1960.

The European data left her "very unimpressed." In an interview, she said she had "lived through cycles before" in which a drug was acclaimed for a year or two—until harmful side effects became unknown.

And, she said, she could not help regarding thalidomide as "a peculiar drug." It troubled her that its effects on experimental animals were not the same as on humans—it did not make them sleepy.

SAME QUESTIONS

Could there be danger in those few people whose systems might absorb it? Could there be a harmful effect on an unborn child whose mother took it? (In other countries obstetricians were innocently prescribing it as an anti-emetic for pregnant women.)

Dr. Kelsey regarded the manufacturer's evidence of thalidomide's safety as "incomplete in many respects." The drug was not, after all, intended for grave diseases, or for the relief of intolerable suffering, but primarily for sleeplessness, for which many drugs of known safety were already on the market.

All of this being so, she saw no need either to hurry or to be satisfied with the approach that, nine chances out of ten, it's safe. She was determined to be certain that thalidomide was safe ten times out of ten, and she was prepared to wait forever for proof that it was.

When the 60-day deadline for action on the application came around, Dr. Kelsey wrote the manufacturer that the proof of safety was inadequate. Perhaps with an understandable feeling of frustration the manufacturer produced new research data, new reasons for action. Each time a new 60-day deadline drew near, out went another letter: insufficient proof of safety.

UPHELD BY SUPERIORS

Dr. Kelsey's tenacity—or unreasonableness, depending upon one's viewpoint—was upheld by her superiors, all the way.

Although she takes her work seriously indeed, her contacts with applicants are, in her words, "usually amiable. We see their point, and they see ours. But the responsibility for releasing a drug is ours, not theirs." And that is the responsibility she would not forget.

In February, 1961, she chanced to read, in a British medical journal, a letter from a British doctor questioning whether certain instances of peripheral neuritis—a tingling and numbness in the feet and the fingers that is sometimes irre-

versible—might not be due to intake of thalidomide. To her this was a danger signal.

She called the letter to the attention of the applicant. His investigators reported that the incidence was apparently negligible, one case among 300,000 adult users. Six months later, Dr. Kelsey said, the incidence among adults who took thalidomide regularly for months at a time was found to be 1 in 250.

But neither she nor the applicant yet had the slightest inkling that the drug could be responsible for the birth of malformed babies. That awful circumstantial evidence became known to the applicant—in a cablegram from Europe—on Nov. 29, 1961.

APPLICATION WITHDRAWN

He reported it to Dr. Kelsey early the next day. Although this was followed by a formal withdrawal of the application, as late as last month the applicant described the birth abnormalities as "alleged effects" of thalidomide.

The story begins, in 1954, six years before Dr. Kelsey, a pharmacologist as well as a physician, went to work in the FDA's Bureau of Medicine. She and her husband, F. Ellis Kelsey, a pharmacologist who is now a speical assistant to the Surgeon General of the Public Health Service, came here from the faculty of the University of South Dakota School of Medicine.

For the account that follows, the primary sources were Dr. Kelsey and reports by Dr. Helen B. Taussig to a medical meeting in April and in the June 30 issue of the Journal of the American Medical Association.

Dr. Taussig, professor of pediatrics at the Johns Hopkins School of Medicine in Baltimore, went to West Germany in January to investigate the relationship between thalidomide and an enormous increase in the birthrate of malformed infants.

Eight years ago a West German manufacturer conceived of the drug, synthesized it—and discarded it after discerning no effect on test animals. In 1958 another West German firm also developed thalidomide and found it to be, by all indications, the best sleeping compound ever devised.

LARGE SALE

The sale was tremendous. It even came to be used for grip, neuralgia, asthma, in cough medicines and to calm children before they were given electroencephalograms.

In Germany it was marketed as Contergan, in the British Commonwealth as Distaval, in Portugal as Softenon. Dr. Kelsey's native Canada accepted it on April 1, 1961, for manufacture by one firm under the name Talimol and by another firm, the William S. Merrell Co. of Cincinnati, under the name Kevadon. It was the 134-year-old Merrell firm that was seeking to market Kevadon as a prescription drug in the United States.

At this time—April, 1961—West German investigators were desperately groping for an explanation of an unprecedented outbreak of phocomelia, the malformation hitherto so rare that it isn't even listed in some medical dictionaries. An 86-year-old Gottingen specialist in human deformities told Dr. Taussig that he had in his whole lifetime "seen as many individuals with two heads as he had with phocomelia."

Usually, phocomelia deprives its victim of one arm. Rudimentary fingers that look, said Dr. Taussig, "like the flippers of a seal" arise from the stub below the shoulder.

CLINIC CASES

In eight West German pediatric clinics there were no cases at all between 1954 and 1959. In 1959 there were 12, in 1960 there were 83, in 1961 there were 302.

These were not the ordinary textbook cases. Not just one arm was affected. These children were without both arms, or without both legs, or without three limbs, or they were without any limbs at all.

In some, the external ear was missing and hearing was grossly impaired. There were deformities of the eyes, esophagus and intestinal tract; and even this is not a complete list.

Once the suspected link with Contergan was established, Contergan was taken off the West German market. The expectation is that the last mothers who could have taken it during early pregnancy, the danger period, will be delivered in August. The estimates are that by the end of next month the total of deformed

children born in West Germany will be between 3500 and 6000. Two out of three are expected to live. Most are apparently of normal mentality.

The drug was withdrawn from the British market five days after the withdrawal in West Germany. The Guardian, Manchester, has predicted that August will see the birth of 800 deformed English children. The Ministry of Health has begun to fit 50 victims with artificial limbs.

EIGHT IN CANADA

An article prepared for the May 19 issue of Maclean's Magazine said that at the time of writing eight victims of phocomelia had been born in Canada, two of them to physicians' wives who had used "samples of thalidomide donated to their husbands."

Because the Department of Health did not order thalidomide withdrawn from sale until March 2, Maclean's said the last Canadian casualties are not expected until November.

The cause of the West German outbreak was hard to trace. Hereditary factors, blood incompatibility between parents, abnormal chromosomes, radioactive fallout, X-rays, detergents, food preservatives—all of these things, and more, were suspected, checked and discarded as possibilities.

A Hamburg pediatrician, Dr. Widukind Lenz, made preliminary studies showing that about 20 per cent of the mothers who brought deformed infants to his clinic had taken Contergan. Dr. Taussig wrote:

"On Nov. 8, 1961, it occurred to him that Contergan was the cause. He requestioned his patients and the incidence promptly rose to about 50 per cent. Many of the patients said they had considered the drug too innocent to mention it on the questionnaire . . .

MAKER WARNED

"On Nov. 15 he warned Grunethal (the manufacturer) that he suspected Contergan was the cause and that the drug should be withdrawn."

Five days later, at a pediatric meeting in Dusseldorf he reported his suspicions and his actions but did not name the drug. That night Dr. Taussig related, "a physician came up to him and said, 'Will you tell me confidentially, is it the drug Contergan? I ask because we have such a child and my wife took Contergan.'

"A couple of days later it was generally known that Contergan was the drug under suspicion. On Nov. 26 Grunenthal withdrew the drug from the market. On Nov. 28 the Ministry of Health issued a firm but cautious and widely publicized statement that Contergan was suspected to be a major factor in the production of phocomelia."

Dr. Taussig reported that an Australian physician, Dr. W. G. McBride, saw three severe cases in April, 1961, and three more in October and November. "He found that all six mothers had taken Distaval in early pregnancy," the Journal article said.

In Stirlingshire, Scotland, Dr. A. L. Spiers saw 10 severe phocomelia victims during 1961 and ultimately "obtained positive proof that 8 out of 10 of these patients had taken Distaval."

DIFFICULT CONNECTION

Making the connection—which some physicians say is not conclusively established—was extraordinarily difficult.

Dr. Lenz, for example, had to contend with the lack of records during the time when Contergan was sold without prescription, and with his patients' natural difficulty in recalling if and precisely when they had taken a sleeping pill months earlier.

"In one instance," Dr. Taussig wrote, a doctor "swore the mother had not received Contergan. He had prescribed an entirely different sedative. On investigation at the pharmacy . . . Dr. Lenz found the prescription was stamped 'drug not in stock, Contergan given instead'."

Dr. Taussig said the investigations of Dr. Lenz in particular indicate that the embryo is endangered if a mother takes thalidomide within about 20 to 40 days after conception, a time when she may not even know that she is pregnant.

He believes that during that sensitive period the chances that a mother who has taken the drug will deliver a deformed baby are at least two in five.

COMPANY VIEW

The Merrell firm says that conclusive proof is lacking for such assumptions and cites a clinic in Kiel at which, Merrell reported, half of the deformed children were delivered to mothers who probably had not taken thalidomide.

"Everyone admits," Dr. Taussig wrote, "that no information is available concerning how many women may have taken the drug in the sensitive period and have had a normal child."

Dr. Kelsey said the molecular complex of thalidomide is being broken down and studied in an effort to determine the causative agent in thalidomide.

In all of this Dr. Taussig sees compelling reason for caution in the use of new drugs by women of child-bearing age. A Canadian physician interviewed by Maclean's said, "There is too much demand on the part of the public for relief of mild or even moderately severe symptoms. People won't put up with even the slightest discomfort or headache; they demand medication from their doctor. If they can't get it from one, they'll go to another."

Dr. Taussig also wants the 1938 Food and Drug Act strengthened to provide greater assurance that new drugs will not harm unborn children. But to Assistant FDA Commissioner Winton B. Rankin, the significant thing about the law is that it gave Dr. Kelsey the weapon she needed to block the marketing of thalidomide in the United States.

"The American public," he said, "owes her a vote of thanks."

The 47-year-old Dr. Kelsey lives at 5811 Brookside dr., Chevy Chase, with her husband and daughters, Susan, 15, and Christine, 12.

She is grateful for the praise—but recognizes that, had thalidomide proved to be as safe as the applicant believed, "I would have been considered unreasonable."

She intends to go on "playing for that 10th chance in 10" to assure safety in new drugs "to the best of my ability." For 20 years she taught pharmacology. She knows the dangers, and she has not the slightest intention of forgetting them.

[From the Journal of the American Medical Association, June 30, 1962, vol. 180, pp. 1106–1114]

A STUDY OF THE GERMAN OUTBREAK OF PHOCOMELIA

THE THALIDOMIDE SYNDROME

(By Helen B. Taussig, M.D.)[1]

In late January of this year I heard that a large number of infants had been born in West Germany with severe malformations of the extremities and that a sleeping tablet was suspected as the cause. I immediately went to West Germany to investigate the situation and traveled throughout West Germany with exception of West Berlin.

It was indeed true that a new clinical syndrome had appeared. The outstanding feature was phocomelia. Phocomelia means "seal extremities"; the word comes from 2 Greek words *phokos* meaning "seal" and *melos* meaning "extremities." In phocomelia the bones between the hand and the shoulder are defective or absent and the hands or rudimentary fingers arise directly from the end of the affected bone as the flippers of a seal. The first 2 such cases were presented by Kosenow and Pfeiffer (1) as an exhibit at the German Pediatric Meeting in Kassel in 1960. At this exhibit Kosenow and Pfeiffer reported that no hereditary factor was found, nor was any blood incompatibility demonstrable and no chromosomal abnormality was detected. Little attention was paid to the exhibit. Dr. Guido Fanconi, however, studied the cases and stated he had never seen the clinical syndrome. In retrospect, it is surprising that so little attention was paid to this exhibit because during 1960 infants with this syndrome had been brought to almost every pediatric clinic in West Germany.

Phocomelia has long been known as a rare malformation but usually affects only one limb. Dr. Grüber of Göttingen, who is now 86 years old and has devoted

[1] From the Department of Pediatrics, the Johns Hopkins University, School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital. Dr. Taussig's trip was supported by the International Society for Cardiology Foundation, the Heart Association of Maryland, and the National Institutes of Health.

his life to malformations in man and animal, told me he had seen as many individuals with 2 heads as he had with phocomelia.

Suddenly in 1961 the incidence of phocomelia increased rapidly. Almost every clinic in West Germany admitted 3 times as many such infants in 1961 as in 1960. The data in Table 1 shows the incidence which was reported to me in March, 1962, by various university pediatric clinics in West Germany and also in 3 centers in the British Commonwealth. By the time of the 1961 pediatric meeting in Düsseldorf almost all pediatricians were aware of the outbreak of phocomelia.

TABLE 1.—INCIDENCE OF PHOCOMELIA IN THE VARIOUS UNIVERSITY PEDIATRIC CLINICS

	1949–59	1959	1960	1961	In 3 years
Bonn		2	19	50	71
Bremen			4	20	24
Frankfurt		1	4	11	16
Göttingen		3	1	10	14
Hamburg (Lenz-person)		1	16	57	74
Hamburg (Lenz-letter)		1	30	154	185
Heidelberg		2	5	9	16
Kiel		2	4	26	32
Munchen	3	2	14	44	60
Munster	[1] 4	3	27	96	126
Birmingham			4	13	17
Liverpool			8	25	33
Stirling					10

[1] These include peromelia, amelia, and micromelia as well as phocomelia—per year.

In September, 1961, Wiedemann (2) reported the first series of 33 such children and delineated the clinical syndrome. As in most malformations, the severity varies but the pattern is remarkably specific. The essential feature of the abnormality concerns the long bones of the extremities (Figs 1 and 2). The prehensile is lost (Fig. 3). The hand arises directly from the distal end of the affected bone. The radius is absent or both radius and ulna are defective; in some instances only one short bone remains; in extreme cases the radius, ulna, and humerus are lacking and the hand buds arise from the shoulders (Fig. 1). Both sides are affected but not usually with equal severity. The legs may be affected in the same manner; in most instances the deformity of legs is less severe (Fig. 2). The tibia fails to form. The fibula also may not form and the femur may be short. The hip girdle is not fully developed and there is a dislocation of the hip with external rotation of the stub of the femur. The feet are externally rotated. Polydactylism and syndactylia of the toes are common (Fig. 3). In the extremely severe cases the arms and the legs are missing (Fig. 4). In some instances the external ear is missing and the internal auditory canal is abnormally low (Fig. 5). Usually hearing is not grossly impaired. Unilateral facial paralysis is relatively common. The vast majority of children are of normal mentality.

Pfeiffer and Kosenow (4) noted that a mid-line facial hemangioma on the forehead which extended over the nose to form a "moustache" on the upper lip was almost pathognomic of the syndrome (Fig. 1). A saddle nose was also common. These features diminish and tend to disappear as the infant grows. In some

TABLE 2.—INCIDENCE OF MAJOR MALFORMATIONS [1]

Type	Personal observations		Letters	
	Number	Percent	Number	Percent
Arms only	43	52.4	103	50.6
Arms and legs	23	28.1	60	29.6
Arms, legs, and ears	2	2.4	7	3.4
Arms and ears	3	3.7	10	4.9
Ears only	7	8.5	14	6.9
Legs only	1	1.2	4	2.0
Other malformations	3	3.7	5	2.5
Total	82		203	

[1] Courtesy of Dr. W. Lenz, Hamburg, Germany.

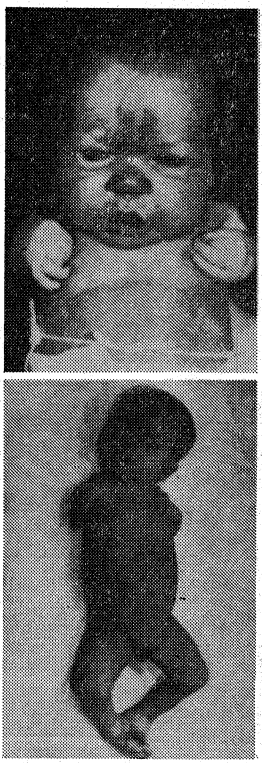


Fig. 1.—Infants with phocomelia (courtesy of Dr. Lenz).

Fig. 2.—Older infant with phocomelia.

TABLE 3.—OTHER MALFORMATIONS OCCURRING IN 203 CASES OF PHOCOMELIA

	Number
Pylorospasm	2
Duodenal stenosis	3
Duodenal atresia	3
Esophageal atresia	[2] 2
Anal atresia	3
Cardiac abnormalities	17
Anencephaly	2
Microcephaly	3
Eye malformations	1
Nasal obstruction	1

[1] Courtesy of Dr. W. Lenz, Hamburg, Germany.
[2] Doubtful.

instances, usually in severe cases the internal organs are affected. Malrotation of the gut occurs with duodenal stenosis and anal atresia (Fig. 6). Asplenia may occur and the musculature of the uterus may be so affected as to make a bihorned uterus. A variety of cardiac malformations have also been reported but these did not fall into any specific pattern. Thus hypoplasia of the aorta, defects of the auricular and ventricular septa, all forms of transposition of the great vessels, tetralogy of Fallot, and pulmonary stenosis have all been reported. The frequency with which the various abnormalities occur in Dr. Lenz's series are shown in Table 2. The variety of other malformations is shown in Table 3. Pfeiffer and Kosenow (4) reported extensive family studies on 34 children. They found no similar traits among the relatives and no consanguinity among the parents. Chromosomal analysis of 12 patients showed no chromosomal aberration either in the number or form of the chromosomes. Four of 6 pairs of dizygotic twins had the same type of malformation but the twins were not equally affected. These investigators thought that the causative factor was exogenous and acted during

the critical phase of development, i.e. between the third and sixth week of pregnancy.

Although the critical time was similar to that of German measles viral infection was excluded by the steady increase in the number of patients over a 2-year period and also by the distribution of the cases. Viruses know no territorial borders. This epidemic remained strikingly centered in West Germany. German pediatricians became aware of the problem. Extensive studies had been instituted in a number of centers. Lenz in Hamburg, Weicker in Bonn, Wiedemann(2) in Kiel, and Pfeiffer and Kosenow(4) in Münster each undertook special studies. Many doctors suspected radioactive fallout. Lengthy questionnaires were sent out inquiring about X-ray exposure, hormones, detergents, foods (and food preservatives), contraceptive measures, and tests for pregnancy. Most of these were retrospective studies. Dr. Lenz's initial studies showed that approximately 20% of his patients had taken Contergan. On Nov. 8 it occurred to him that Contergan was the cause. He requestioned his patients and the incidence promptly rose to about 50%. Many of the patients stated that they had considered that drug too innocent to mention it on the questionnaire.

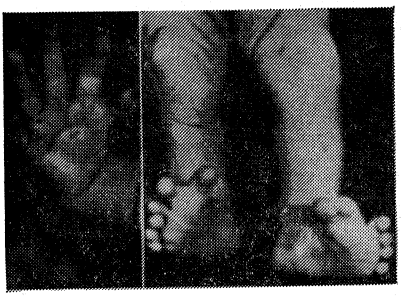


Fig. 3.—Malformation of hand and foot.

Fig. 4.—Malformation of ear. *Top*, slight abnormality; *bottom*, severe malformation.

Fig. 5.—Infants with severe phocomelia (Wiedemann[2]).

Contergan is the West German trade name for thalidomide. The chemical structure is shown in Figure 7. Thalidomide is a synthetic drug which, as the story is told in West Germany, was first conceived and made by Ciba and found by them to have no effect on animals; therefore, it was discarded. In 1958 Grünenthal developed the drug and tried it on animals; they, too, found it had no effect on animals. Thereupon it occurred to the inventors that it might be useful in epilepsy and was marketed as an anticonvulsant drug. It was soon found to be worthless for epilepsy but it caused sleep. Thereafter, it was sold as a sleeping tablet, a sedative, and tranquilizer. It had a prompt action, gave a natural deep sleep and no hangover. It appeared innocent and safe. Man could not commit suicide with it. It became West Germany's most popular sleeping tablet and was widely used in hospitals and in mental institutions. Thalidomide was added as a sedative to other drugs such as algosediv (thalidomide and acetylsalicylic acid), peracon expectorans, grippex, and polygripan; thus it was used for grippe, neuralgia, asthma, and as a cough medicine. A liquid form was made for children. It was used in hospitals to quiet a child for an electroencephalogram. It became West Germany's baby-sitter. It was also found useful as an antiemetic in pregnancy. The drug was manufactured "by the ton" and sold without prescription. Inasmuch as the drug was cheap and an excellent sedative, the sale was tremendous. The rights to market the drug were sold to pharmaceutical firms in other countries. In the British Commonwealth it was marketed by Distillers (Biochemicals) as Distaval. In Portugal it was sold as Softenon and it was manufactured in the United States as Kevadon (but it was never passed by our Food and Drug Administration). It was sold both as Kevadon and Talimol in Canada. Thalidomide was also added to the English drugs known as Valgis, Tensival, Valgraine, and Asmaval. I do not know whether the drug was added to any Portugese preparations.

In April, 1961, a new form of polyneuritis appeared: tingling of the hands, sensory disturbance, and later, atrophy of the thumb and motor disturbances. It was soon recognized that the long continued use of Contergan in adults was responsible for polyneuritis; furthermore, unless the drug was promptly discontinued, the polyneuritis was irreversible. Thereafter, the drug was placed upon prescription. Nevertheless, it remained a very popular drug and continued to be widely used in hospitals and also in the home.

As previously stated, on Nov. 8 it occurred to Dr. Lenz that Contergan was probably responsible for the catastrophic outbreak of phocomelia. On Nov. 15 he warned Grüenthal that he suspected Contergan was the cause of phocomelia and that the drug should be withdrawn. On Nov. 20, 1961, at the Düsseldorf Pediatric Meeting, Lenz (5) reported he suspected a specific drug was the cause of the "Wiedemann syndrome" and that he had warned the company that the drug should be withdrawn. He did not name the drug. That night a physician came up to him and said, "Will you tell me confidentially, is the drug Contergan? I ask because we have such a child and my wife took Contergan." In the next few days he received a half dozen letters asking the same question and saying, "My wife took Contergan and we have such a child." A couple of days later it was generally known among the doctors that Contergan was the drug under suspicion. On Nov. 26 Grüenthal withdrew the drug from the market. On Nov. 28 the Ministry of Health issued a firm but cautious statement that Contergan was suspected to be a major factor in the production of phocomelia and stated that the drug had been withdrawn from the market. Women were warned not to take the drug. The announcement was carried on the front page of every newspaper, on the radio, and on television.

Phocomelia not only suddenly appeared in Germany, but the same unusual type of malformation equally suddenly made its appearance in Australia. In April, 1961, Dr. W. G. McBride (6) in a relatively short time saw 3 babies born with severe phocomelia. He saw no more such infants until the fall of 1961. In October and November, 1961, he saw 3 more such infants. Thereupon he reviewed the 6 cases and he found that all 6 mothers had received Distaval in early pregnancy. Dr. McBride communicated his findings to the Australian Branch of Distillers Limited and they in turn cabled their London office on Nov. 27, 1961. Distaval is the English trade name for Contergan. Thus, within a couple of days the English firm received similar reports from 2 widely separated countries. The drug was promptly withdrawn from the market. The latest report is that it is available to hospitals in limited sales.

McBride (7) in a brief note in the Dec. 16 *Lancet*, reported a 20% increase in severely malformed babies from the use of Distaval in early pregnancy. The malformation affected the mesenchymal tissue, both the long bones, and the musculature of the gut. Had anyone else seen anything like it? Lenz 8 replied to his letter in the Jan. 12 issue of the *Lancet*.

Spiers (9) in Stirlingshire, Scotland, had seen 10 infants with severe phocomelia during 1961. He immediately set to work to ascertain whether his cases were associated with Distaval. On questioning mothers and doctors he obtained a history of Distaval in 2 of the patients. Then he went to the office where all prescriptions are filed and with the names of the patients and the approximate date on which the medicine was given, he asked to have the prescriptions checked. It took 3 weeks. During this time he interviewed the mothers and in 2 instances the mothers finally remembered they had taken sleeping tablets and produced the bottles from which the tablets had been taken. The tablets therein were stamped DT/DL. Ultimately, he obtained positive proof that 8 out of 10 of these patients had taken Distaval in early pregnancy.

Thus, between Nov. 20, 1961, and January, 1962, the circumstantial evidence rapidly accumulated in different parts of the world which indicated that thalidomide played an important role in the production of phocomelia.

Further studies were instituted everywhere. Many clinics reported a history of the ingestion of Contergan could readly be obtained from the women in one-half of the instances but not in all cases.

A few, but remarkably few, prospective studies were instituted. One obstetrician asked each of 65 patients whether Contergan had been taken in early pregnancy and obtained a positive reply in only a single instance. He said if that woman had an abnormal baby he would believe Lenz. She did!

Professor Von Masselbach made a prospective study of 350 patients in his obstetrical clinic. Thirteen women had taken Contergan, 6 in the second half of pregnancy and 7 in the first half, i.e., in the first 4½ months. Among these 7 women, 2 had babies with phocomelia, 1 had a baby with an anal atresia, and 4 were normal.

In Düsseldorf, in a group of 300 women who had not taken Contergan, all the babies were healthy, whereas one-half of the women who took Contergan had abnormal children. These investigators also had collected 40 cases over a 2-year period. Seventy-five per cent of these mothers gave a history of Contergan. Since

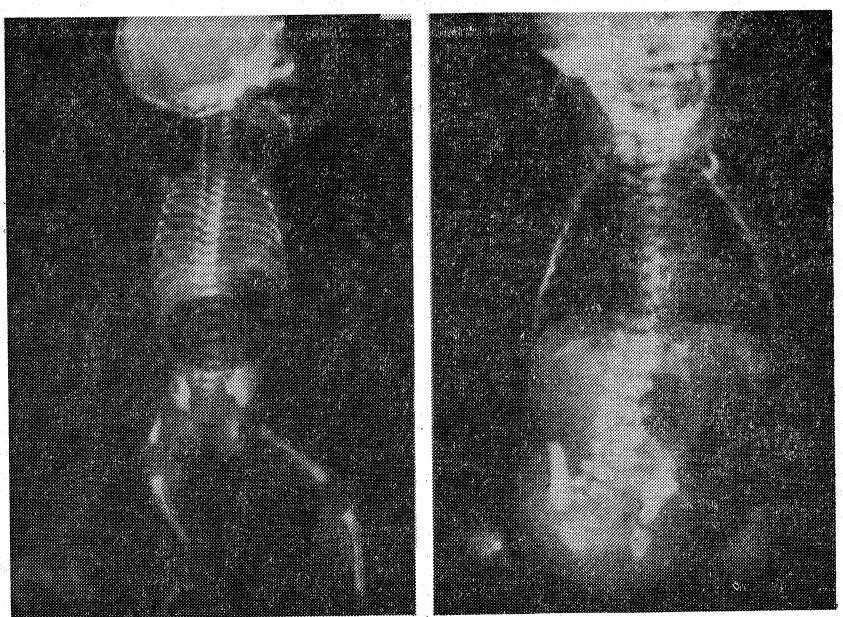


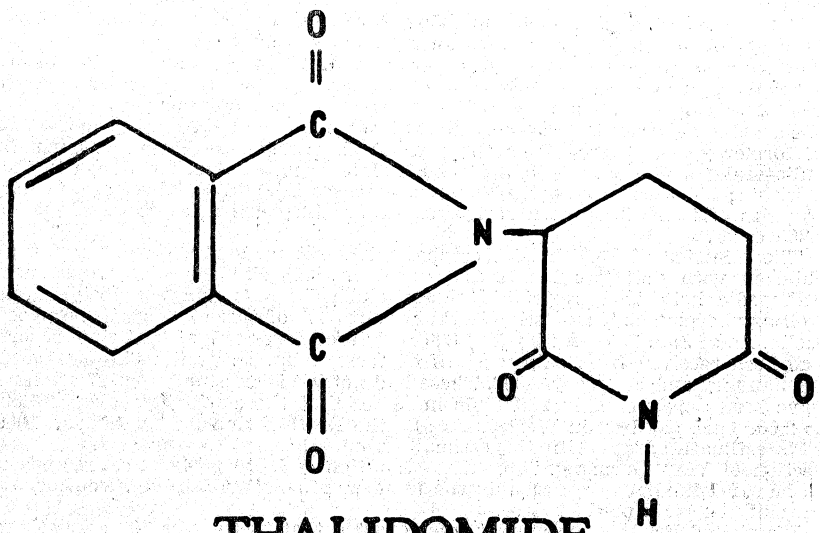
Fig. 6.—Radiologic evidence of intestinal obstruction and defects of bones of extremities.

the records were not checked, the history of Contergan was recorded as probable but not proven. Dr. Weicker 10 in Bonn was collecting 100 cases of phocomelia with a history of Contergan. In March, 1962, when I was in Bonn, he had over 90 such cases.

Dr. Lenz (13) undertook a study to ascertain in how many patients who had given birth to infants with phocomelia he could obtain proof that the mother had taken Contergan during early pregnancy. He considered a case as proven only by a photostatic copy of a prescription or by a hospital record showing the date and amount of Contergan given. The difficulty in obtaining such information was great because prior to April, 1961, the drug was sold without prescription. By and large, women in the early months of pregnancy are not cared for in a hospital. Dr. Lenz, however, found that a number of women had been admitted to a hospital for some minor operation before they knew they were pregnant. Many of these patients had received a sleeping tablet while in the hospital and thereby Dr. Lenz could obtain proof that Contergan had been prescribed. In many West German hospitals sleeping tablets are given by the nurses as freely as laxatives are given in the United States.

Few of us can remember what medicine we took a year or more ago. Far less, exactly when and how much we took. In some instances, however, special events enabled the patient to remember the date or the approximate time during which she took a sleeping tablet. Travel was a common event. Many people do not sleep well when traveling. Such persons usually know if and approximately when they took sleeping tablets. One woman knew the date she took a sleeping tablet: it was the night the neighboring farm house had burned down.

Another woman recalled she had taken Contergan for 3 nights after her father-in-law had been murdered. The date was clearly imprinted on her mind. Two other incidents reported by Dr. Lenz illustrate how difficult it may be to obtain accurate information. In one instance in which the mother gave birth to a baby with phocomelia, the doctor swore the mother had not received Contergan. He



THALIDOMIDE
Alpha (N-phthalimido) glutarimide

Fig. 7.—Formula of thalidomide.

had prescribed an entirely different sedative. On investigation at the pharmacy where the mother had bought the medicine, Dr. Lenz found the prescription was stamped "drug not in stock, Contergan given instead."

In another instance in which Dr. Lenz talked with the parents for more than one-half hour and both denied the mother had taken Contergan, 3 weeks later Dr. Lenz received a letter (I read the letter) saying: "I have been told not to write but I can no longer sleep without telling you I did take Contergan but, as my husband was once in a hospital for drug addiction, I had promised I would never take such a drug; I could not tell him I had broken my promise."

By the middle of March, 1962, Dr. Lenz had analyzed 50 cases (13) in which he interviewed parents, reviewed hospital records, and determined the date of the last menstrual period and in many instances he obtained the date of conception and also had proof of the date on which Contergan had been taken. Forty-five of 50 women had taken the drug between the 30th and 50th day and 5 had taken it between the 50th and 60th day after the last menstrual period. Among the 21 instances in which the date of conception was known, the mothers had taken contergan between the 28th and 42nd day (inclusive) after conception. Although the exact time during which the drug has a teratogenic action may be found to vary slightly, the period in which it affects the development of the embryo appears to be relatively brief.

These observations clarify the finding of Dr. W. Hillmich (14) of Göttingen who made a prospective study of 99 patients who had taken Contergan during pregnancy. He found none had taken the drug in the first 3 weeks; one had taken it in the fourth week, none in the fifth, one in the sixth, none in the seventh, and one in the eighth week. All of the remaining patients had taken the drug after the ninth week of pregnancy. The mother who had Contergan on the 42nd day after the last menstrual period was the only one who had an abnormal baby. The woman who had taken Contergan in the 6th week had taken it on the 51st day after her last menstrual period which is probably safe provided she had a normal ovulation time. All others had taken the drug well after the sensitive period.

The incidence of phocomelia in West Germany is terrific. Studies from the Institute of Human Genetics in Münster showed that between 1949 and 1959 they saw an average of 4 children per year with severe malformation of the extremities. These malformations included peromelia (amputation of a limb), amelia (absence of a limb which may be the extreme either of peromelia or of phocomelia), micromelia (a small limb), and phocomelia. Even the phocomelia of former years differed from the present phocomelia in that it was usually unilateral. Suddenly, in 1959, 3 cases of bilateral phocomelia were seen in that institute; 26 cases occurred in 1960 and 96 cases in 1961. Furthermore, to date 13 pairs of twins have been registered; hence they estimated there should be 1,300 cases.

The Minister of Health of Westphalia has set up a name registry for all children with defective hands and arms, i.e., all children who would need orthopedic help. This registry included clubbed hands and polydactylism as well as phocomelia. They estimate that about 80% of these cases will be phocomelia. As of Jan. 1, 1962, they had 800 registered cases and at that time reports had been received from only one-half of Westphalia. I saw the pile of records for January and February, 1962. These had not yet been counted but there must have been approximately 200. This indicates that there will be probably 1,500 to 2,000 such children in Westphalia and the North Rhineland by August, 1962. This estimate agrees with the estimate from Münster. Westphalia is but one section of West Germany. Thus the estimation of 3,500 to 4,000 cases appears to be a minimal figure. Probably the number will be far larger. Two-thirds of the children are expected to live.

We visited Freiburg because it was reported that there were 100 cases there. At the University Clinic, Dr. Keller advised me that they had seen approximately 10 or 20 cases and showed me one infant in the hospital. He kindly offered to look up the exact number. Subsequently, he wrote me that they had seen 37 infants in the clinic and they had received reports of 200 such infants born in the environs of Freiburg.

In contrast to these findings, Dr. Immon at the Headquarters of the United States Army of Occupation in Heidelberg told me on March 6 that he was reasonably confident that there had been no cases of phocomelia among the 16,000 babies born in the U.S. military hospitals in Germany in 1961. He had

traveled extensively and had visited all their hospitals. He had been shown the unusual cases but had seen no infants with phocomelia up to March 12, 1962. Further, they were certain that any and all such infants would be immediately evacuated to the United States. All evacuations passed through their office and no case of phocomelia had been reported. As of April 14, no such cases had been received from overseas at the Walter Reed Hospital in Washington, D.C. In a recent letter, Dr. Immon reported one infant born with phocomelia in a U.S. Army hospital. The infant's mother, who was a German, volunteered the information that she had taken Contergan in early pregnancy.

Alas, the incidence in England is also high. Reports are steadily appearing in the *Lancet* of the occurrence of phocomelia in infants born of women who have taken thalidomide in early pregnancy. Dr. Clifford Parsons (15) advised me that at a recent medical meeting almost everyone in the audience had seen at least one such case. The total incidence is expected to be in the hundreds but fortunately not in the thousands.

Reports are still coming in from all over the world which show that phocomelia has occurred where Contergan has been used. As of March 22, 7 cases were reported in Sweden in which Contergan had been purchased in Germany; 2 cases in Belgium and the Contergan was known to have been bought in Germany; 4 cases in Switzerland with a history of the ingestion of Contergan; 7 cases in Lebanon where the Portuguese preparation, Softenon, is available; 1 case in Israel and the mother took Distaval; 1 case in Peru and the father had obtained Contergan in Germany. Seven cases have been reported in Canada in women who had taken Kevadon in early pregnancy. One sad instance in the United States is that of a German woman who had married an American, and brought Contergan with her to the United States. She took the drug and has given birth to twins; one has phocomelia and the other duodenal atresia and a rectovaginal fistula. As yet, I have received no information of the incidence of phocomelia in Portugal. Dr. Lenz, however, has written me that he has learned of an outbreak of phocomelia in Brazil associated with thalidomide.

There are, however, still many perplexing problems. One concerns twins. Usually both twins are affected even when they are dizygotic but not always to the same extent, as in the above mentioned case. Another case is known in which one twin died at 5 months and was delivered at term with the living twin. The living twin had a phocomelia and the bones of the dead twin were normal.

I learned of a physician who had taken Contergan until she developed peripheral neuritis. Thereupon she stopped taking the drug until she was pregnant and then took it again through 2 successive pregnancies and both children were normal. The question arises as to how early in pregnancy did she take the drug, or is she one of the fortunate women?

Everyone admits that no information is available concerning how many women may have taken the drug in the sensitive period and have had a normal child.

Some doctors in Germany are still doubtful about the exact role of Contergan. Most doctors, however, believe that Contergan plays a major role. Dr. Pfeiffer remarked that most phenomena are more complicated than they seem and therefore he cannot believe that the cause of phocomelia is as simple as Contergan alone. Nevertheless, he, too, believes that Contegan plays a major role. Many English physicians believe there must be some other substance or factor which also causes phocomelia because a history of Distaval cannot be obtained in every case. No relation has been found between the amount of the drug ingested and the severity of the malformation. A single dose of 100 mg. is thought to be sufficient to cause severe phocomelia and repeated doses may give only a mild abnormality.

The only other drug with which I am familiar[1] which is similar to Contergan is glutethimide (Doriden). Although in a few instances, a history of glutethimide, not Contergan, has been obtained glutethimide has been widely used in Switzerland since 1955 and phocomelia was not known until 1961 and then only a few cases were seen and in most instances, a history of Contergan was obtained.

Little is known concerning the metabolism of thalidomide or how it is excreted from the body, nor the length of time the teratogenic factor persists in the body. Virtually all that is known is that it is insoluble in water and in fat.

[1] My attention has recently been called to 2 other drugs which contain radicles similar to thalidomide, namely, bemegride (Megimide) and chlorthalidone (Hygroton).

It affects the nervous system of mature people and the mesenchymal tissue of the embryo.

Few animal experiments have been done. As previously mentioned, thalidomide does not induce sleep in the usual laboratory animals. Grünenthal has tried to reproduce phocomelia in rats, mice, and rabbits and has failed. In Keil the drug was fed to hens and the chicks were normal.

Grünenthal has shown that the drug passes through the placenta of rabbits but in their experience the offspring were normal. Somers (16) has, however, recently reported the production of abnormalities in rabbits which are remarkably similar to those in infants. Although the offspring were not equally affected, the extremities did appear to be grossly abnormal and radiological examination of the extremities showed that the long bones were defective. Although Somers believes the ill effects of thalidomide are proven; others disagree. Murphy (17) has recently reported the production of phocomelia in the offspring of a rat by intraperitoneal injection of an enormous dose of thalidomide on the 12th day of pregnancy. Clearly these observations require confirmation. Should the observation not be confirmed, it should be remembered that thalidomide makes a horse sleep. Therefore, the horse might be found to react as man does. Simian experiments would also be of interest.

Once a susceptible animal has been found, a new avenue of approach to malformations will be available. It is quite clear that the drug acts during the period in which the embryo is developing as is the case with the virus of German measles. It is equally clear that it acts at a different point or in a different way than does the virus of German measles; the resultant malformations are totally different. Furthermore, thalidomide is a synthetic chemical and it should be possible to test the action of the separate chemical radicals from which the drug is compounded.

Even though this drug has not been conclusively demonstrated to have the same effect on animal and man, it does indicate that all new drugs which circulate through the blood stream should be screened for their effect on the offspring of pregnant animals. Distillers Limited is already attempting to develop tests by which to screen drugs for this serious untoward effect. It is, however, an extremely difficult problem and it demands extensive study. Our Food and Drug Act, although better than most of the other countries, should be strengthened. Women in the childbearing age must be educated not to take new drugs. Often the harm is done before they know they are pregnant and with the best of medical knowledge some other harmful preparation may be incorporated into some drug. We do not know how to completely eradicate such a danger, but let us do what we can.

Thus the tragic effects of thalidomide have opened up a new avenue of approach to the etiology of malformations. What is the precise factor that causes phocomelia? Where does it act? How does it inhibit growth? Many physicians have also asked how about its effect on cancer? One sad story is, we hope, coming to an end. It should be the dawn of new and better control of drugs. Let us hope that it is also the dawn of new knowledge.

SUMMARY

In 1960 Kosenow and Pfeiffer reported a new clinical syndrome; the essential feature was phocomelia. The incidence of the malformations rapidly increased and by the end of 1961, thousands of children had been born with severe malformations of the extremities. The causative factor appeared to be an exogeneous agent. Many retrospective studies were instituted.

Almost simultaneously Lenz in Hamburg and McBride in Australia suspected that the malformations were caused by taking thalidomide in early pregnancy.

Thalidomide is a synthetic drug deveoped by Grünenthal and marketed in Germany as Contergan, in England as Distaval, in Portugal as Softenon, as Kevoadon in the United States (though not released by our Food and Drug Administration) and as Kevadon and Talimol in Canada. It was an excellent sleeping tablet and tranquilizer and was added to a number of other compounds which were used for the relief of grippe, migraine, and asthma and also for expectorants.

The circumstantial evidence is overwhelming that this drug does cause severe malformations of the extremities. Grünenthal showed that the drug passed through the placenta of rabbits. Distillers, Ltd., in England, have reproduced the malformations in rabbits by feeding the drug to pregnant animals. Murphy has

produced phocomelia in the rat by an enormous dose of thalidomide given intraperitonerally to a pregnant animal.

Certainly new drugs, which are of use to persons of all ages and which enter the blood stream, should be screened for possible teratogenic action. Futhermore, young women must learn that nothing is foolproof and new drugs should not be taken unless absolutely necessary, as the damage often occurs before the woman knows she is pregnant.

This drug shows how serious the side effects of drugs may be and it also opens up a new avenue to the study of the etiology of malformations.

GENERIC AND TRADE NAMES OF DRUGS

Thalidomide—*Contergan* (West Germany), *Distaval* (British Commonwealth), *Softenon* (Portugal), *Kevadon* (United States and Canada), *Talimol* (Canada).
Thalidomide is also a constituent of the following drugs: algosediv, peracon expectorans, grippex, polygripan (West Germany); Valgis, Tensival, Valgraine, Asmaval (British Commonwealth).
Glutethimide—*Doriden.*
Bemegride—*Megimide.*
Chlorthalidone—*Hygroton.*

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THE THALIDOMIDE SYNDROME

A MILD AND SUPPOSEDLY SAFE SEDATIVE TAKEN BY PREGNANT WOMEN HAS DEFORMED THE LIMBS AND OTHER ORGANS OF SEVERAL THOUSAND INFANTS IN WEST GERMANY ENGLAND, CANADA AND OTHER COUNTRIES

(By Helen B. Taussig)

Two grossly deformed infants were the subject of an exhibit at the annual meeting of the pediatricians of the Federal Republic of Germany held in October, 1960, in the city of Kassel. Photographs and X-ray pictures showed that the

long bones of the infants' arms had almost completely failed to grow; their arms were so short that their hands extended almost directly from their shoulders. Their legs were less affected but showed signs of a similar distortion of growth. Both infants were also marked by a large hemangioma (strawberry mark) extending from the forehead down the nose and across the upper lip; one of them was also found to have a duodenl stenosis, that is, a constriction of the beginning of the small intestine. The physicians who presented these cases, W. Kosenow and R. A. Pfeiffer, members of the staff of the Institute of Human Genetics in Münster, had never seen quite this combination of anomalies in a single infant. They regarded it as a new clinical entity.

The deformity of the limbs was characteristic of a malformation known as phocomelia, from the Greek words *phoke*, meaning seal, and *melos*, meaning limb. Phocomelia is so rare that most physicians never see it in a lifetime; moreovre, it usually affects only one limb. Kosenow and Pfeffer reported that they could find no hereditary indication for the condition in the history of either family, no incompatibility in the blood types of the parents and no abnormality in the chromosomes of the tissue cells of either child. Guido Fanconi, a Swiss pediatrician who has long been interested in congenital deformities, declared that he too had never seen infants afflicted this way. Otherwise little note was taken of the exhibit. I missed it myself, although I was at the meeting

In retrospect it is surprising that the exhibit did not attract a great deal of attention. During 1960 almost every pediatric clinic in West Germany had seen infants suffering such defects. In Münster there had been 27, in Hamburg 30 and in Bonn 19. There had been perhaps a dozen cases of phocomelia in 1959, whereas in the preceding decade there had been perhaps 15 in all of West Germany. During 1961 the incidence of phocomelia increased rapidly; hundreds of afflicted infants were born.

When the West German pediatricians gathered for their 1961 meeting in November at Düsseldorf, almost all of them were aware of the mysterious outbreak of phocomelia. At the meeting Widukind Lenz of Hamburg made the disclosure that he had tentatively traced the disease to a new drug that had come into wide use in sedatives and sleeping tablets. The generic name of the drug was thalidomide. Under the trade name Contergan, it had been marketed as freely as aspirin in West Germany from 1959 into the spring of 1961. Lenz had found that many mothers of "seal limb" infants admitted to the Hamburg clinic had taken this drug early in pregnancy. Contergan and other preparations containing thalidomide have now been withdrawn from sale. But infants injured by the drug are still in gestation. When the last of them has been born by the end of this summer or early in the autumn, thalidomide will have produced deformities in 4,000 or even as many as 6,000 infants in West Germany alone, and probably more than 1,000 in other countries where it has been marketed. The one-third who are so deformed that they die may be the luckier ones.

It happens that thalidomide-containing drugs did not reach the market in the U.S. This was because of a lucky combination of circumstances and the alertness of a staff physician at the Food and Drug Administration—not because of the existence of any legal requirement that the drug might have failed to meet. If thalidomide had been developed in this country, I am convinced that it would easily have found wide distribution before its terrible power to cause deformity had become apparent. The marketing techniques of the pharmaceutical industry, which can saturate the country with a new drug almost as soon as it leaves the laboratory, would have enabled thalidomide to produce thousands of deformed infants in the U.S. I believe that it is essential to improve both the techniques for testing and the legal controls over the release of new drugs.

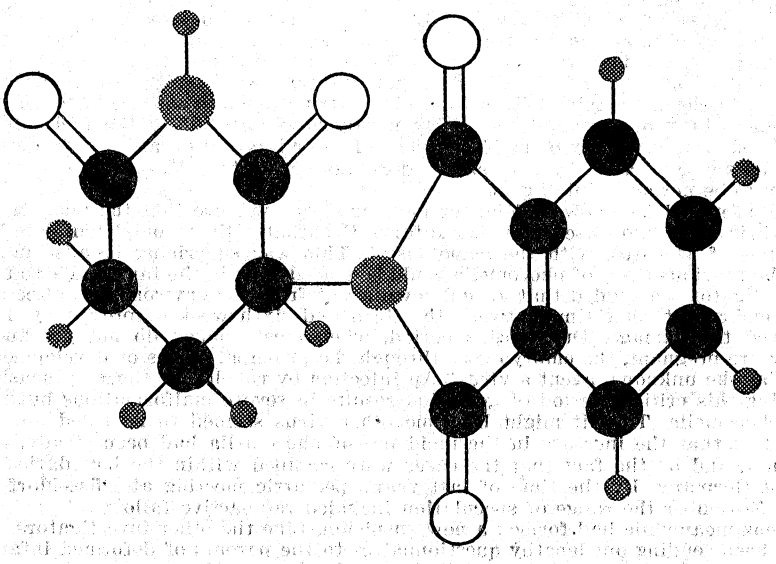
The news that a large number of malformed infants had been born in West Germany and that a sleeping tablet was suspected as the cause first came to me in late January of this year. I was particularly concerned because of my lifelong interest in malformations. That a drug was implicated was of especial interest, because little is known about the cause of the various congenital anomalies that arise in the course of gestation. I immediately went to West Germany to investigate the situation, and I have also conferred and corresponded with physicians in other countries where thalidomide, under various names, has been sold.

In West Germany I was told that a Swiss pharmaceutical house, interested in producing a new sedative, had first synthesized thalidomide in 1954. Because it showed no effects on laboratory animals the company discarded it. Then the West German firm Chemie Grünenthal undertook the development of the compound. Once again thalidomide showed no effect on laboratory animals.

Since the structure of the molecule suggested that it should work as a sedative, Grünenthal tried it as an anticonvulsant for epileptics. It did not prevent convulsions, but it worked as a hypnotic, acting promptly to give a deep, "natural" all-night sleep without a hangover. Given the trade name Contergan, it became during 1960 the favorite sleeping table of West Germany, inexpensively available without a prescription and widely used in homes, hospitals and mental institutions. It turned out to be as safe for humans as for animals. Would-be suicides who tried it after it came on the market survived large doses of it without harm.

Grünenthal combined thalidomide with aspirin and other medicines. Germans consumed these compounds—Algosediv, Peracon Expectorans, Grippex and Polygrippan—for such conditions as colds, coughs, grippe, nervousness, neuralgia, migraine and other headaches and asthma. A liquid form made especially for children became West Germany's baby sitter. Hospitals employed it to quiet children for electroencephalographic studies. As an antiemetic, it helped to combat the nausea of pregnancy, and of course Contergan gave many a pregnant woman a good night's sleep. Grünenthal was manufacturing it almost by the ton.

Soon pharmaceutical companies in other countries began to make or market thalidomide under license from Grünenthal Distillers (Biochemicals) Ltd. sold it as Distaval in the British Isles, Australia and New Zealand. Combinations received the trade names of Valgis, Tensival (a tranquilizer), Valgraine and Asmaval. An advertisement in Great Britain emphasized the safety of the drug with a picture of a small child taking a bottle from a medicine shelf. From Portugal it went into local and international channels of distribution as Softenon. In Canada Frank W. Horner Ltd. of Montreal marketed it as Talimol and the



THALIDOMIDE is a synthetic drug. In this diagram of its molecule, carbon atoms are represented by black balls, hydrogen by small gray balls, oxygen by white balls and the two nitrogen atoms by large gray balls.

Canadian branch of the Wm. S. Merrell Company of Cincinnati as Kevadon. In September, 1960, the Merrell Company applied to the Food and Drug Administration for clearance to sell Kevadon in the U.S.

At that time no one had reported any untoward side effects from thalidomide. During the next few months, however, German medical journals carried reports of a new polyneuritis associated with long-term use of the drug. Patients complained of tingling hands, sensory disturbances and, later, motor disturbances and atrophy of the thumb. By April, 1961, there was a sufficient number of ill effects reported in West Germany following the use of the drug to place the thalidomide compounds on the list of drugs for which prescriptions were required. (It was under prescription from the beginning in most other countries.) Nevertheless, thalidomide remained popular and continued in widespread use in the home and in hospitals.

By the summer of 1961 physicians all over West Germany were realizing with alarm that an increasing number of babies were being born with disastrous deformities of their arms and legs. In Kiel, Münster, Bonn and Hamburg four different investigations were under way. From a study of 32 cases in Kiel and its environs H. R. Wiedemann found that the malformations followed a specific pattern, although they varied in severity.

Abnormality of the long bones of the arms characterizes the great majority of the cases, with the legs involved in half of these. The radius or ulna (the forearm bones) or both may be absent or defective. In extreme cases the humerus (upper-arm bone) also fails to appear. Typically both arms are affected, although not necessarily equally. When the legs are involved, the hip girdle is not fully developed. Dislocation of the hip and outward rotation of the stub of the femur turns the deformed feet outward. The worst cases have neither arms nor leg; since they cannot turn over in the crib or exercise they usually succumb to pneumonia.

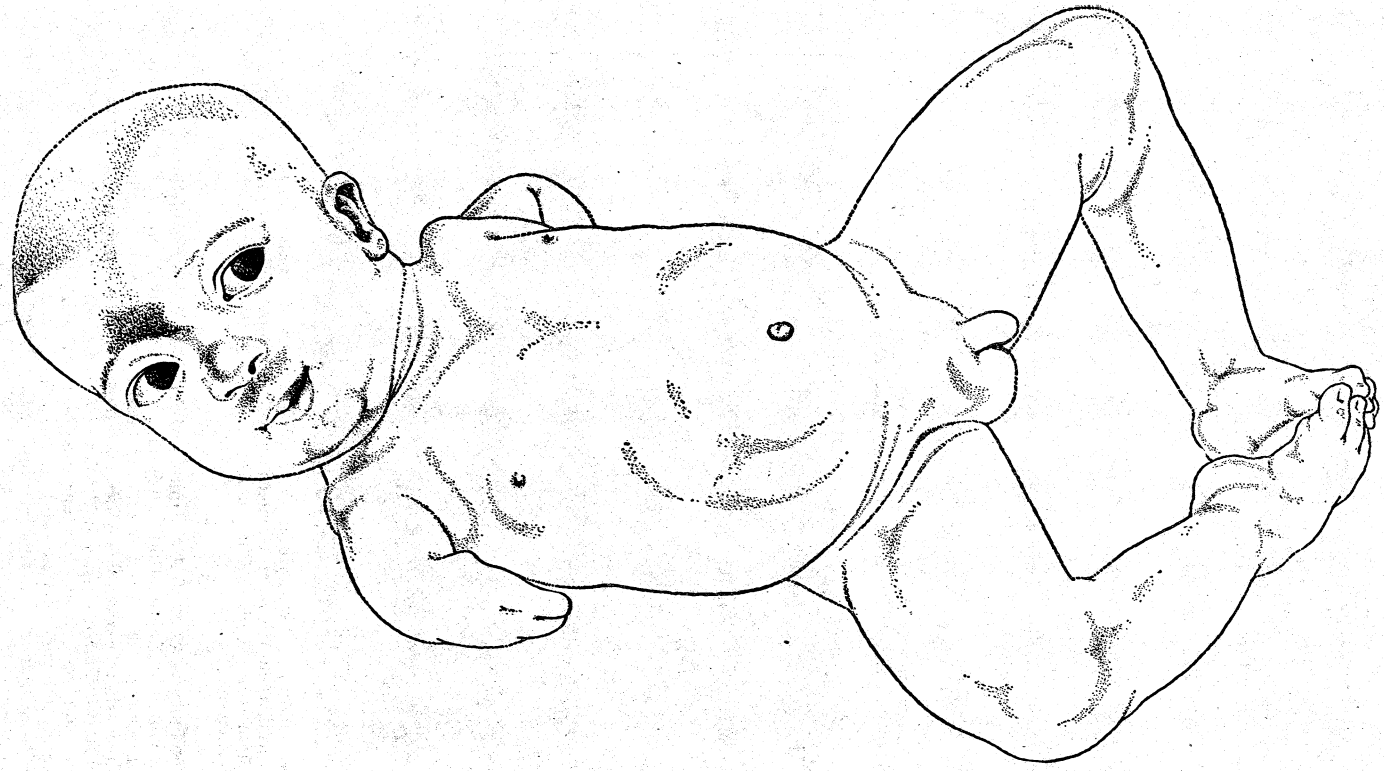
The hemangioma of the face, as Pfeiffer and Kosenow pointed out, is possibly the most characteristic feature of the syndrome. It is, however, neither harmful nor permanent. A saddle-shaped or flattened nose is common. In some cases the external ear is missing and the internal auditory canal is situated abnormally low in the head. In spite of this deformity hearing tends to be fairly good if not normal. Many of the children display paralysis of one side of the face. Many suffered from a variety of malformations of their internal organs, involving the alimentary tract and also the heart and circulatory system. Most of the children seem to be normally intelligent.

Pfeiffer and Kosenow in Münster had found no evidence that the phocomelia in their first two cases was hereditary. Eventually they completed detailed studies of 34 cases, with the same result. This was surprising because many of the previous cases of phocomelia could be traced back in the family. These two investigators concluded that an unknown agent from the environment, affecting the embryo at some time between the third and sixth week of pregnancy, had caused the damage. During this period, when most women do not yet know they are pregnant, the embryo goes through the principal stages of development.

Was the unknown agent a virus? An infection by rubella, or German measles, during this critical period of gestation results in severe malformations but not in phocomelia. That it might be some other virus seemed to be ruled out by the fact that the increase in the incidence of phocomelia had been steady, not abrupt, and by the fact that the cases were confined within the boundaries of West Germany. By the time of last year's pediatric meeting at Düsseldorf in late November the range of speculation included radioactive fallout.

Lenz meanwhile had formed a new suspicion. Like the other investigators, he had been sending out lengthy questionnaires to the parents of deformed infants and to the physicians who attended them, asking about X-ray exposure, drugs, hormones, detergents, foods and food preservatives, contraceptive measures and tests for pregnancy. In his initial returns he noted that approximately 20 per cent of the mothers reported taking Contergan during pregnancy. On November 8, he recalls, it occurred to him that Contergan might be the cause. He now asked all the parents specifically about Contergan, and 50 per cent reported use of the drug. Many of the mothers said that they had considered the drug too innocuous to mention on the questionnaire.

On November 15 Lenz warned Grünenthal that he suspected Contergan of causing the catastrophic outbreak of phocomelia and he urged the firm to withdraw it from sale. On November 20, at the pediatric meeting, he announced that he suspected a specific but unnamed drug as the cause of the "Wiedemann syn-



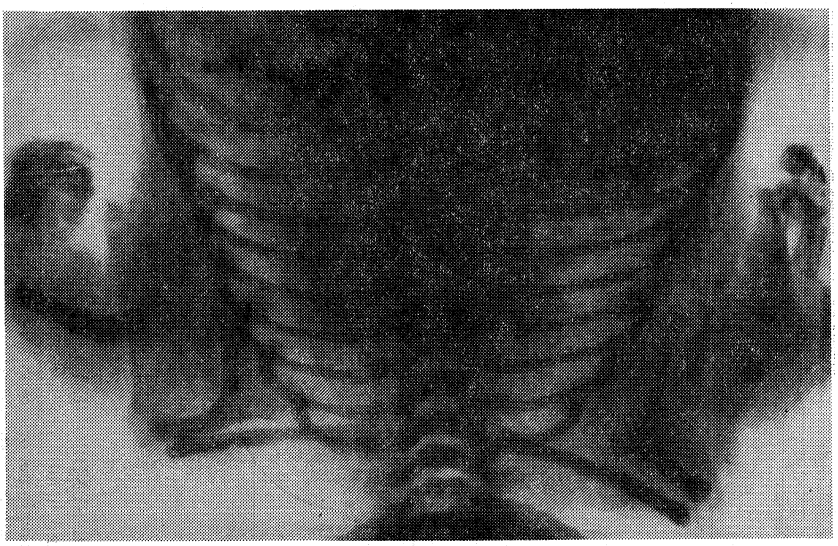
VICTIM OF THALIDOMIDE SYNDROME typically has short, deformed and useless arms and hands. The actual case shown in this drawing displays the hemangioma, or strawberry mark, on the forehead, nose and upper lip, which is the most characteristic (although harmless) feature of syndrome. Other abnormalities that may occur include deformed legs and feet and a wide variety of deformations of the ears, digestive tract, heart and large blood vessels. Most of the afflicted children have normal intelligence.

drome" and said that he had warned the manufacturer. That night a physician came up to Lenz and said: "Will you tell me confidentially, is the drug Contergan? I ask because we have such a child and my wife took Contergan." Before the meeting was over the doctors generally knew that Lenz suspected Contergan.

On November 26 Grünenthal withdrew the drug and all compounds containing it from the market. Two days later the West Germany Ministry of Health issued a firm but cautious statement that Contergan was suspected as the major factor in causing phocomelia. Radio and television stations and the front pages of newspapers promptly carried announcements warning women not to take the drug.

On the other side of the world W. G. McBride, a physician in New South Wales, Australia, saw three newborn babies with severe phocomelia during April, 1961. In October and November he saw three more. From the histories of the mothers he found that all six had taken Distaval in early pregnancy. McBride notified the Australian branch of Distillers Ltd. and it cabled his findings to the London headquarters on November 27. This and the news from Germany caused the firm to withdraw the drug on December 3. Because of the demand by physicians it has been returned to limited sale in England, but in Germany it is now illegal to possess thalidomide.

The news of the Australian experience prompted A. L. Speirs, a physician of Stirlingshire, Scotland, to review 10 cases of phocomelia that he had seen in his practice during the preceding months. By checking prescription records and medicine cabinets in the victims' homes, he obtained positive proof that eight of the mothers had taken Distaval in early pregnancy.



Typical Phocomelia, or "seal limb," is readily apparent in this X ray of chest, shoulders and arms of West German infant. In "classic" phocomelia usually only one arm was affected. Phocomelia caused by thalidomide almost always deforms both arms.

Thus in the last weeks of 1961 circumstantial evidence accumulating in various parts of the world indicated that thalidomide played an important role in the causation of phocomelia. Physicians now began asking women who were still pregnant about their experience with the drug. One obstetrician in Germany asked 65 pregnant women if they had taken Contergan in early pregnancy. Only one said that she had. The physician declared that if she had an abnormal baby, he would believe Lenz. She did!

A drug with a molecular structure similar to that of thalidomide is Doriden, also used as a sedative. Although in a few cases of phocomelia the mother says she took Doriden, not Contergan, Doriden has been widely used in Switzerland