prepared than the individual practitioner to make judgment, "there is nothing to suggest that variations in formulations are causing any problems in the treatment of patients."

Mr. CONZEN. I cannot comment on the findings of these scientists, pharmacologists, chemists, and physicians. All I can testify to is to the quality and efficacy of our own brand.

Senator NELSON. The Chair, of course, won't argue with that. I am sure it is of very high quality, one that ranks with all the other 22 as meeting USP standards. But the Medical Letter is so concerned about the great price spread that they suggest the desirability of prescribing by generic name. Are you suggesting that the Medical Letter is not qualified to make a judgment about this, after the tests they have made and the consultations they have made with distinguished clinicians and pharmacologists around the country?

Mr. CONZEN. Sure they are, but I have not seen any clinical evidence conducted by the Medical Letter or anybody else to prove that other brands of prednisone are therapeutically, in patients, more or less or equally effective.

Senator NELSON. What we are really concluding here is that there is no clinical evidence to prove that any one of these 22 is any better or any less effective, including Schering's?

Mr. CONZEN. That is right.

Senator NELSON. Isn't that correct?

Mr. CONZEN. Yes.

Senator NELSON. Then, the doctor who is prescribing the drug for $17.90, when Merck has one available for $2.20 and Upjohn for $2.25, is simply charging his patient a lot of dollars for a drug on which there is no proof that it is any better than these that are available at a cheaper price; isn't that correct?

Mr. CONZEN. No; I differ.

Senator NELSON. Then we get back to where we started. What is the proof?

Mr. CONZEN. The proof is the abundant experience of a practicing physician of the results which he has achieved in his patients. Each patient, each case, differs, and if he is satisfied that he gets the best response with our product, Meticorten, he obviously feels justified to continue to prescribe it, notwithstanding the fact that he knows that there are less expensive prednisone preparations available.

Senator NELSON. What about the doctor who is prescribing Merck's Deltra?

Mr. CONZEN. That is his judgment, but I believe their sales are very insignificant, and it is more of a service item probably than a widely prescribed brand product.

Senator NELSON. I don't want to put words in your mouth, but what you are really saying is that whatever doctors prescribe the most provides a satisfactory scientific judgment of what is best?

Mr. CONZEN. I would agree with this.

Senator NELSON. Since Schering is confident that its drug has greater therapeutic value than any of the other 21, why doesn't Schering sponsor clinical double blind tests versus half a dozen of the rest of these drugs, so that you would be able to come before the subcommittee and say that the clinical double blind tests prove that ours is the best? Since this is a very important item in the sales of your company, and it wouldn't be very expensive to conduct a double blind

test in terms of what it would mean to you in the market if you are correct, why hasn't the company conducted them?

Mr. CONZEN. First of all, it is a relatively small item in our total sales.

Senator NELSON. It is $1 million a year.

Mr. CONZEN. $1 million; yes.

Senator NELSON. Out of a $3 million market, and if you are correct in what you say, you probably could have the whole $3 million market.

Mr. CONZEN. It is a $40 million market in which we compete with Meticorten, because prednisone is just one corticosterioid within a large number of other corticosteroids. The share of the market of prednisone and Meticorten has been constantly declining and will continue to do so, and this is simply the result of our research-oriented industry where product obsolescence is a very serious matter in our competitive society and we have to live with it. In other words, I do not think we would be justified to expend the money and effort to carry on double blind clinical studies with our brand against over 100 brands of prednisone to prove this point, since we have such abundant evidence that our product is the best, which does not imply that it is better than others.

Senator NELSON. Are you suggesting, then, that when the Defense Supply Agency purchased a 1,000 prednisone tablets on a bid basis, at $4.94, the DSA is supplying Walter Reed—where Presidents, Congressmen, and generals are treated—and Bethesda, and the soldiers overseas, are you suggesting that when they buy Upjohn's tablets at $4.94 on a competitive bid, that they are buying a drug that is not equivalent in its therapeutic value to Schering's?

Mr. CONZEN. I cannot say whether it is therapeutically equivalent. I can say that they are definitely buying a first-class drug which complies and meets the tests and standards of the agency, which are very exact.

Senator NELSON. But you see the Government is buying millions of dollars' worth of drugs, tens of thousands of dollars' worth of prednisone, and they test it. They use it in veterans' hospitals, they use it in Walter Reed, an excellent hospital. The city of New York, where Senator Javits comes from, buys it generically. They are buying prednisone that is not Schering's, and buying it on a bid basis. Are you suggesting that the Defense Supply Agency and all the veterans' hospitals, the soldiers overseas, purchasers like the city of New York that test their drugs, use them in their hospitals and see the clinical results, are you suggesting that they are buying a drug that is not equivalent to what Schering sells?

Mr. CONZEN. Therapeutically it is not proven that they are equivalent, but I do not suggest that they are buying inferior drugs for their patients.

Senator NELSON. What is there about Meticorten that makes it worth $170 a 1,000 when the Government is buying it for $4.53, New York City is buying it for $4.58 a 1,000, the Government is buying it in various bids for $4.52 to $4.94? What distinguishes Meticorten which should justify this price differential is what I am trying to get at.

Mr. CONZEN. Several points. One, the overwhelming clinical evidence as to the efficacy of our brand which is unmatched by any other brand or make of prednisone.

Second, our continuing research and the contributions which the sale of Meticorten make to enable us to continue to compete in this business as a research-oriented company, which strives for innovation, and plays its part in bringing benefits to the public which, in terms of health and anything else, are unsurpassed anywhere in the world.

Senator NELSON. But doesn't Upjohn do research and U.S. Vitamin do research?

Mr. CONZEN. Certainly.

Senator NELSON. And since you do not separate your research so that you can tell how much it costs you to develop Meticorten, I suppose neither do they. Don't they have exactly the same problem?

Mr. CONZEN. I don't think, and I am not aware that, they have done and continue to do research on prednisone.

Senator NELSON. No.

Mr. CONZEN. They do it on other drugs.

Senator NELSON. That is correct.

Mr. CONZEN. And our share of the Meticorten market supports our overall research.

Senator NELSON. You are basing your statement on the overwhelming selection by individual physicians in prescribing Meticorten in the retail market around the country, is that correct?

Mr. CONZEN. Yes.

Senator NELSON. Do you think the judgment of an individual practicing physician is better than the judgment of all the combined doctors, surgeons, physicians, pharmacologists, in Walter Reed Hospital who have an opportunity in a clinical situation to observe the value of the drug prednisone that they are using? Do you think the individual doctor's judgment is better than that of a fine hospital in New York or Walter Reed?

Mr. CONZEN. I would say that the practicing physician who is faced with a particular case history of illness in a particular patient uses his own best judgment, based on his experience with the drug and his diagnosis and his prognosis, and that this will be, I hope, always the overriding consideration of the practicing physician.

Senator NELSON. I would agree that that is exactly what the practicing physician does, but that does not answer my question which is this. Is his individual judgment better than the combined judgment of all the various medical services in the distinguished hospitals such as Walter Reed, in determining the value and quality and therapeutic effectiveness of a brand of prednisone?

Mr. CONZEN. I find it difficult to relate the conclusion which is reached by a large Government agency to put it into juxtaposition with the problem with which the physician is faced when he has his patient in front of him and has to make this judgment. I find it difficult to do this.

Senator JAVITS. I am troubled by another aspect of this matter. I must say I am also troubled by the aspect which troubles Senator Nelson. But what about the built-in failure to allocate all the research costs which you speak of, the initiatory costs, and the commendable initiative in your company which produced this drug, when you bid on Government business? For example, this Defense Supply Agency chart shows that in October 1965 Schering bid on the same contract that Upjohn got. They bid $9.20 a 1,000. According to our chart, you

are selling at $170 a 1,000 to the druggist, or a difference there of over 1,800 percent. How do you justify the failure to allocate in your bid enough of all of these built-in costs, et cetera, to a Federal Government bid as against taxing so very heavily the patient of the doctor and the customer of the druggist?

Mr. CONZEN. I would like to comment on this. First of all, the basis of our business is the prescription business and the business which flows through the pharmaceutical wholesale and retail trade. Government agencies purchase pharmaceutical products in large quantities on the basis of competitive bids. Such orders may be highly attractive and many companies are convinced that these orders should be sought even at prices which would be unprofitable if normal accounting practices were followed.

They do this in the belief that such business should be regarded as incremental business, and that only additional cash out of pocket incremental costs directly traceable to the specific order should be considered. Incremental costs are the specific net additional cash costs of that order alone, namely raw materials and variable direct labor costs. They do not include even such other manufacturing costs as those for labor supervision or for plant and equipment and its maintenance.

No thought is given to any other costs of business operation, be it research and development, for marketing, for administration, taxes, and so forth.

They also sometimes ignore even these low incremental costs, if this is done, on the theory that widespread use of a branded product in Government hospitals has a net insignificant promotional value, and that doctors who use products in Government institutions or military practice will carry over their experience to private practice.

The effect of this practice is to establish a two-price system, a normal price for regular sales on the basis of which the business is built, and a lower price for incremental or "plus" volume. This is not unlike the system of printers who quote a base price for the first 1,000 copies of a job, and a much lower price for a second 1,000. Even though there are substantial economies in handling single large orders, as well as economies in sale to Government agencies as opposed to wholesalers and retailers, any real accounting effort to determine the full cost of products sold to Government agencies would show the cost to be higher than the prices which are typically quoted for Government prednisone business, not only by others in the industry, but also by Schering. We at Schering could no more operate our whole business on the basis of prices quoted to the Government or its agencies than could printers on the basis of prices for "extra" copies.

Senator JAVITS. Now, what about the differential between what you charge domestically and what you charge abroad for the same type of customer?

Mr. CONZEN. There are many reasons why there are differences in pricing abroad and at home.

Senator JAVITS. What is the difference first? Can we get that?

Mr. CONZEN. First the difference. There has been in our newspapers over the last weeks, they have carried the story that Schering sells prednisone, Meticorten tablets, 30 for 37 cents, stated in U.S. dollars, in Mexico when its price in the United States is $5.65 to the drug trade.

Now, we do not sell in U.S. dollars in Mexico. We sell in pesos and the price for 30 tablets of Meticorten in Mexico is 46 pesos. Now, the officially recognized exchange rates is 12 pesos and 50 centavos to the U.S. dollar. Somebody in converting this peso price into U.S. dollars at this exchange rate apparently made an arithmetical error by moving a decimal point in the wrong direction, because if you convert 46 pesos into U.S. dollars, you have a price of $3.68 in Mexico, which is a very different story from the one which I read in the paper; namely, of 37 cents.

Senator JAVITS. I don't follow you, sir. What quantity is this that you are selling at $3.48?

Mr. CONZEN. Thirty tablets.

Senator JAVITS. Now, you are selling 100 tablets then at $17 in this country; is that right?

Mr. CONZEN. That is the drug list price. This does not mean that we realize $17.90. We have computed that in 1966 the average price for 100 tablets of Meticorten realized in the United States was $11.36. This price in Mexico——

Senator NELSON. May I interrupt for a moment?

Mr. CONZEN. Yes.

Senator NELSON. You said the average price in the United States?

Mr. CONZEN. Yes.

Senator NELSON. But what is your price to the retail druggist?

Mr. CONZEN. The price which appears in our price list as the drug list price, at which the retail druggist buys, is $17.90.

Senator NELSON. You are including in your average price sales to other than retail druggists?

Mr. CONZEN. Yes. The bulk of our business goes to wholesalers to start with, and they too have a margin of profit.

Senator NELSON. But you list in your book $17.90 to the druggist, is that not correct?

Mr. CONZEN. That is the price to the retail pharmacist, yes.

Senator NELSON. In purchasing on the open market for purposes of their tests, the Medical Letter said a price of $17.90. In other words, the druggists they checked were paying $17.90.

Mr. CONZEN. That is right.

Senator NELSON. Are you saying that you sell to many other druggists at less than $17.90?

Mr. CONZEN. No. What I tried to convey is that these druggists buy usually from wholesalers, and that the wholesalers who buy from us buy at a lower price than the drug list price of $17.90.

Senator NELSON. But is the druggist around the country paying $17.90 when he gets it from you or the wholesaler?

Mr. CONZEN. That is right.

Senator NELSON. So then when you say the average price of 11 something, you aren't referring to what the druggist pays?

Mr. CONZEN. That is correct.

Senator JAVITS. Go ahead with your foreign sales. You say in Mexico you are still selling it for your average equivalent; is that right?

Mr. CONZEN. In Mexico our price is, as I indicated, 46 pesos for 30, or $3.68.

Senator JAVITS. What about other countries; is that the same?

Mr. CONZEN. Now, take Brazil, which was another country mentioned in the press reports. We introduced Meticorten in Brazil in

1956 at 320 cruzeiros for 20 tablets, which at that time was the equivalent of $4.41. Now, between 1956 and 1967 the price for Meticorten in Brazil has been increased eight times, and has risen from 320 cruzeiros to 2,480 cruzeiros. If one relates these steep price increases to U.S. dollars, because of the galloping inflation and the devaluation in Brazil of the cruzeiro, the price has actually come down to $1.05. Now, we have no control over the prices which the government in Brazil permits the pharmaceutical industry, because when there is a devaluation, prices in these planned economies are frozen, and then after a while the Government usually permits an arbitrary increase in price for all commodities including drugs.

Senator JAVITS. We have some information which indicates that in Rio de Janeiro and in Bern, Switzerland your prices are very low, going down to $1.59 and $1.37 respectively for 30 tablets.

Mr. CONZEN. In Brazil my information is the price is $1.05 for 20 tablets.

Senator JAVITS. What about Bern, Switzerland?

Mr. CONZEN. In Switzerland our price is five francs and 95 centimes, which, for 30 tablets, would be, at the usual rate of exchange of $4.20, the equivalent of $1.37.

Senator JAVITS. How do you account for that very marked difference between the Swiss price and the U.S. price?

Mr. CONZEN. I account for this difference as follows. The price has gradually come down in Switzerland where we do not operate ourselves, but where the business in Meticorten tables is in the hands of an accredited sole distributor who sets his own price, and these again are usually the result of negotiations with Switzerland, in other words, their social security system.

Senator JAVITS. Is the distributor taking the loss between what he pays you and what he sells it for at $1.37?

Mr. CONZEN. He carries this item as a service item I would say, because the total sales in Switzerland of Meticorten in 1966 amounted to the equivalent of $6,340.

Senator JAVITS. Nonetheless, in selling to him, are you accommodating your price to his need?

Mr. CONZEN. It is part of our overall foreign business to accommodate him, yes.

Senator JAVITS. So that there are wide differences between your prices to governments, which you call incremental, and your prices abroad—between those and your prices in the United States?

Mr. CONZEN. Yes, sir.

Senator JAVITS. This morning I explained to Mr. Burrows the problem of passing the cost at the retail level on to governments through the medicaid program, for example. Do you feel any need for adjustment, in order to deal with indirect governmental sales, to wit, where the Government pays the bill—as it does under medical aid—to your governmental sales where you sell direct to Government? How do you rationalize those two? In that one case apparently an enormous premium is being paid, if the Government pays indirectly through medicaid. On the other hand, if it seeks to get bids directly, it pays a very small amount. Now, doesn't that dictate that Government just ought to pick it up and distribute your product, or a product equivalent to it instead of letting the medicaid client go to the drug store?

Mr. CONZEN. I would say, Senator Javits, that this would amount to adopting a national policy of cheap drugs, which in my opinion would be extremely shortsighted and would constitute a direct threat to medical progress and impair substantially the leading role which the United States today has acquired throughout the world. It is a significant part also of what our industry contributes to the balance of payments.

The economics of our company and of our industry are based on innovation, and a cheap drug policy would take this leadership away from our industry and our country.

Senator JAVITS. I do not pretend to expertise, but just as you want us—and I agree with you thoroughly—to encourage initiative and invention in our country in the flowering of the private enterprise system which it represents, I think we have a right to turn to the private enterprise system and say, in view of what has been revealed, that we think you had better have a pretty hard look at your own situation. I don't think the public is going to take very kindly to a 1,800 percentile difference between sales to them and incremental sales, or a 200 or 300 percent difference between domestic sales and sales abroad. I am no inexperienced person in business, as you know, but I do think that a case is being made out here for a very critical review and appraisal by the industry itself of the situation which is being laid before the people of the country. Especially is this true, sir, because a new situation has occurred.

A good deal of what is now paid for drugs is indirectly paid by Government, and hence it becomes a very critical aspect on our part. I tell you again that as one Senator, I am anxious to preserve this system, and I am very troubled about whether these differentials can be justified in order to preserve it.

I would beg the industry itself to give consideration to that, not only in the interests of its own situation, but in the interests of the economic system of the Nation, of which this is a very critically important part. We have always rewarded invention, and we should, magnificently. It is very necessary to us, and yet there is a question of degree even there. That is what I lay before you as an intelligent man heading a very great company.

Mr. CONZEN. May I make a comment, Senator Javits?

Senator JAVITS. Surely.

Mr. CONZEN. On this point, on this differential between U.S. prices and foreign prices, there are a number of other points which I could make. It is a very complex business. But the living standards and purchasing power of people abroad differ greatly from those in our country. The expense of doing business abroad varies greatly from country to country. The purchasing power of an average workman in terms of minutes worked to earn the equivalent of a dollar differs very greatly by hundreds and hundreds of percent compared with the United States.

I have already mentioned the fluctuating exchange rates and the different places in which we do business. The discount pattern differs significantly from each country to each country, and again vis-a-vis the United States.

Senator NELSON. May I ask one question. You referred to the purchasing power of the citizens of these countries.

Mr. CONZEN. Yes, sir.

Senator NELSON. Switzerland, England, Rome, Italy, and Germany are all very prosperous countries. Is their purchasing power lower than the purchasing power of poor citizens who live in ghettos throughout America, who have almost no income at all? They buy these drugs, too.

Mr. CONZEN. It is very difficult to compare these in terms of U.S. dollars. I have lived and worked in this industry in practically every continent of this world, and I am struck by the high standard of medical care which prevails in this country and which I sincerely believe is unmatched by any other country in the world, and I would hate to see anything done to jeopardize this outstanding position which we enjoy in this country.

That there are poor people, this is understandable, and it is the obligation of society and Government to do something about it.

To revert briefly to Senator Javits' impression that we might be doing business abroad which is subsidized in a way by the U.S. citizens who pay our prices for prescription drugs, I do not think this is quite correct, because as can be seen from our annual reports, our foreign business is actually more profitable than our domestic business, so there cannot be any question that our citizens here help to support lower-priced drugs of our company in foreign countries.

Senator JAVITS. Do you meet competition abroad that you do not meet here?

Mr. CONZEN. Yes, sir.

Senator JAVITS. In this very product?

Mr. CONZEN. Yes, sir.

Senator JAVITS. So that is a factor, too, isn't it?

Mr. CONZEN. Certainly.

Senator JAVITS. Nonetheless I will say, sir—and I hope you will understand I am not accusing anybody of anything—here is a problem the anatomy of which is being laid bare to the country, that the percentages involved, I must say, certainly are very troublesome in terms of the relationships which I have described.

Now, may I ask you a summary question which Mr. Burrows suggested to us this morning? He said that they would have eliminated profit entirely if they had reduced prices across the board 20 percent, which gave some order of magnitude that he felt it is in the abyss with a runaway profit operation. I just wondered whether you would subscribe to that for your company, or whether there is some other standard of judgment which would indicate the reasonableness of the overall profit, whatever might be our complaints. I think there is a serious complaint frankly, about the weighting which is being given to various customer elements in the total sales.

Mr. CONZEN. I would prefer to answer this question as follows. If we were faced with an overall price cut of X percent, 20 percent, we would have to conduct, from that point onward, a very different business from the one we have been able to conduct until now; and I sincerely believe that this would not be in the best interest of our people and our country.

Senator JAVITS. One last question. Do you have any suggestions for us on this subject; or do you just say let it run as it is?

Mr. CONZEN. I think the point that there are indigent patients who find it difficult or impossible to pay for medical care suggests that

something has to be done, but I would also suggest that the price of drugs in this overall picture plays a very small and rather insignificant role. In the report to the President which was published by HEW in April of this year, it was confirmed that our industry has done something which nobody else in this country I believe has been able to accomplish, namely, to keep the overall cost for its commodities level over the last 10 years, when the other much more significant parts of health care have risen very significantly.

Senator JAVITS. Of course, that may only indicate that prices in your industry were already very high. Therefore, you did not have to raise them. But I am not drawing that conclusion invidiously. I just say it could be accounted for this way.

I would like to ask you just one other question which stems from what you have said. You have not said anything about your licensing policy. Now, it is a fact, isn't it, that your licensing policy does bring about competition with your own product; is that right?

Mr. CONZEN. Correct; sir, yes.

Senator JAVITS. And would you say that the 6-percent license fee—which is 6 percent of what, by the way, selling price?

Mr. CONZEN. Of the price which the seller realizes when he sells.

Senator JAVITS. Would you say that your 6-percent licensing fee is a very reasonable one, which does develop the kind of competition which apparently you yourself are faced with in Government orders?

Mr. CONZEN. I would say yes, sir.

Senator JAVITS. Now, what philosophy of your business dictates your establishing that fee, which you consider very modest?

Mr. CONZEN. This fee is in line with—it varies, of course, from product to product and situation to situation, but it lies within the general range of royalties which the industry charges and pays throughout the world; and in terms of a contribution to our research budget, it makes a contribution, but we wouldn't be able to exist economically on this 6-percent because we spend 9 or 10 percent of our own sales on research, for instance.

Senator JAVITS. Is this license available to any firm of probity and credit, or do you pick and choose among licensees?

Mr. CONZEN. We have adopted a liberal licensing policy, and we have not declined any request or application for a license.

Senator JAVITS. May I suggest, Senator Nelson, that we develop and have the staff find out if there are any complaints about the licensing policy pursued in this field? I think that might be a very useful point.

I yield.

Senator NELSON. When you say you follow a liberal policy of licensing, are you referring to prednisone?

Mr. CONZEN. Yes, sir.

Senator NELSON. You have a number of patents on the drugs, I assume, is that correct

Mr. CONZEN. Yes, sir.

Senator NELSON. When you have patented a drug, have you always forthwith licensed a number of companies to sell it, or have you sometimes waited out the 17-year patent period?

Mr. CONZEN. It is not the usual policy to license liberally as has been done in the case of prednisone because otherwise we would not be able to conduct our type of business.

Senator NELSON. Let me ask you what your policy is. If Schering discovered a new and very valuable drug, and you patented it, would you license a number of other drug companies to sell in competition or not?

Mr. CONZEN. This would be a question of business judgment in each particular case. If it is a drug which we believe we cannot handle ourselves alone in sufficient volume and sufficient degree to insure that it is widely available to all those who need this drug, we might license somebody. If we think we can take care of it ourselves, we do it ourselves.

Senator NELSON. You have testified that Meticorten accounts for less than or around one-half of 1 percent of the total income of your business and your sales in the United States of this product are $3 million. Would you license because your company wasn't capable of producing and supplying the market for $3 million worth of prednisone.

Mr. CONZEN. In 1955, when this drug was marketed for the first time, this was definitely one factor in our consideration, but there were other factors. At that time we were faced with the situation in the Patent Office where other companies laid claim to this invention or discovery by filing patent applications and an interference was declared. At that time we could not be sure, until the Patent Office had finally ruled, who in the end would be permitted to sell and who would not be permitted to sell, so this was an additional factor why we adopted this licensing policy with prednisone.

Senator NELSON. If the company discovers a new drug that is patentable and in great demand, because of its value, isn't it the normal practice unless there is patent interference or some other compelling reason, for that company to market it exclusively domestically for the next 17 years of the patent?

Mr. CONZEN. For whatever period the company may decide in its best business judgment, the answer is yes, because neither the industry nor Schering Corp. could afford the investment necessary in developing these drugs, unless we would have our patent system, and it is interesting to note that in those countries where we do not have a patent system, not one single novel drug has been made available to mankind over the years.

Senator NELSON. Does Germany have a patent system?

Mr. CONZEN. Oh, yes, sir, very much so.

Senator NELSON. Do they have a product patent or just a process patent?

Mr. CONZEN. There is a process patent, but about 4 or 5 weeks ago the Bundestag in Bonn passed a new law which is tantamount to recognizing product patents.

Senator NELSON. Do they have product patents in France?

Mr. CONZEN. Yes, sir.

Senator NELSON. In Italy?

Mr. CONZEN. In the pharmaceutical field? In Italy there are no patents at all in our field, and this is one of the reasons why in my judgment never has a product been developed and discovered in Italy, that is of significant importance to public health. The same applies to Russia incidentally.

Senator NELSON. The staff asserts that there are no product patents in France on drugs. I do not know whether that is correct or not.

Mr. CONZEN. There is a patent system which in effect in our particular field of pharmaceutical therapy is to all intents and purposes as far as I know as effective as the product patent system.

Senator NELSON. Is there any competitive prednisone on the market in Europe?

Mr. CONZEN. Yes, sir.

Senator NELSON. Who competes with Schering? What foreign companies compete with Schering in supplying prednisone to the European market? Do you happen to know?

Mr. CONZEN. I do not know the number, but there are innumerable companies that are marketing and selling prednisone preparations.

Senator NELSON. They are not licensed by you?

Mr. CONZEN. In Europe where we have patents they are licensed by us. In countries where there are no patents or which are behind the Iron Curtain of course they are not licensed by us. They are just pirates.

Senator NELSON. Is there competition from foreign companies in Italy on prednisone?

Mr. CONZEN In order to do business in Italy, the drug has to be registered and approved by the Italian health authorities, and in order to get this approval, the drug has to be made in Italy, so these are all prednisone preparations actually manufactured in Italy.

Senator NELSON. Are they manufactured there in your case, or do you send the compounds over and then just tablet there, final finishing?

Mr. CONZEN. The pharmaceutical manufacturing is done by us in Italy.

Senator NELSON. What do you mean by pharmaceutical?

Mr. CONZEN. The tableting. In other words, the Italian-affiliated company of Schering Corp., buys bulk prednisone.

Senator NELSON. And it is all prepared except the tableting?

Mr. CONZEN. Only the active ingredients are imported into Italy.

Senator NELSON. The mechanical process of putting it in tablet form is performed there?

Mr. CONZEN. It is more than a mechanical manipulation, inasmuch as it involves, in our particular case, it involves 93 checks and tests between the arrival of the bulk active ingredient and the final release of the packaged and labeled product to the trade.

Senator NELSON. Let me ask this. In Switzerland is there competing foreign-produced prednisone on the market?

Mr. CONZEN. I would guess yes. I do not know for sure, because I have not any personal first hand knowledge of this particular product in that particular market today.

Senator NELSON. Would your company know? I would think that your sales people would know——

Mr. CONZEN. Sure.

Senator NELSON (continuing). Whether or not prednisone is foreign produced and sold competitively, in Switzerland, wouldn't they?

Mr. CONZEN. The answer is "Yes."

Senator NELSON. Do any of the gentlemen with you know for sure?

Mr. CONZEN. No. I think I know about the international business more than my colleagues, because I have worked in it for most of my

life, and I would feel pretty sure that there is both Swiss made and imported foreign prednisone tableted and packaged forms available today in Switzerland.

Senator NELSON. And is foreign-produced, competing prednisone available on the market in Italy?

Mr. CONZEN. Not in terms of the finished packing. As far as I remember, you cannot sell an imported finished packing today in Italy. It has to be registered and made in Italy.

Senator NELSON. But I mean to say, does any foreign corporation in Europe produce prednisone, in competition with Schering's Meticorten?

Mr. CONZEN. Yes, sir.

Senator NELSON. And is it on the market in competition in Rio?

Mr. CONZEN. Certainly; yes, sir; everywhere.

Senator NELSON. Foreign-produced competing prednisone is what I am talking about.

Mr. CONZEN. I would like to avoid any misunderstanding as to the term "foreign-produced."

Senator NELSON. Foreign to us.

Mr. CONZEN. It is made in Brazil. Brazil does not permit the importation of finished packaged prednisone products, so what happens is that the active bulk substance is imported into Brazil from various sources from different countries, and then manufactured into finished products and packages under Brazilian labels.

Senator NELSON. And is that true of Mexico?

Mr. CONZEN. Yes, sir.

Senator NELSON. Is that true in Australia?

Mr. CONZEN. Yes, sir.

Senator NELSON. Is it true in Canada?

Mr. CONZEN. Yes, sir.

Senator NELSON. Not one of these companies from Europe or elsewhere may market prednisone under any label in the United States, may they, unless they are licensed by you?

Mr. CONZEN. That is right.

Senator NELSON. Well, then, doesn't it really appear that the reason the price is lower in Rome, Mexico City, Rio, Bern, Australia, is due to the fact that you have competition there?

Mr. CONZEN. No, sir.

Senator NELSON. Why don't you sell it for more money then?

Mr. CONZEN. It is impossible for the reasons which I tried to explain. We have a 12-year market history now in each country, and each country has different circumstances and factors which has influenced the price structure in that particular country over the years to the point that we have today a price in Brazil of 2,840 cruzeiros, when it was only 320 cruzeiros when we introduced it.

Senator NELSON. But that is only $1.59. Their cruzeiros are——

Mr. CONZEN. At the exchange rate.

Senator NELSON. They are inflated?

Mr. CONZEN. Yes.

Senator NELSON. So for $1.59 you are selling packages of 30 in Brazil versus $5.65 in the United States?

Mr. CONZEN. That is right.

Senator NELSON. You have to send it down there, distribute it, package it, finish it down there, and yet it is selling for a third of the price

you sell it for in the United States. Now, isn't it competition that is doing it?

Mr. CONZEN. Not only competition. One of the main reasons has been the galloping inflation, and the devaluation of the cruzeiro in terms of the U.S. dollar.

Senator NELSON. Was that true, is that the reason—there isn't galloping inflation that I am aware of in Bern, Switzerland, and it sells there for less than it does in Brazil. It sells for $1.37, according to the State Department.

Mr. CONZEN. This is a price which, as I indicated before, was established by our distributor with the Swiss social security authorities, and has gradually come down to this price, to this level.

Senator NELSON. In Australia it sells for $7.07 per 100. We transposed that to $2.31 for 30. How do you account for that price in Australia? That is not a destitute country.

Mr. CONZEN. This is the price which probably, I can find this out, lies substantially above the price of other prednisone brands in that country. Moreover, the cost of doing business in Australia is a very different one from doing business in this country.

Senator NELSON. Well, I must say just for myself that it is not a very convincing explanation. Wherever you have competition, you charge a substantially lower price than you do in the United States, where there is not any competition except as you have licensed it.

Mr. CONZEN. I think we have at least as much competition here as we have in other countries.

Senator NELSON. Let me read something to you from testimony of a former president of the Schering Co., Mr. Brown, who appeared before the Kefauver Committee on December 7 and 8, 1959. This is on page 7,888 of the hearings on administered prices:

Senator KEFAUVER. I know but the problem is that we want to get cheaper medicine in that one house where one percent is sick. What would you have done—

This is to Mr. Brown, president of the Schering Co. at the time—

what would you have done if Merck had offered to sell their Deltra product—

Which is their prednisone—

at $25? Would you have gone down?

Mr. BROWN. Senator, in this industry you don't sell your product if a company of equal standard has a lower price, so you have to meet their price.

Senator KEFAUVER. So had Merck gone down, you would have gone down?

Mr. BROWN. We would have been forced to go down just as we were forced to price our product in competition with cortisone and hydrocortisone when we first brought it out.

Now, Merck reduced the price of its prednisone called Deltra, in January of this year from about $17.90 to $2.25 per 100. Your president, Mr. Brown, said in 1959 that you would have to go down to meet competition. The competition lowered its price in January. How come you haven't gone down to meet the competition as your president insisted that your company would have to do?

Mr. CONZEN. I believe that this statement was a correct one in 1959 when prednisone was the leading corticosteroid in the market. Today we have an entirely changed set of circumstances. The bulk of the corticosteroid tablet market no longer lies in prednisone but in other products, and our price today of Meticorten is not out of range with

the other corticosteroids which compete in this particular therapy area.

Senator NELSON. But they are way out of line with other prednisones?

Mr. CONZEN. That is right.

Senator NELSON. President Brown of Schering said in 1959:

> We certainly would have to reduce our price to meet the competition if Merck reduced its price.

What has happened since then to invalidate that judgment and statement by President Brown?

Mr. CONZEN. What has happened is that the market in corticosteroids has so drastically changed in these intervening 8 years that this statement of 1959 is no longer applicable to today's market situation in this product.

Senator NELSON. But $3 million worth of prednisone is being sold annually on the market here, and if the reduction in Merck's price of 1959 would have forced Schering to go down to meet the competition, I still don't understand why it would not force it to go down to meet the competition in this $3 million market.

Mr. CONZEN. I think the answer lies in that Merck, to my knowledge, does not sell prednisone to any significant degree, so it is no longer an important factor in the market.

Senator NELSON. I think that is exactly correct. I think that is the reason. There is no competition on the retail market. This demonstrates what I have been trying to say all along. The one thing known on the market is Meticorten and Merck can reduce its price to a nickel, and no doctor is going to prescribe it because he does not know that Merck, or any of the other producers, meet the Medical Letter's standards or USP standards. The dominant name on the market is Meticorten; isn't that the case?

Mr. CONZEN. I would say that with 130 different manufacturers products of prednisone available on the market, there are few items in today's armamentarium to the physician which have that much or more competition. In other words, there is more competition in this than in many other instances I know of.

Senator NELSON. I cannot answer the question of my own knowledge, but before we are through we are going to check some drugstores. I think you will find out what I found out from half a dozen checks that all the drugstores have Meticorten. You can take the list of firms mentioned in the Medical Letter to your independent drugstores. Most of the druggists have never heard of them, they do not stock their products for the very reason that the doctor does not prescribe them. Therefore, you can hold your price any place you please, because if the physician does not know about comparable products—and it is said that he does not—then you have no competition. But in the foreign market, where you have to compete, where there are competing prednisones on the market, your price is down. That explanation is, I must say with all due respect to you, more convincing to me than your explanation.

Mr. CONZEN. Senator Nelson, I would submit that——

Senator NELSON. I think you have done an excellent job. I am not critical of you.

If I were running your company and could make my product dominant on the market, and that is the rules of the game, I certainly would do it. I am not saying there is anything wrong with that from the standpoint of your company ethically or anything else. I have some concern about the way the system works, but I do not have any criticism for you and your success in convincing the doctors that Meticorten is the one they ought to buy. I am not critical of that at all.

Mr. CONZEN. But I would like to submit that first of all Meticorten is not the leading seller in the prednisone field.

Senator NELSON. Retail?

Mr. CONZEN. Anywhere, because it is——

Senator NELSON. A little while ago I asked you what percentage of the market you had, and you could not tell me. Now, how do you conclude that it is not the leading one in the retail market?

Mr. CONZEN. I said in my prepared statement that we estimate the total market in prednisone tablets in this country to be approximately $3 million, out of which we have $1 million, so the majority of the market is serviced by other brands. The other point——

Senator NELSON. May I ask this one question at this point?

Mr. CONZEN. Yes.

Senator NELSON. Is there any other company in the United States that sells more prednisone on the retail market than you do?

Mr. CONZEN. In terms of dollars?

Senator NELSON. Yes.

Mr. CONZEN. No; not that I know of.

Senator NELSON. How many firms, did you say, sell prednisone?

Mr. CONZEN. 130.

Senator NELSON. 130. It may very well be that you could be like General Motors. They are very dominant in the market. They have got 50 percent. They have only three other competitors. You have 130 and they may each have a percent or two, or three or five or six, but I would guess from my checks around that Meticorten seems to be the one that is dominant. I don't have the facts. I want to get them.

Mr. CONZEN. That is in dollar volume. If you think in terms of units, actual tablets prescribed and taken by the patient, Meticorten amounts to approximately 5 percent, and 95 percent of the rest of the market is handled by other brands.

Senator NELSON. On the retail market?

Mr. CONZEN. Yes, sir; on the total patient market.

Senator NELSON. Pardon?

Mr. CONZEN. On the total market, including I would say retail, it is probably 90 percent of other makes.

Senator NELSON. In the retail market 90 percent of tablets sold are sold by?

Mr. CONZEN. By other companies.

Senator NELSON. Other companies.

Mr. CONZEN. Competitors, yes.

Senator NELSON. And 5 percent or 10 percent is sold by Schering?

Mr. CONZEN. That is right.

Senator NELSON. On the retail market?

Mr. CONZEN. That is right, roughly.

Senator NELSON. And yet through your sales you represent one-third of the total of the $3 million market, is that correct?

Mr. CONZEN. That is right; but I also believe that it would be hard to find a practicing and prescribing physician in this country——

Senator NELSON. Pardon me?

Mr. CONZEN. It would be hard to find a practicing physician in this country who is not aware of the fact that prednisone is available at much lower prices than Meticorten, because physicians are highly trained and educated people. They have been solicited by salesmen and by mail for years now that prednisone is available at these much lower prices, so I do not think it would be right to assume that physicians are unaware of this price spread.

Senator NELSON. I think you have to make two different assumptions about that based upon our experience. We have had testimony, as you probably know, from very distinguished professors in our medical schools, pharmacologists and doctors who assert quite flatly that it is impossible for a practicing physician, busy as he is, to keep up with the names of the various drugs, to say nothing about prices. I do not know whether their testimony is correct or not. I hope to find out. But I have a suspicion that there is a substantial element of truth in their claims that it is impossible for the doctor to keep up, and whichever firm does the best job of convincing the doctor about its product is the one whose product he prescribes. But that is my feeling. I might be wrong and we will find out in the course of these hearings.

Mr. CONZEN. If I may suggest a pharmacologist and university professor who does not treat patients may be less aware of this than the practicing physician who has to deal with this individual patient and who is constantly solicited by the industry and the trade for the products which we make available.

Mr. GORDON. I have a question in the nature of a summary. You stated before that the differences of prices throughout the world depend on conditions, on the income of people and so on and so forth. Now, aren't you really saying, when you say that, that you charge what the traffic will bear? That the markets outside this country will not bear high prices? Here they will bear higher prices? Aren't you really saying that?

Mr. CONZEN. No, I am not.

Mr. GORDON. You are not?

Mr. CONZEN. No.

Mr. GORDON. I am not sure that I understand what the explanation is then.

Mr. CONZEN. If we take the specific price which is charged today for Meticorten abroad——

Mr. GORDON. Let's take Australia as a specific concrete example.

Mr. CONZEN. Yes.

Mr. GORDON. From where do you import the bulk material into Australia? From the United States?

Mr. CONZEN. I don't know where they buy, but let's assume from the United States.

Mr. GORDON. Let's assume from the United States.

Mr. CONZEN. Yes.

Mr. GORDON. And since this bulk material is not something small, the transportation costs are not too low, isn't that correct?

Mr. CONZEN. It is minimal, because it is small.

Mr. GORDON. But you have transportation costs?

Mr. CONZEN. Small transportation costs, yes.

Mr. GORDON. From here to Australia which is half way around the world?

Mr. CONZEN. Yes. In terms of value of the material it is insignificant.

Mr. GORDON. Now, how about all other costs? Are there any costs there that are any lower than here?

Mr. CONZEN. Oh, yes. For instance, we do maintain a research establishment which costs us over $10 million a year in this country, but not in Australia.

Mr. GORDON. All right, you did the research in the United States. But don't you have to pay for the research that you conduct here?

Mr. CONZEN. We continue to do so.

Mr. GORDON. Why aren't you asking the Australians who used prednisone to help pay for the research?

Mr. CONZEN. They have to pay their share, and the total foreign business, as I said before, yields a profit which compares favorably with the profit which our domestic business contributes to the overall corporate earnings. Incidentally our total volume in Australia on Meticorten is about $2,000 a year.

Mr. GORDON. That is beside the point. Are you saying that you are making as much profit selling it at $7.70 in Australia as you are when you sell it here for $17.90?

Mr. CONZEN. Oh, no; I am not saying this.

Mr. GORDON. Then they are not paying for their share of the research costs, isn't that right?

Mr. CONZEN. They are paying a share but we cannot break it down to a few dozen bottles of Meticorten in Australia as to what their share to our overall $11 million budget is. It is impossible.

Senator NELSON. But I do not think you could claim a lower cost of doing business in Australia because the research plants are located in the United States any more than you could claim lower costs in Los Angeles if your research plant is in New Jersey. You are selling the product some place.

Mr. CONZEN. Yes. The difficulty is the allocation.

Senator NELSON. That is a rollcall vote. I think we are going to spend some money and I do not like to miss it, so I have to go up there and vote. I have asked all the questions I had in mind, and you have been a very gracious and fine witness. Even though we may have asked a sharp question or two, it is all in the objective of seeking information. We appreciate your coming very much. You have been very helpful and your testimony has been valuable to the committee.

We have some charts that I have used in part which will be printed in full in the record.

(The charts referred to follow:)

Estimated NIH intramural research expenditures[1] related to prednisone and prednisolone, fiscal year 1953–67

Fiscal year	NCI	NIAMD	NINDB	NIAID
1953	0	15,000	0	0
1954	0	50,000	18,000	
1955	0	40,000	18,000	
1956	$10,000	30,000	10,000	
1957	57,000	20,000	10,000	
1958	13,000	10,000	0	
1959	74,000	10,000	0	
1960	19,000	0	0	
1961	29,000	0	0	
1962	11,000	0	0	
1963	84,000	0	0	
1964	231,000	0	0	
1965	394,000	0	0	
1966	409,000	0	0	
1967	552,000	0	0	
Total	1,883,000	175,000	$56,000	0
Total, NIH				$2,114,000

[1] Funds spent for purchase of drugs for the treatment of NIH Clinical Center patients not included.

NIH extramural research grant obligations, fiscal year 1953–67[1]

Fiscal year	Total funds	Number of grants
1953	$156,237	12
1954	327,711	12
1955	394,817	18
1956	350,554	15
1957	326,554	21
1958	655,725	37
1959	783,502	44
1960	930,866	52
1961	1,134,729	56
1962	1,229,653	68
1963	1,338,872	60
1964	1,384,401	60
1965	1,683,464	69
1966	1,695,827	61
1967	1,991,232	[2] 54
Total	14,384,144	639

[1] Extramural obligations overestimate funds devoted to prednisone and prednisolone since all grants in which prednisone and/or prednisolone were named were counted in the total.
[2] Incomplete data for fiscal year 1967.

Prednisone—International price comparisons—Price to druggists

SCHERING

	United States	Rome	Mexico City	Rio	Bern	Australia	Canada
5mg. 30's	$5.65	$3.66	$3.68	$1.59	$1.37	[1] $2,31	[1] $6.81
5 mg. 100's	17.90	[2] 12.20	[2] 12.26	[2] 5.30	4.37	7.70	22.70

[1] Derived from 100's price.
[2] Derived from 30's price.

Source: Foreign prices secured by U.S. State Department through Embassies. U.S. prices secured from the Red Book

Prednisone—1,000 5 mg. tablets

DEPARTMENT OF PURCHASE, NEW YORK CITY

Om PA No.	Period of agreement	Successful vendor	Award price	Estimated amount (bottles)	Merck, Sharp & Dohme price	Schering price	Parke, Davis price
3543 (1 yr)	Apr. 1, 1967 to Mar. 30, 1968	Lannett	$4.58	1,500	$9.73	$12.00	(1)
3356 (1 yr.)	Apr. 11, 1966 to Mar. 30, 1967	Davis-Edward	4.69	1,500	26.00	12.00	$7.70
3170 (1 yr.)	April 1965 to Mar. 30, 1966	Pan Ray	4.95	1,500	26.00	12.00	(1)
3081 (6 mo.)	Oct. 1, 1964 to Mar. 30, 1965	No contract			26.00	12.00	(1)
2961 (6 mo.)	Apr. 1, 1964 to Sept. 30, 1964	do			26.00	12.00	(1)
2891 (6 mo.)	Oct. 1, 1963 to Mar. 30, 1964	Davis-Edward	6.65	600	26.00	11.00	(1)
2804 (6 mo.)	Apr. 1, 1963 to Sept. 30, 1963	do	5.25	500	26.00	17.00	13.80
2231 (6 mo.)	Oct. 1, 1962 to Mar. 30, 1963	do	5.65	500	26.00	16.25	(1)
2677 (6 mo.)	Apr. 1, 1962 to Sept. 30, 1962	Success	7.90	700	28.00	14.00	20.25
6119 (6 mo.)	Oct. 1, 1961 to Mar. 30, 1962	do	8.25	400	28.00	14.00	(1)
2583 (6 mo.)	Apr. 1, 1961 to Sept. 30, 1961	Bryant Pharmaceutical.	8.75	650	28.00	9.98	(1)

[1] No bid.

Prednisone tablets 5 mg. (1/12 grain) 1000's unit: Bottle

Contract No.	Date	Method	Successful bidder	Unit price	Total price	Other bidders	Prices bid	Price to druggist	Percentage difference
1	Dec. 8, 1966	Adv	Upjohn Co	$4.94	$43,630.08	Nysco Labs	$5.35		
						Panray Division, Ormont Drug & Chemical Co	5.80		
						American Pharmacal	7.00		
2	Dec. 9, 1965	Adv	do	4.98	16,732.80	Upjohn	4.94	$20.94	424
						Panray Division, Ormont Drug & Chemical Co	6.17		
						American Pharmacal	7.00		
						Dome Chemical	6.25		
						Schering Corp	8.20	170.00	2,073
3	May 20, 1966	Adv	Strong Cobb Arner	4.72	19,484.16	Upjohn	4.95	20.94	423
						do	4.95	20.94	423
						Halsey-Drug	5.29		
						Kirkman Laboratories	5.88		
						Panray Division, Ormont Drug & Chemical Co	5.95		
						American Pharmacal	7.00		
						Schering	8.20	170.00	2,073
4	Oct. 29, 1965	Neg	Upjohn Co	4.95	22,809.60	Schering (commercial item)	9.20	170.00	1,848
5	Dec. 27, 1966	Neg	Strong-Cobb Arner	4.52	22,129.92	Upjohn	4.95	20.94	423
						do	4.95	20.94	423

Senator NELSON. Again thank you all very much for coming. We appreciate your appearance.

Mr. CONZEN. May I thank you, Senator Nelson, for the opportunity you gave me to appear here today.

Senator NELSON. We are very pleased to have you.

Mr. CONZEN. Thank you.

(The prepared statement of Mr. Conzen follows:)

STATEMENT OF W. H. CONZEN, PRESIDENT, SCHERING CORPORATION

Mr. Chairman and Members of the Subcommittee, I am W. H. Conzen, President of Schering Corporation. Schering is an international pharmaceutical company serving the medical profession throughout the free world. Its administrative and research headquarters are in Bloomfield, N.J.; its manufacturing facilities are in New Jersey, Wisconsin, and a number of foreign countries.

We are here in response to your invitation of June 12th to appear and to answer your subcommittee's inquiry concerning the price of our product Meticorten. It is our purpose to cooperate fully so that you may hear all sides and reach a fair evaluation of the criticisms of prescription drug prices that have been made here.

In your letter to me, you asked that I discuss pricing policies and practices of our brand of prednisone. You said that "striking differences in prices of prednisone among various manufacturers" had been referred to in recent testimony before your subcommittee.

During these hearings there have been frequent references to the price of Schering's Meticorten tablets and comparisons of that price with the prices charged for so-called "generic" prednisone tablets. Obviously, the reference to "striking differences * * * among * * * manufacturers" pertains to these comparisons in the testimony.

However, so that there is no misunderstanding as to precisely what is being discussed, I believe a few words of explanation are in order as to what prednisone is, what Meticorten is, and how significant they are in the pharmaceutical field.

Prednisone is the official, or established, name of a chemical substance which was discovered by Schering research scientists in 1954. It is what is known in chemistry as a steroid, more specifically, a corticosteroid. We have developed and marketed a number of pharmaceutical products which contain prednisone and its sister compound prednisolone—14 to be exact. These products provide a variety of pharmaceutical dosage forms, many of which are offered in several package sizes. In addition to plain tablets, there are injectables, creams and ointments for dermatological use, ophthalmic preparations, and a number of combination products.

Meticorten is Schering's brand name for tablets formulated with prednisone as the active ingredient; it is a typical example of what many people have chosen to call "miracle drugs." It is used by people of all ages for the treatment of a variety of short and long term medical problems such as, allergies, asthma, arthritis, skin and eye inflammations. Elderly people with chronic arthritis represent a relatively small portion of its users.

Prednisone, in addition to being the official name for the chemical compound, is also the so-called "generic" name for pharmaceutical products made available by many generic distributors, which contain, as the active ingredient, this particular chemical substance.

Before I address myself to your specific question, I think it would be helpful if I explained for the subcommittee some of the magnitudes involved to establish the relative significance of what we are discussing.

In the first place, the domestic ethical pharmaceutical industry is estimated to have a volume of about $3 billion at the manufacturers' level. The term "ethical pharmaceuticals" as used here refers to those products which are promoted only to the medical and allied professions, and available through pharmacies. The sales volume of *all* corticosteroid tablets totals approximately $40 million; this not only includes prednisone, but all other corticosteroid tablets. The estimated volume of prednisone tablets is $3 million. Consequently, this product represents 1/10th of 1 percent of his country's total ethical pharmaceutical market.

Secondly, within the pharmaceutical industry, Schering is about 16th in size, with a domestic ethical sales volume of some $65 million. Of that total, Meticorten tablets represent less than $1 million.

In other words, Meticorten tablets amount to only about 2½ percent of the total corticosteroid tablet market. The relative importance of Meticorten volume, both in terms of the consumer's drug bill and with respect to Schering, is certainly not large.

Nevertheless, those who require this medication have every reason to ask why Meticorten tablets should cost more than products which contain the same active substance available from other companies at much lower prices.

The answer lies in the basic difference in the nature of the functions and services performed by Schering Corporation in our economy, as contrasted with those performed by distributors of generic prednisone. Schering Corporation and the generic distributor operate in such different ways as to be engaged in totally different businesses.

I am not, however, going to discuss the merits of the so-called generic products and the so-called brand-name products and the question of therapeutic equivalence. There is a considerable difference of opinion in the scientific community on that subject. The study now going on under Government auspices hopefully will throw light on this question.

Let me explain what I mean by "different kinds of businesses."

Schering Corporation is fully equipped and fully staffed with highly skilled research scientists to discover and to develop new drugs, to produce them under the most rigid standards of good manufacturing procedures and quality control, to disseminate promptly throughout the scientific and professional world full and complete information about such new drug discoveries, to make available a wide range of dosage forms to meet all physician needs, to market them widely in all parts of the free world, and to continue to service its discoveries for the medical profession.

These are the characteristics of our company; it is research-oriented, it manufactures products of the highest quality, it markets its products worldwide, and it is devoted to total service to the medical profession for the benefit of its patients. Implicit, however, this succinct statement is a host of detail, activity, and responsibility.

What follows is an oversimplified and only a partial list of what Schering does, and must do, to fulfill its role in today's complex and highly competitive world of medicinal products. Moreover, it is what Schering actually did for prednisone.

In the first place, we must search constantly and continuously for new and better compounds which may be formulated into new and better medicines. The industry's average, as you know, is one success for every 6,000 probes. We must investigate each promising new compound in a series of costly, time-consuming steps: first in the laboratories and then in animal testing, to determine the usefulness, and more importantly, to insure the safety, of any such compounds for testing in human beings. We must then develop pharmaceutical formulations so that the useful compound can be made available as a medicine in a variety of dosage forms. Additionally, we must develop manufacturing procedures, often novel and frequently complex; we must learn how to make, initially, limited quantities for release to a limited numbr of doctors for clinical investigation of the compound's effectiveness and safety in human patients; and later, if successful, larger quantities for marketing throughout the world. These investigations on the part of clinical investigators must be carefully supervised and monitored, the results meticulously correlated and analyzed, and a host of detailed information accumulated, which would take much too long here to catalogue.

Suffice it to say that the research work that has to be done in conneciton with the investigation of a new and promising medicine, in view of the elaborate and strict rules and regulations of the Food and Drug Administration in our country—and similar requirements abroad—is costly, time-consuming, and involves a myriad of details. All this takes a number of years—nowadays usually from 5 to 8 years. In the meantime, considerable additional investigation proceeds, more data are developed, more reports prepared and filed with the FDA.

Other areas of our company's operations are involved:

Our engineers must learn how to make the new drug in large quantities for commercial use—both economically and accurately.

Quality control scientists must develop standards, design tests to validate them, so that up to 24 different factors contributing to the safety and effectiveness of a single tablet or capsule or vial of injectable liquid can be guaranteed.

A marketing organization must be established and continually maintained.

to assure that the product will be speedily available throughout the United States and the free world.

Scientific and clinical documentation about all aspects of the new drug must be carefully created and produced by us and then cleared by the FDA in Washington.

Our representatives—or detail men—receive a thorough, in-depth course of training so that they are fully knowledgeable concerning every aspect of the new drug—its usefulness, its limitations, its advantages, its "problem points"—in short, they must be thoroughly briefed to be able to provide full information and to answer the questions about the new drug which the physician might ask.

Our detail men must then call on those doctors who might possibly use the new drug in their practice, brief them fully on the drug's properties and recommended uses, and provide them with samples so that they can become acquainted with the drug. These personal calls on physicians, hospitals and pharmacies must be supplemented with further information in medical journals, in direct-mail literature, in brochures and the like—all of which must be consistent with FDA requirements.

I could easily devote more time to explain to you the wide scope of the activities that actually did go into our discovery, development and marketing of prednisone. I could, for example, refer to the symposia on prednisone which we sponsored for the scientific and medical community, the brochures we prepared, the films we created and distributed, the host of things we did to make this new and dramatically useful product known to the physician and available to his patients throughout the world.

How completely different is the business carried on by the large majority of the distributors of generic prednisone. For the most part, they are essentially distribution operations; in fact, many of them have the finished product manufactured for them. These companies do not develop new drugs. They do not have the scientific staffs nor the facilities to develop them. They do no animal testing or clinical investigation. Usually generic distributors do not work for years to gain government approval.

They do not introduce new drugs. They lack the personnel and skill necessary to communicate to doctors all that needs to be communicated to them about the indications for the drug, the dosage regimen, the methods of application, the side effects and precautions, and so on. They cannot answer questions about the drug's use in individual cases or provide other services to the doctor. They do not supply samples liberally to provide the doctor free trial and experience with the drug and free materials to use on indigent patients.

They do not provide special formulations of the drug to use in treatment of eyes, ears or other organs, or special strengths for treatment of children, the elderly or other groups. These markets are usually too small and specialized. They limit quality control activities to legal requirements. They do not, in short, encounter the major burden of costs necessary to develop and launch a new drug successfully and prove its worth.

Without these activities, generic distributors contribute little to medical progress.

On the other hand, after someone else has developed a drug and after someone else has incurred the costs of introducing it properly, so that it gains widespread usage, they are able to copy it as soon as copying is legal. When the active ingredient is well known and highly regarded, they take advantage of this to sell it cheaply, in quantity, and frequently on a mail order basis. They concentrate on the one or two forms in widest use and on types of users easiest to reach. Sometimes such companies concentrate on Government bids only and operate in such a way as to minimize investment in facilities and personnel. Their entire business is built upon the pioneering work of others. Their appeal is based solely on their contention that their cheaper versions have the same active ingredient.

In fact, this is what happened in the marketing of prednisone.

When all is said and done, it was Schering's research which discovered prednisone, Schering's development which gave that product to the world and to the medical community, Schering's marketing and distribution which made it known and used throughout the world, Schering's activities which broadened its usefulness, and Schering's licensing which made it available from so many distributors. Without all this, there would not be today any generic prednisone at all.

We at Schering are proud of our discovery of prednisone; it represented a real breakthrough. Indeed, every corticosteroid tablet preparation introduced since

the discovery of prednisone embodies the unique principle that characterizes the prednisone molecule and that distinguishes it from cortisone and hydrocortisone. Prednisone blazed a new trail in anti-inflammatory steroid therapy.

Moreover, as the discoverer of prednisone, we are even today involved in servicing that compound, continuing research with it, in seeking to broaden its application and to expand the line of prednisone products. As the discoverer of prednisone, we carry, and must assume, the responsibility of continuing research not only with respect to that product, but with derivatives of it. At this point, some 12 years after we first introduced prednisone, we continue to supply clinical investigators with experimental forms of prednisone for further exploration of its potentials. These things, costly as they are, are not performed in any way by any of the generic distributors of prednisone.

To achieve our objectives, to maintain the kind of organization we are—research, development, Government clearance, worldwide marketing, total service to the physician and the trade—all this far exceeds to cost of operating a generic enterprise which ordinarily requires bare manufacturing cost and nominal sales expense. Many of our costs apply to failures, as well as successes, but only the successes are copied.

The "striking differences" in price you referred to are the inevitable consequence of these contrasts. In my judgment, they are fully justified. At generic level prices, we cannot have new discoveries. At generic level prices we will stifle research and the development of new medicines, and soon we will have neither the new drugs nor the generics.

If we were to attempt to compete at the same price level as the generic distributor, we would have to eliminate a large proportion of the activities and services which I have described as characteristic of our company. We would have to limit our activity to simple manufacture and distribution of drugs discovered, proven, and established by others—as they do—and one important source of new drugs for the treatment of sickness will have been removed from this country. I do not believe this would be in the public interest—certainly it would not advance medical science nor contribute to further development of higher health standards.

You also asked me to discuss our pricing *policy* with respect to prednisone. Let me answer that by giving you some of our guidelines in pricing—the highlights of the criteria we consider in establishing, and subsequently in reviewing, the prices for Schering products.

The ultimate responsibility for pricing policy at Schering rests with me as president. Pricing decisions and approvals, in each marketing division, must be in accordance with procedures and practices which I approve.

Schering prices are established at a level which covers our research budgets, including the cost of both our successes and our failures, the cost of materials and of efficient manufacture at reasonably attainable volumes, the cost of quality control under the highest standards, the cost of efficient marketing, including that of communicating product facts and benefits, the administrative cost of operating the company, and the taxes payable to national, regional or local governments. The cost of the active substance is a small portion of total costs.

Our pricing should also provide an average, long-run corporate-wide, after-tax return on stockholders' equity at a rate at least equal to that of the pharmaceutical industry as a whole, since we require earnings to support continued corporate growth and to compensate investors for the use of their capital.

All of this is evaluated against a background of the high risk involved in bringing a new pharmaceutical to market.

We consider the expected response, based on analysis of value of the product to the user, as compared with the value and price of alternatives he may have. We attempt to forecast the attainable sales volume for the product at various possible price levels, and at various times during the expected product life cycle. We give thought to the significance of the product with respect to our entire product line and its effects, if any, on the prices, sales and profit margin of our other products. And finally, we consider the magnitude of the investment required and the degree of risk we undertake.

These are broad principles—and like all broad principles, there are exceptions. We make exceptions under certain circumstances; for example, where economies in production or marketing are attainable in serving certain types of customers and where making a product available at a special price is expected to result in increased long-term usage.

There are also situations where we believe we have an obligation to provide vital drugs in rare and unusual conditions, even though they must be provided at a loss.

In pricing Meticorten and in our periodic review of its price, we have sought to apply these principles. Throughout the entire period that we have been marketing Meticorten, prednisone has been generally available to the public from a number of sources, and for the last 8 years, at a wide range of prices, so that the carrying out of our business judgment in this respect has in no way been in conflict with the public interest, but in fact has served to advance it by enabling us to continue the creative development of the compound itself, and of succeeding therapies.

Many physicians prescribe Meticorten, knowing that prednisone is available at lower prices. We think there is sound reason for their doing so. We think Meticorten is the best product—the one fully proven in patients and the most carefully prepared and controlled. Their experience has confirmed this. They continue to prefer Meticorten for their patients, despite its higher price. We think they are right.

Schering Corporation's Annual Report for 1966 indicates that the application of this pricing policy has not resulted in excessive profits. Over the past 5 years, Schering has averaged a return on investment which is slightly below the median for the industry, and certainly not out of line with the risks and competitive situation with which it is faced.

We have on a number of occasions considered reducing the price of Meticorten tablets and have consistently arrived at the conclusion that this would not be sound business economics, given the nature and scope of the services the medical profession and the public expect from us. As I indicated earlier, the volume of Meticorten tablets and the sales of Meticorten tablets are such that any substantial reduction in the price to meet the "generic" price level would simply mean that we diminish our capacity to provide these services.

If Schering is to discharge successfully its responsibilities and achieve its objectives in our society, if it is to be the source of breakthroughs in the future, if, as I am persuaded, the community expects it to discover, to test, to produce, to market, and to service the new, high-quality, safe and effective medicines of the future—and to continue to make available those on the present scene—and to do all this in active and aggressive competition with companies like itself, then it must have the resources to take all the risks implicit in these activities and to attract the scientific manpower that is necessary to do that job successfully.

I believe that the large majority of our society expects this of us and is prepared to accept, and does accept, the fact that the economics of these circumstances demands that our prices be substantially higher than the prices which the generic distributors charge. To them the community does not look for, and from them it does not expect, these necessary services and activities. From them the community expects and receives only price-oriented distribution.

That is why our price for Meticorten is what it is and why the generic distributor's price is what it is, and in my judgment these striking differences are justified by the contrasts I have attempted to put before you here today.

Nevertheless, I should not leave you with the impression that we are unaware or unmindful of the continued critical attacks in these hearings and in the press. Even though we regard our position as sound, for the reasons I have outlined, we have always reviewed our judgments in the light of the challenge of criticism; we plan to continue to do so.

We are not callous to the difficulties which our older citizens face because, due to their limited, fixed incomes, and often chronic illnesses, medical costs, including drugs, are high. Because of their limited incomes and greater needs, the difficulty they face in keeping pace with our inflationary economy is augmented. They need to be helped, and governmental and voluntary programs are doing just that. Moreover, under our present economic system and structure, we must look to the continued development of these programs to provide the help that is needed.

It will serve our society poorly if, in seeking to resolve these difficulties, we limit the ability of our creative pharmaceutical industry to serve the professions and the public through the discovery of new drugs.

(Whereupon, at 2 p.m. the subcommittee was recessed, to reconvene subject to the call of the Chair.)

81-280—pt. 2—67——15

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, AUGUST 8, 1967

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Javits, and Hatfield.

Also present: Benjamin Gordon, staff economist; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Out first witness this morning is Dr. Martin Cherkasky, director of Montefiore Hospital and Medical Center, of New York. Dr. Cherkasky, the committee appreciates very much your taking the time from your busy schedule to come down here and present your testimony for the benefit of the committee. You may proceed to present your statement in any way you see fit.

If you don't mind, I might interrupt with questions as you go along.

STATEMENT OF DR. MARTIN CHERKASKY, DIRECTOR, MONTEFIORE HOSPITAL AND MEDICAL CENTER, AND ON BEHALF OF THE GREATER NEW YORK HOSPITAL ASSOCIATION, NEW YORK, N.Y.; ACCOMPANIED BY KURT KLEINMANN, DIRECTOR OF PHARMACY SERVICES

Dr. CHERKASKY. I would like to do it the way that you would like, Senator. Shall I go ahead and read parts of this?

Senator NELSON. That is the best way, from my viewpoint. You may extemporize or elaborate on any statement you make at any stage if you wish, but if you follow the text I think it would be helpful to me.

Dr. CHERKASKY. Thank you, Senator.

I appear before you today on my own behalf as director of Montefiore Hospital and Medical Center, in New York City, and on behalf of the Greater New York Hospital Association.

Montefiore Hospital and Medical Center is one of the large teaching hospitals in the city. As of July 1 we had 766 beds rendering treatment in all major clinical areas with the exception of obstetrics. We are not against obstetrics, Senator. I want you to know that.

All of our chiefs of service are on full time and are salaried, and we have over 100 other full-time physicians. There are over 800 attending physicians, all of whom are board eligible and/or certified in one or several areas of specialization.

In 1966, 226,404 days of care were given to almost 12,800 patients. Our operating expenses for 1966 amounted to more than $19 million in the operation of the hospital. We have a very extensive research program. As of July 1, 1967, our research program amounted to $6.8 million, of which $6.6 million came from the Federal Government.

Senator NELSON. Are those NIH funds?

Dr. CHERKASKY. Mostly NIH funds.

Senator NELSON. What kind of research does your hospital do?

Dr. CHERKASKY. Across the board, Senator, we do research in heart cancer, neurological disorders. We actually are doing some drug research in the sense that we are using therapeutic agents in drug therapy in cancer.

Senator NELSON. I assume that since this is federally supported research, that it is on a contract basis for specific research projects.

Dr. CHERKASKY. Yes, it is substantially on a project basis. There are certain broad Federal funds that we can use as we see fit, but the bulk of it is on a project basis.

Montefiore Hospital and Medical Center is a primary teaching affiliate hospital for the Albert Einstein College of Medicine in the Bronx of which I am acting chairman of the department of preventive medicine and community health. Third- and fourth-year medical students serve clinical clerkships and subinternships, respectively, at Montefiore as part of their medical school education. As of July 1, we had 69 interns, 248 residents, and 20 fellows participating in an active medical education program.

You know we have had serious difficulty in the city of New York with the quality of care in the municipal hospital system, and since 1962, Montefiore Hospital, by contract with the city, has assumed the responsibility for the professional services at the Morrisania City Hospital, a 400-bed institution.

We also have a medical group program which we have had for some 20 years, and through this group program we provide total medical care for more than 30,000 people in the community in which we live.

Senator NELSON. Who manages the group program?

Dr. CHERKASKY. We operate it. We own and operate the group. It is a prepaid group practice unit, one of the units of the health insurance plan of Greater New York.

Since I also represent at this hearing the Greater New York Hospital Association, just a note that it is the largest of its kind in the country. It represents 124 institutions, 81 nonprofit voluntary hospitals, homes, 25 municipal institutions with a total of about 55,000 beds.

I have appeared on this subject before, before the Kefauver drug hearings in 1961 and 1962. It appears to me, Senator Nelson, that we are still faced with substantially the same problems that we faced at that time. While the Food and Drug Administration, under Dr. Goddard's very vigorous leadership, has become a much more effective instrument, there are still grave defects in the ethical drugs field.

I am here because as a physician, as a hospital administrator, as one who has devoted my life to medical care, I would like to see proper things happen in the field of prescription drugs. It is clear that whatever regulations or recommendations come from this committee, we must encourage by rules and regulations the kind of sound research

and development needed to devise the cures for the many serious disease problems which still plague us.

However, I would like to feel secure, and I think this is almost the main point that I wish to make here today, Senator, I would like to feel secure for our hospitals and our doctors, and all of our people, that when a drug is ordered, it will be of the quality, purity, potency, and safety that it is purported to be.

Senator NELSON. Under the present law, all drugs are required to meet USP standards; isn't that correct?

Dr. CHERKASKY. Yes.

Senator NELSON. The issue you are raising here is that they do not meet those standards with sufficient consistency so that physicians can rely upon them all over the country?

Dr. CHERKASKY. Well, I think that that is one of the points, but there is also I think we are dealing partly with fact and partly with fiction, but the fiction in some ways is as disturbing as the fact. We are told that even if it meets USP standards, that does not necessarily mean it has a therapeutic efficiency that it should have. Maybe the granules should be of a different size.

As I say, partly in fact and partly in fiction, the whole climate has been created in this country with regard to drugs, primarily generic drugs, and with drugs as well from some of the major houses which makes us feel very uneasy about the use of a drug, depending upon its source of manufacture and so forth, and this to me is an intolerable situation.

Senator NELSON. You cite quality, purity, potency. Those are all factors for which USP sets standards. I don't know exactly what you mean by safety.

Dr. CHERKASKY. Make sure that it is not contaminated.

Senator NELSON. Those are all factors for which the USP sets standards and, according to the law a drug must meet those standards before it goes onto the market. Now we know from some tests conducted by the FDA that around 7 percent of the generic and trade-name drugs in a 4,600 sample test they made did not meet the standards. They were either under, or over potency or deficient in some other ways.

But you also claim that even if all drugs meet USP standards, they may not necessarily be therapeutically equivalent. Dr. Lloyd Miller of USP testified here that it is his opinion that if drugs met USP standards, there is no reason to believe or evidence, as I recall, that would show that they are not therapeutically equivalent. Do you have any observations on that?

Dr. CHERKASKY. Well, the drug companies, the major drug companies, should be authorities; I don't necessarily mean that they are. On the plane coming up, one of my colleagues gave me this handsome red book, which is entitled "Statements on Chemical Equivalence and Therapeutic Efficacy of Generic Drugs," given to us by Warner-Chilcott Laboratories, and the first item in the first section says:

> It has been shown by means of several examples—

This quotes an article—

> that neither USP or NF standards nor FDA regulations assure the therapeutic equivalency of generically identical pharmaceutical products.

Well, if presumably responsible publications or firms make this kind of statement, I think that all of us have to be assured more effectively than we have to date that USP or FDA or these other standards are, in fact, providing safe, secure, potent drugs.

Senator NELSON. Would you suppose that you could rephrase the statement you quoted and substitute a couple of words and come out the same, such as, even though two drugs meet USP standards, and each of them has a distinguished brand name, they may not be therapeutically equivalent?

Dr. CHERKASKY. This is apparently true, Senator Nelson, I think, as I said before, part of this is fiction. It is obvious there has been a campaign to throw question upon the efficacy of "generic drugs," and I think this must be laid to rest.

Senator NELSON. Of course, you are very well aware of the fact that many of the most distinguished drug manufacturers also make generic drugs. Do you suppose they are suggesting that the generic drugs made by major brand-name companies aren't as reliable as——

Dr. CHERKASKY. No.

Senator NELSON. Do you assume they are talking about generic drugs made by companies that aren't brand-name houses?

Dr. CHERKASKY. As you know, and previous testimony here has shown, that where we have examined the recalls, for example, that the brand-name houses have very serious faults. I believe that last year among some 15 citations, we had such distinguished names as Squibb & Abbott and Charles Pfizer, so that while I am concerned about being secure when we purchase a generic drug from a small company, that it will be what it purports to be, I must tell you that I feel quite insecure at the same time about the performance of some of the major drug companies in this country.

Senator NELSON. Did you happen to see the June 2 issue of the Medical Letter, volume 9, No. 11, issue 219, which is devoted to tests of prednisone tablets?

Dr. CHERKASKY. No; I did not see that, Senator.

Senator NELSON. The interesting thing about that to me was that they tested 22 prednisone products put out by 22 different companies, and found that they all met USP standards, and though there were variations, they were within the USP——

Dr. CHERKASKY. Limits.

Senator NELSON. And they state that:

> There is nothing, however, either in reports of clinical trials or in the experience of Medical Letter consultants to suggest that the variations in formulation are causing any problems in the treatment of patients.

Then they go on to say:

> The great price spread among tablets purchased from different pharmaceutical companies suggests the desirability of prescribing by generic name and specifying at least for patients of limited means that the prescripions are filled with low priced prednisone tablets.

In the course of his testimony before this subcommittee, the president of the Schering Corp., stated that Meticorten, which sells for $17.90 a 100 to the pharmacist, is better than other prednisone products, and obviously many doctors are convinced that it is better. However, the company has no clinical evidence to support its contention. And the variation in price is so dramatic that it is a matter of great sig-

nificance to the patient. It varies from tablets selling at $17.90 a hundred to the pharmacist, to as low as 59 cents a hundred supplied by the Wolins Pharmacal Corp. That is an incredible difference in price, with the Medical Letter saying that there is no clinical evidence to support any conclusion that one is therapeutically more effective than the other.

Now, based on this conclusion by the Medical Letter, and the testimony by the president of the Schering Corp. that he has no clinical evidence that Meticorten is better, would you have any hesitation in following the recommendations of the Medical Letter in prescribing a lower priced prednisone?

Dr. CHERKASKY. No. As a matter of fact, we do. We don't buy Schering's Meticorten, and I think that what the president of Schering was saying is a bunch of nonsense.

This is part of the problem, Senator. I think that doctors and the public have been intimidated. They have been made fearful by that sort of statement, and as I said earlier, I think someplace along the line we must once and for all deal with this particular problem. I will note further on in my testimony that in many instances we use the generic equivalent, feeling very secure that we are providing for our patients the best possible drug that is available.

Senator NELSON. I think the FDA itself, and Dr. Goddard, will be testifying on Thursday, states that chemical and clinical testing ought to be expanded. Would it be your view that one of the problems here is that from the standpoint of a prescribing physician, you don't feel absolutely certain that if the drug is on the market and it meets USP standards that it is therapeutically equivalent, or that enough evidence has been developed to either prove or refute it?

Dr. CHERKASKY. I don't think there is any question about that, Senator. I think that where charges have been raised that Meticorten is better than prednisone, there are testing mechanisms available to pharmacologists and physicians that can definitively settle this issue, and I think that when some of these things are dealt with definitively, we are going to have a new climate which is going to enable us to take much better advantage of inexpensive but just as potent and just as pure drugs in the future. I think this is a medical and an economic consideration of great importance.

Senator NELSON. Thank you.

Mr. GORDON. May I ask one question here?

Dr. CHERKASKY. Yes, Mr. Gordon.

Mr. GORDON. Isn't it to the economic advantage of the large drug manufacturers to create this climate of fear?

Dr. CHERKASKY. I think, like most other groups, they do things which they see to be in their interests, and it is clearly in the interests of the major drug houses who have brand names to make people feel more secure with their brand name than with the chemical equivalent which may be therapeutically equivalent. There is no question about this in my mind. This document which I showed to you before is just that kind of document.

Any physician reading the various items in this booklet would quiver when he ordered prednisone, or any other generic drug, and this is obviously the objective.

Senator NELSON. Is there any place in that document where they

take any drug and assert that they have done double-blind clinical testing and proved that different products are not therapeutically equivalent?

Dr. CHERKASKY. I haven't had the chance to look. I just read the first couple of pages on the way down here, Senator. I haven't had a chance to look through it so I can't answer that question.

Senator NELSON. I haven't been able thus far to find any place where the drug companies, who assert that their brand name is better, produce clinical evidence of it. Why do you suppose that is?

Dr. CHERKASKY. I would say it would be highly unlikely that they would be willing to undertake that kind of study. I think that sort of study has to be undertaken under other auspices for with all due reference to the great drug companies and the great names they have made they are self-serving. They have biased interests. I think the kind of testing you are talking about must clearly be done under auspices which are more devoted to the public interest than any proprietary drug company.

Senator NELSON. The president of the Schering Co. asserted that the proof that Meticorten is better is that doctors prescribe it.

I said:

Well, is your test the test of how many doctors prescribe it as to whether or not it is clinically better?

And he said:

Yes.

I said:

If the drug is really therapeutically more effective, wouldn't it be in your interest to contract with an independent scientific laboratory or contract with a hospital to do double-blind testing? Then when you had the evidence that it was better, you would have the whole market, because the medical profession wants to do the best it can do by its patients.

He said that he didn't think that such testing would be worthwhile.

Dr. CHERKASKY. I think he is right, but not for the reasons that he implies. It is almost like Alice in Wonderland. You know a drug has a chemical formula, and persumably if it is produced properly, to claim that because you put some "magical" different label on it that this then gives it other than some psychological appeal makes no sense. If these claims were true, the whole fundamental basis of our chemistry would be in question.

Senator NELSON. I know, and you probably reach the same conclusion, you did, in fact, make some reference to it earlier, that it is possible that in some of these drugs a different size crystal or something may cause a different therapeutic result. This could be true whether it is a brand name or generic name. But what strikes me as strange is why the major brand-name companies which have items selling in large amounts to the public would assert that their products are better without offering any clinical evidence. Can you explain why they don't?

Dr. CHERKASKY. Because I don't think that the testing would validate their statements, and I would say, Senator, I feel like I have been here before. We were talking about this same thing 5 or 6 years ago.

It is time that the Federal Government, which in my view has the prime responsibility for the protection of the health and security of

our people, should see to it that these studies are made, so that we can deal with the innuendo, which it often is.

Senator NELSON. I have some other questions that are more pertinent to your testimony a little later on, so you go ahead.

Dr. CHERKASKY. One of the things that I would like to see done, and I am sure that is what we are all here for, is to see drug costs brought down to a reasonable level with reasonable profits for manufacturer and dispensing pharmacists, not only to curb exaggerated costs, but to deal with new inflationary trends that we are facing in medical care.

The costs of medical care are increasing at a faster rate every year, with no letup in sight. I won't go through the figures here, which show how they have outstripped every other item in the consumer index.

During 1966, the costs of hospital care have escalated at an almost unbelievable rate of 16.5 percent, as reported by the Department of Health, Education, and Welfare in a recent report to the President on medical care prices.

I hesitate to even give you this next sentence, because it frightens me. It now looks as if Montefiore's costs may increase 20 percent during 1967, and I must tell you that in my discussions with other people in the field, it looks like we are not going to be alone in this. In other words, we are going to have a huge incremental increase in medical care costs.

Senator NELSON. You say that Montefiore may experience increasing costs. When you say "our costs," are you talking about hospitals alone?

Dr. CHERKASKY. At Montefiore.

Senator NELSON. You are not talking about medical costs or pharmaceuticals.

Dr. CHERKASKY. It is all inclusive; the total per diem cost of our hospital, the cost of caring for a patient for 1 day, including the pharmaceutical costs, the doctors costs, and everything else, is going to go up 20 percent.

Senator NELSON. When people talk about hospital costs, they are talking about the management, the cost of the bed, the medical cost, the physician cost, drug costs, and others. You are talking about the total cost.

Dr. CHERKASKY. I am talking about the total per diem cost of the hospital. Now that in some instances includes doctors and in some instances does not include doctors.

In other words, if a patient comes in as a private patient with his own doctor, the per diem cost would not include this doctor's coverage.

Senator NELSON. So that figure is a little difficult to deal with.

Dr. CHERKASKY. I think the figure as generally understood, when you use the term per diem cost, includes all the costs of providing care for the patient except the private doctor's fee.

Senator NELSON. Are all of your physicians part of a full-time paid staff?

Dr. CHERKASKY. They are a part of our per diem cost, except that these full-time physicians' primary responsibility in the hospital is not with the direct provision of patient care. They provide supervision and teaching, and some patient care. It is really difficult to extract the entire medical component from the per diem cost. When you talk

about per diem costs in hospitals which have full-time staffs, you are including some doctoring, but most hospitals in the country do not have full-time staffs.

When you talk about the per diem cost, that means exclusive of most doctoring. Unfortunately, it is not simple. Anyway, what is simple is that it is going up a great deal, Senator.

Senator NELSON. Twenty percent in 1 year seems like an incredible amount.

Dr. CHERKASKY. That is over 16.5 percent the previous year, over 12 or 13 percent the previous year. It is a very distressing and frightening escalation and, of course, drugs are only one part of it. We are faced with a serious problem.

The Federal Government, with its medicare and medicaid programs which pays these costs, are going to face very serious actuarial problems, no question about it.

Senator NELSON. What are the main factors going into the increase in costs?

Dr. CHERKASKY. The major factor is personnel. Two-thirds of our costs are personnel. Doctors are in very short supply. Therefore, doctors' salaries and other things are going up. Technicians are in short supply. Nurses are in short supply. And, of course, other items, including the item of drugs.

At Montefiore in 1962 we filled about 170,000 prescriptions. It cost us $326,000, or 2.7 percent of the total hospital budget. In 1966, we filled 220,000 prescriptions, for $550,000 or 3 percent of our budget. The United Hospital Fund, voluntary nonprofit hospitals in the city of New York, spent more than $12 million in their drug bill so that drugs in hospital and out of hospital represent a very significant and important part of the medical care bill.

One of the things that we are concerned with is that one of the items in the report to the President on medical care prices showed that people over 65 spend more than two and a half times other age groups for drugs, and as you know, medicare does not provide drug coverage for these people outside of hospital, and the purchase of drugs for older people can be a very serious and threatening fiscal problem.

I remember that back 6 or 7 years ago, 10 percent of the people over 65 were spending more than $200 a year on drugs, and that figure must be much higher today.

Senator NELSON. Ten percent of the people over 65?

Dr. CHERKASKY. Ten percent over 65 were spending more than $200 a year on drugs.

Senator NELSON. What year was that?

Dr. CHERKASKY. It was about 1960 or 1961. One of the ways hospitals and an increasing number of consumer groups have found effective in helping to reduce drug costs and maintain high quality and standards of care is by use of a formulary system, and we have enclosed a copy of our own formulary.[1]

According to a Public Health Service study project on the audit of pharmaceutical services in hospitals, published in 1964 by the American Society of Hospital Pharmacists, a formulary system is defined, and I presume I had better read this one:

. . . method whereby the medical staff of a hospital, working through a pharmacy and therapeutics committee which it appoints, evaluates, appraises,

[1] Retained in committee files.

and selects from among the numerous medicinal agents available those that are considered most useful in patient care, together with the pharmaceutical preparations in which they may be administered most effectively. Drugs compiled in this manner, then, comprise the hospital's formulary. Thus, the hospital formulary is a compilation of pharmaceuticals which reflects the clinical judgment of the medical staff. Continuous provision is necessary to maintain an up-to-date formulary.

According to this study, over 50 percent of the Nation's hospitals operate under a formulary system, and an additional 25 percent of chief pharmacists would like to operate under such a system.

Senator NELSON. When you say 50 percent operate under a formulary system, what percent would that 50 percent be of the total beds?

Dr. CHERKASKY. I would presume it would be more than 50 percent of the total beds. This is a presumption, because the large hospitals, almost without exception, have found that a formulary is essential for the protection of the patient, the education of the doctor, and for fiscal reasons.

Dr. Charlotte Muller did a study reported in 1966, which again showed that the overwhelming proportion of hospitals in the city of New York, 89 percent, had a formulary.

The Governor of the State of New York, seriously concerned about medical care costs in the State, created a commission under the chairmanship of Marion Folsom, the first Secretary of Health, Education, and Welfare, which became known as the Folsom Committee or Governor's Committee on Hospital Costs.

The report to the Governor stated:

The most effective technique for controlling the cost of drugs to hospital patients——

Senator NELSON. Excuse me 1 minute.

Dr. CHERKASKY. Yes, sir.

Senator Javits, how are you, sir? Good to see you.

Senator JAVITS. Senator Nelson, while we have a moment's halt, I am sorry that I came a moment late. I have other committee responsibilities, and I may not be able to stay all through the hearing. I wish to express my satisfaction at having one of our most distinguished medical leaders, who is personally known to me, as today's primary witness.

I have gone through the whole statement, Dr. Cherkasky. I find it most informative. I know it will be very helpful to us. I express the satisfaction of the Senator from New York to be able to contribute through you so markedly to the deliberations of this subcommittee.

Dr. CHERKASKY. Thank you, Senator.

Senator NELSON. Thank you, Senator.

Dr. CHERKASKY. That is very generous of you.

This committee recommended to the Governor:

The most effective technique for controlling the cost of drugs to hospital patients and for assuring the highest standards of prescribing is a well-organized and efficiently run hospital drug formulary system.

They go on to make two other recommendations:

Those hospitals in the State that have pharmacies but do not have effective formulary systems should be required to initiate them.

And then:

The State board of social welfare should make payment for the care of public charges to hospitals contingent upon the existence of effective drug formularly systems and generic prescribing programs in such hospitals.

Senator NELSON. Your educated guess a moment ago was that it is probably the smaller hospitals that don't have a formulary system. To respond to the suggestion made by the Governor's Committee of New York, would it be feasible for some of these smaller hospitals who may not have the adequate number of pharmacists or clinical experts to adopt the formulary of another hospital in the State?

Dr. CHERKASKY. I would think that that is really the way that it should be done, and a case in point, Montefiore had been very vigorous in this area, and when we became intimately related to the Albert Einstein College of Medicine, they were very much concerned about the drug problem. They turned to us and said, "We would like to use your formulary for our institutions," and now the formulary which started out as a formulary for Montefiore Hospital alone, with 700 beds, is the formulary for over 3,000 beds.

We have involved some of the physicians from the other institutions in our pharmacy committee, and thus have been able to serve a substantial part of the Borough of the Bronx. I think it will be necessary and advisable for groups of hospitals to get together and to create joint formularies.

Senator NELSON. Is your formulary available to any hospital that would like to use it?

Dr. CHERKASKY. Yes; it is.

Montefiore Hospital and Medical Center uses a joint formulary developed by a strong and active pharmacy committee. The committee has broad representation from full-time people and participating physicians, and represents all the important specialties in medicine.

We also have an adverse drug reaction committee. I guess in the last couple of years one of the things that has come to the forefront are that drugs are not only therapeutic and curative but can also produce illnesses of their own, and this requires a lot more attention than we have heretofore given, so that we have a very aggressive group following up drugs and drug reactions to find out why and how.

Senator NELSON. Later on in your statement you state that Montefiore publishes quarterly information on adverse drug reactions.

Dr. CHERKASKY. Right.

Senator NELSON. In a bulletin?

Dr. CHERKASKY. That is right, sir.

Senator NELSON. Is this information about adverse drug reactions available in any orderly fashion to the rest of the medical profession?

Dr. CHERKASKY. I am sure—now I am going to—may I turn my back to you for a moment and I will find the answer to that question.

Senator NELSON. Yes.

Dr. CHERKASKY. It is transmitted to the FDA. That was my pharmacist I talked with.

Senator NELSON. You may invite him to sit with you, if you would like.

Senator JAVITS. Dr. Cherkasky, if I may, Senator Nelson, while you are interrupted anyhow, may I ask you this question? I gather from your statement that hospitals are not too much the victims of these tre-

mendous price differentials which distinguish the generic from the trade name or trademark ethical drug; isn't that a fair statement?

Dr. CHERKASKY. I think that that is substantially correct. However, we purchase a great many brand names, and I think that the prices for those are higher than they should be if the entire practices of the drug industry were sound, but other than that reservation, yes, Senator.

Senator JAVITS. And what is endemic in this situation as it has been gradually demonstrated to us is apparently the unbelievably large advertising and promotion content which even invalidates the idea that the overall profit is necessarily so sky-high as to be shocking.

Yes, they do very well, these drug companies, extremely well, but apparently the built-in promotion and advertising expense is beyond belief. We might just as well eliminate possibilities as a conclusion. Are you aware of any impropriety in the relationship between prescribing doctors and druggists?

You know, there was a time in the past where that was quite scandalous. I gather because it hasn't even been referred to, that these are things that happened before, but there is no attribution of any relationship to any propriety practice insofar as these high prices for ethical drugs that are trademarked and trade brands, as a matter of general repute.

Dr. CHERKASKY. I think that is correct. I think it was a problem at one time. I think that if it is one, it is not a major one.

Senator JAVITS. Exactly.

Dr. CHERKASKY. That particular abuse.

Senator JAVITS. Now, Doctor, I think what we are after is two things. I don't want to characterize the subcommittee which has been led in a very gifted and, I think, a very able way by our chairman, Senator Gaylord Nelson.

One, is all of this promotion and advertising necessary to the dissemination and acceptance by the medical profession of the latest advances? That would be point one.

And point two, if it is necessary, assuming it is necessary, is it being done in an extremely wasteful way and at extremely high cost, far more than its economic worth?

Dr. CHERKASKY. Well, I would say to you that I think the advertising campaign is destructive. In fact, Senator, it confuses. I think that it is a huge expenditure. I won't make any comment about what the return is on that expenditure because I am not able to do that. I think, however, that one of the serious problems that we must deal with is to bring this whole terribly costly campaign of advertising, which I guess costs upward of three-quarters of a billion dollars a year, under some kind of control. Unfortunately, what has happened, because of the blandishments of our terribly clever advertising people, is that advertising has become a substitute for doctor education, and a very poor one. I think that a large part of this advertising expense clearly makes no contribution to the community, to the doctor, and, as you have indicated, maybe not even to the profits.

Senator JAVITS. There is, however, some expense factor which is necessary. In other words, there is some dissemination of information to the doctor, or even to the hospital, perhaps even some advertising to give the public a sense of institutional confidence. I notice you speak of

something which we all realize, that there is a certain premium cachet of the name of the top drug house on anything, even if it is a generic drug, and I suppose that there is a certain amount of institutional advertising that would go into that, and really, Doctor, just to narrow the problem, aren't we talking about what techniques in law or practice, or both, could be employed as between this upper and lower bracket, the lowest bracket being what is really necessary to get the information around, some institutional advertising, because they are competing, which is part of our system, and the top bracket of what they are doing now, which you feel has just gotten inflated beyond all reason.

Dr. CHERKASKY. I think that I would fully agree with that. I would like to make the point that this advertising leads us to other unnecessary expenditures. I don't have the latest data, but in the early 1960's a report was put out that in the United States over 400 "new drugs" were produced by the pharmaceutical industry and advertised, to capture the prescription pad of the doctor.

On examination, only 29 of those were really new contributions. The rest of them were gimmicks, new dosages, new combinations that really hadn't much value. It would seem to me that this activity goes hand in hand with the promotion. Huge amounts of money could be saved because that manipulation I referred to is not what I consider research.

Senator JAVITS. Now, Dr. Cherkasky, just one other question. If we found a way, therefore, perhaps the Government has to move into the field, of bringing the information to the doctor: Couldn't the doctor himself put an end to the payment of these tremendously inflated patient costs by the method and nature of his prescription, and isn't that the most effective and the most targeted way in which we can bring about the results of which we speak?

Use the very competitive system itself, which has produced this, to end it, because if the customer isn't buying, that is going to be the end of the matter. These drug companies are going to turn to some other methods of distribution, other exploitations, other techniques, and not engage in these inflated practices, which are so costly to the public.

Dr. CHERKASKY. I would think that one of the things that we need to do for the express purpose you noted is to provide the doctor with a more rational, unbiased, continuous, critical flow of information about drugs.

I feel very sorry for the doctor, because we all attribute great validity to things in print, especially when it is credited to important establishments. The doctor is in a state of confusion about drugs, and I would agree with you that if we could develop some more effective method of conveying adequate information to the physician, and also preparing him in medical school to more effectively deal with this kind of problem, we would begin to resolve this difficulty.

Senator JAVITS. Doctor, the formulary system can be used perhaps on a regional basis by the Public Health Service of the United States.

Dr. CHERKASKY. I would agree. We have 550 drugs in our formulary. About 400 of them are so-called ethical drugs. There are literally thousands and thousands of drugs available for the physician to purchase. Yet we feel that we can meet 99 or 99.5 percent of all the needs of our patients with that small number of drugs.

I would agree with you if the whole city of New York were to use a formulary like ours, allowing a small number of exceptions, the care would be better, the savings would be huge.

Senator JAVITS. I think you have helped us very much, Doctor, and I am very grateful to you.

Thank you, Senator Nelson.

Senator NELSON. I would like to continue with the question I raised a few moments ago about the availability of the information accumulated by your hospital on adverse drug reactions. As I understand it, you publish a quarterly bulletin, and furnish that information to the FDA.

Dr. CHERKASKY. Yes; and we also furnish that bulletin to all of our physicians.

Senator NELSON. In what form is this bulletin on adverse reactions? How would you characterize the scientific status? In other words, do you have some evaluation as to whether it is a peculiar reaction of a particular patient? Do you include all the clinical information that you gather?

Dr. CHERKASKY. Yes, we try to determine whether it is the drug, whether it is the patient, whether it is his particular disease, and so forth.

Senator NELSON. And if you are using a drug and you get an adverse reaction, do you attempt to decide whether it is due to the peculiarities of the particular patient?

Dr. CHERKASKY. Or the drug.

Senator NELSON. Of course, we are going to have Dr. Goddard here and he can speak better to that perhaps than you, but do you know whether or not any place in the United States centrally collects adverse-drug-reaction information, collates it, and makes it available for physicians?

Dr. CHERKASKY. I would say to you that the FDA, so far as I know, is the one area that does that, and tries to make that information available.

Senator NELSON. Is there some place where a privately practicing physician, without the benefits of a drug formulary committee, can find out very quickly whether there is clinical evidence of adverse reactions for any drug?

I realize that the advertising in the Physicians' Desk Reference and in other places may cite adverse reactions, but is there any place where all of this information is gathered together and evaluated? Does the AMA do it?

Dr. CHERKASKY. Dr. Goddard can address himself to this authoritatively. It is, however, quite clear that an effective continuous method of informing the doctor about these sorts of things is not yet available, and should be.

It would seem to me that under governmental aegis we would have to make sure that this kind of information is forcefully available to the physician.

Senator NELSON. Senator Hatfield.

Senator HATFIELD. Doctor, I would like to just go back to a little bit of the testimony you were giving to Senator Javits a moment ago. Did I understand you to use the word "destructive" in reference to and in identification of, the drug advertising program? There was a destructive factor?

Dr. CHERKASKY. In some ways, yes, Senator. That is what I said.

Senator HATFIELD. I would like to have you spell that out a little

bit further to clarify my understanding of your use of the word "destructive." Will you?

Dr. CHERKASKY. Well, I think in the sense that it confuses the physician, in the sense that it makes it quite difficult for the physician to exercise sound judgment, because of conflicting claims and counterclaims which he has great difficulty sorting out, because, as we know, there has been drug advertising which has overlooked dangers.

I remember we talked about this defect in advertising when I testified 5 or 6 years ago, and you would presume that the problem was now resolved. I just came across an ad which had appeared in the American Medical Association Journal for several months, and in June, at the direction of the FDA, the manufacturer sent a letter to all doctors pointing out a whole list of restrictions and concerns and dangers. By allowing this we are tempting the drug companies, because obviously they want to sell their product. The result of this kind of loose advertising has been physical damage, and we have seen created very serious economic problems in the drug field.

I think also that the rewards which advertising will produce, in itself leads to haste, to shoddy research. You know they quip about this. They had a whole list of tranquilizers that were coming out and the doctors used to say that you had better use them quickly before they lost their efficacy. We unfortunately know that there have been drugs which have made huge profits for companies which have then turned out to be very, very dangerous drugs.

So I would say to you that the present inadequately controlled advertising is dangerous—you know, when an ad appears in the Journal of the American Medical Association, it carries with it, you know, all kinds of authority. I know it is not supposed to but it does.

Senator HATFIELD. Then, as I understand it, you feel that the average physician is not in a position today to know or to determine the efficacy, the potency, all the other characteristics of certain drugs, and is inevitably led into some of these actions and pathways through advertising?

Dr. CHERKASKY. There is no question that that happens more frequently than it should.

Senator HATFIELD. And then as I understand it, not only did you use the word "destructive," but you also make an economic observation or evaluation about the ratio of the costs of advertising to the benefits received. Would you spell out a little bit more the economics of this as you see it?

Dr. CHERKASKY. Well, there are all kinds of figures given. I don't know, maybe Mr. Gordon of the committee has more accurate figures, but we are told that at least $3,000 a year per doctor is spent by the companies in advertising.

Senator HATFIELD. Is this in prescription-only drugs or does this include such things as aspirin, Compoz, Bufferin, Alka-Seltzer?

Dr. CHERKASKY. As far as I know, it relates to ethical-drug advertising. In fact, the figure that I used 6 years ago was $5,000 per physician, so that the new figure we are using is $3,000, and that adds up to about three-quarters of a billion dollars.

Senator HATFIELD. What would be a reasonable figure do you think, or are you opposed to advertising per se?

Dr. CHERKASKY. Well, I would say to you that I—on my list of priorities, advertising of drugs and the amount of their advertising is

low. Now it may be as Senator Javits pointed out, there may be some reason for very modest advertising. When I say modest, I am talking about a 10th of what they are spending.

Senator HATFIELD. Are you talking now about the economics of it or are you talking about the destructive character of it?

Dr. CHERKASKY. I am talking about both aspects. First of all, I think it is an expenditure of money which ultimately is paid by taxes or the patient, which is an unnecessary burden. It also is damaging to the practice of medicine. It creates confusion.

I noted in my statement that a very well known physician in a very well known hospital who didn't get the effect that he expected from the drug then ordered another drug. What he didn't know is that he was ordering the same drug by another name. I understand that there are drugs in the thousands. Where you have drugs in the thousands, and you only need them in the hundreds, you are talking about huge expenditures, as well as confusion for the physician.

Senator HATFIELD. Will you address yourself to the economics of advertising, are you opening up a whole field here? Your argument could be applied in the field of advertising tobacco products. Your argument could be used in the advertising for time payment sales, for people who are not economically in a position to commit themselves so deeply, and yet time payment plans are attractively presented to them by advertising.

Dr. CHERKASKY. No, I don't think so.

Senator HATFIELD. Are you opening up the question of politicians being wrapped up in pretty ribbons and being presented and marketed in the public political arena? Are you opening up the whole question of advertising in its relation to American products, other than those in the drug field only?

Dr. CHERKASKY. I would suspect that those extensions could be arranged, but I think that the problem of advertising, mind you, advertising to 250,000 doctor people, because that is all we are talking about, and to some institutions, in a highly professional area is by no means the same as advertising other kinds of products.

Senator HATFIELD. No, usually the professional people have more education, perhaps a greater ability to differentiate between fact and fancy than maybe a lot of the general public has as far as being put upon by some shrewd advertising.

Dr. CHERKASKY. I wouldn't argue with you on that one, Senator.

Senator HATFIELD. I only point up the fact that I think we are talking about——

Dr. CHERKASKY. I am moving a little bit out of my area of competence, as you know.

Senator HATFIELD. I think we get into a whole question of advertising and the ratio of costs of advertising to the product field and to its general gross income and so forth. These factors, I think, are meaningful to us on this committee, but I don't think it would be restricted just to the drug industry. I wouldn't point to the drug industry here with an accusing finger without being willing to go to the whole field of advertising and its relation to the public.

Dr. CHERKASKY. Well, I would say to you, Senator, that I haven't thought about the areas you touched on very carefully. I think that probably something needs to be done.

I believe, however, that when you are dealing with drugs, which are really quite a different category from washing machines, and when you are dealing with a sharply focused scientific population, it seems to me that we can deal, or should be able to deal, with this particular problem, to bring it under more control and make it more rational and more responsible, without necessarily, for example, at the same time saying that we have got to not package politicians in fancy ribbons.

Senator HATFIELD. But I would also point out that the tobacco industry is trying to convince the American public that cancer is desirable.

Dr. CHERKASKY. Well, I understand that if you spend enough on your advertising budget, you can do that.

Senator HATFIELD. They are succeeding, evidently, according to the sales.

Senator JAVITS. Senator Hatfield, I think from what you have said and developed with the witness, it might enable us to make a basic point. In the first place, what Dr. Cherkasky is really testifying about is that he feels the advertising budgets are considering their impact on the physician as getting out of hand.

Now, what I would like to ask is this: Perhaps our committee ought to consider very seriously how to restore the competitive situation which seemingly has escalated these costs, according to this witness and other witnesses, and deescalate these costs by the same application of the competitive system, and that is why I suggest the possibility of our giving thought to the formulary idea.

Perhaps if projected on some kind of a regional or national level, we could be setting the standard to which drug companies would be required, would have to repair as a competitive proposition, and that may cause the same competitive situation to deescalate, which has brought about in the judgment of this and other witnesses such an out-of-hand escalation.

Senator HATFIELD. I would certainly agree with my colleague from New York. I would only point out that when we do open up this Pandora's box of trying to establish a measurement of what is a reasonable ratio of advertising costs to the general business budget, that the escalation that has taken place here is reflected in many other areas of our national life.

If I may just be personal a moment, I had a budget of $80,000 when I ran for my first statewide office in politics in Oregon in 1956. It cost the immoral sum of $350,000 this last year to run in a State that has only 900,000 registered voters, and so consequently the costs in this whole field have escalated in advertising not only in the drug industry, I am sure. I am not defending the drug industry, but I am just pointing it out as not exclusively a characteristic of the drug industry. I think it is true in every field.

Senator JAVITS. If the Senator will yield further, I would agree thoroughly with the Senator, and also I think the thrust of my own thinking on the question is the fact that we cannot forbid any physician from prescribing any drug he wishes to, including every one of the thousands that are available. The only thing we can do is to try to capitalize standards equally with those which the drug companies are trying to popularize, which will competitively bring down the height of the pyramid. That is what I had in mind. I didn't have in mind cutting anybody off. I don't think you can do that.

Dr. CHERKASKY. No, and I don't think anybody would really want to do it.

Senator HATFIELD. Thank you, Senator Nelson.

Senator NELSON. You cited a few moments ago an ad that was run in the American Medical Association Journal. The FDA required the company to send out a whole series of disclaimers or explanations. I take it that what you are saying is that if you are advertising to a professional group who have to make a judgment which affects the health of the public, that there are some different rules that ought to govern that kind of advertising as against the advertising of other products.

Dr. CHERKASKY. I think that is true. As an American, I am, of course, interested in all the extensions that Senator Hatfield raised, and would be delighted at some time to comment on them, but I do think that here we are dealing with a highly specialized situation, and with a very small and select group—doctors—and this professional group is not really able to make critical judgments about advertising for drugs.

You are dealing with complex advertising in pharmacology and really the best doctors can do is to have responsible people advise them. They really are not in the position to make these kinds of individual judgments themselves. Their professional knowledge and their critique doesn't extend that far.

Senator NELSON. Isn't there also this rather fundamental difference in that the doctor is the patient's purchasing agent, and the patient has no way in the world of knowing whether the doctor is prescribing the best quality product for him? There is a public interest among all the people in this country in being assured that the patient's health is best protected when the purchasing agent, the doctor, has the best scientific information available before he prescribes.

Dr. CHERKASKY. I think that is exactly correct, Senator.

Senator HATFIELD. Doctor, you have returned to a subject that is very dear to my heart, and one as to which I have interrogated previous witnesses. It is your, just stated, comment that doctors are not in a position to make such professional judgments on these various drugs that are advertised. I am wondering, though, where can we—I say "we" collectively here as a part of society, not of this committee—where can we in our educational program or in professional training experience, fill this particular void? If I understand your statement correctly, eliminating advertising is not going to solve our problem, because if the doctor has read no advertisements, and still has all of these various manufactured products lined up on the table, he still isn't in any better position, if I understand your statement, to make a judgment than if he had read an ad. So what are we going to do to correct this situation? Advertising and its elimination is not going to correct that.

Dr. CHERKASKY. No. What has happened to the physician is that advertising has become synonymous, though it really can't be, with education. Let me point out to you, for example, about a formulary. Let's say that we were to create a national formulary. Let's say we were to have a formulary which was going to be applied for all drug programs which are supported or paid for by State, local or Federal funds.

That formulary in itself is an extraordinarily educational device,

and a continually updated educational device, because we do have new drugs and new developments.

In other words, I don't think that the only way that we can provide information is through either advertising, or as you have said, just put all the items on the doctor's desk and let this very busy man try to find his way through dozens of drugs.

We do have expertise in this society which can make those judgments, about drugs and their value, and you can take the 4,000 or 5,000 drugs and you can narrow them down to a reasonable group and provide all the information that the doctor can assimilate and use, no question about it.

In other words, it isn't that this job can't be done. It is that no one has really brought together the forces necessary to do this. I suggest later on in my paper that the FDA, along with the medical schools who have the expertise, along with responsible drug people ought to put their heads together to come up with the kind of informational program which would enable the doctor, to keep abreast of new developments under the best of circumstances, with the expansion of medicine and new techniques and new drugs, we have a tough time keeping the doctor up to date, when this difficulty is compounded by all kinds of items which may produce a profit, but which are not contributory, you make the educational problem that much more difficult.

Senator NELSON. The ultimate answer then is the formulary.

Dr. CHERKASKY. The formulary and a broad educational program. The education and particularly the continuing education of the physician in this country is inadequate. Unfortunately the drug problem is just one of the features, though an important feature.

A program to bring proper information about drugs to physicians, must be extended to keeping the physician abreast of what goes on elsewhere in medicine, which again is done very poorly. No doctor can wade through all the literature produced. Public funds under the cancer, heart, and stroke program provide a great deal of money for continuing education, and we ought to use the opportunity to extend the education of the physician broadly, which would clearly include an education having to do with medications.

Senator NELSON. Is there any other area of medicine in which the continuing education of the doctor is left substantially or in some substantial part in the hands of a private product manufacturer? In other words, do the instrument manufacturers tell the doctors how to perform surgery, or is there any other field where there is so much——

Dr. CHERKASKY. I wouldn't make that suggestion.

Senator NELSON. Is there any other field where the private manufacturer of a product is so deeply involved in the continuing education of the doctor?

Dr. CHERKASKY. No.

Senator NELSON. Any other field of medicine?

Dr. CHERKASKY. No. I would think not.

Senator HATFIELD. One last question. Do you have——

Dr. CHERKASKY. I hope not a last one, Senator.

Senator HATFIELD. Well, for me. Taking these two phases of the educational life of the doctor, the continuing educational phase and the initial medical school phase, do you see the present curriculum that is followed in general medical schools today as sufficient in pro-

viding the doctor with that initial exposure to this problem and the technique to make a more profound determination of such drug uses? Or do you see a void or inadequacy or what in this respect in present medical school programs?

Dr. CHERKASKY. Very inadequate, Senator. I don't think that this is being given anywhere near the attention and consideration that it merits. I am pretty sure the schools don't even know exactly how to do it. I would say to that, one of the things I would like to see done is an examination of how the medical curriculum could more fully encompass and prepare the doctor in the matter of drug advertising.

I noted that the Albany Medical College did run a program for a couple of years, in which it tried to prepare the physician to withstand the onslaught of the detail man, and I think that we have to do much more of a job than we are doing now.

Senator HATFIELD. What about the graduate area in the field of such a specialty as internal medicine. What do you consider is the adequacy of the curriculum and the teaching and learning experience in that area?

Dr. CHERKASKY. Well, most of that learning, of course, as you know, is the part that takes place during the hospital.

Senator HATFIELD. Yes.

Dr. CHERKASKY. And here I think that our formulary thing is having a very good effect. Everything is by generic name, even if purchases of a trade-name drug, and I think we are beginning to have some effect.

However, again so that we shouldn't lull ourselves, it is very hard for the doctor, once he leaves that sheltered environment and becomes busy, not to slip and begin to rely upon the attractive readily available crutches.

You have got to do both ends of it. I think we must do much with medical education, and must do much about continuing education. I think also that we must do something about lessening the blandishments which seduce them.

Senator NELSON. You mentioned that there was an ad run in the AMA Journal, and that after some period of time the FDA intervened. Was it the FDA?

Dr. CHERKASKY. The FDA.

Senator NELSON. The FDA intervened and required the company to send notices out to the physicians?

Dr. CHERKASKY. Yes.

Senator NELSON. There were various inaccuracies or improper claims made for the drug, or something to that effect?

Dr. CHERKASKY. That is correct, sir.

Senator NELSON. Do you have the ad?

Dr. CHERKASKY. Someplace in this mess I brought.

Mr. GORDON. Dr. Cherkasky, wasn't this ad run after an article had appeared in the Journal of the American Medical Association?

Dr. CHERKASKY. Raised some questions about it?

Mr. GORDON. Raised some questions about it.

Dr. CHERKASKY. I testified to that effect on a previous occasion. An article appeared in a journal which pointed out serious defects and dangers in a drug, the same journal had been advertising that drug and that advertising continued in the journal for 3 months after a sound scientific article pointed out that there were such hazards that

this drug should not be used as advertised. Well, that is history. That is some years ago.

Mr. GORDON. How do you account for that, Doctor?

Dr. CHERKASKY. Well, again you are going to get me into the areas of speculation. Is that permissible in this kind of hearing? It has been said that the advertising parts of the AMA Journal and the professional part don't—they sort of operate independently.

Senator NELSON. Last year the Congress became so concerned about the safety of citizens on the highway that they passed legislation requiring the automobile companies when a defect is discovered in a car, to make public notice of it and to require the dealers to contact all the people who have that automobile in order that the defect may be corrected. Tens of thousands of automobiles were recalled for that purpose. Yet at the same time there is no law apparently that requires the AMA to be sure that the claims made for a very important drug are accurate, and that as a consequence, claims have been made that aren't accurate, and ads which fail to enumerate serious side effects have appeared in the AMA Journal. Doesn't that strike you as a rather ironic circumstance?

Dr. CHERKASKY. Well, it does, and more than that, it is a matter of concern that one of the things that we are constantly faced with is post hoc, after the fact.

It would seem to me that the circumstances that cause the FDA to require the manufacturer to send out a letter to physicians with a whole series of warnings could as easily have been done before the ad appeared.

Ads are in one day and patients are getting it the next day. This is one of the ways that some doctors maintain status, by getting the newest drug the most quickly. In the meantime I will guarantee you people were damaged because this ad ran for a couple of months before the warning letter came out to the physician.

What is the haste? I could see the reason for haste, for example, if we are talking about a drug that is going to cure cancer or some great new discovery that you don't want to withhold and you want to take the chances. I understand that. But in ordinary circumstances before a drug can be widely advertised, the advertisement and the evidence having to do with the drug and its efficacies and its dangers should be reviewed by the FDA, not after the fact.

Senator NELSON. Go ahead, doctor.

Dr. CHERKASKY. We have covered some of the things in my prepared statement so I will just skip. On page 7 I note that Montefiore's formulary covers one-third of the beds in the Bronx and also that we find it necessary only to go outside of our formulary of 400 ethical drugs about 1 percent of the time. I think that is of considerable significance. In other words, with 400 or 500 drugs, you can really cover just about everything.

Mr. GORDON. When a drug is excluded from your formulary would it be fair to conclude that your pharmacy committee has decided that there are better drugs available to treat a particular illness, namely the ones that you put on the formulary?

Dr. CHERKASKY. Or that they are combinations, for example, which are noncontributory. Let me point out something that I think is a little amusing. There is a drug called Fiornal, which is used for headache. The drug was developed at Montefiore Hospital. In fact the name

"Fiornal" comes from Montefiore. Our pharmacy committee a year ago reexamined this drug. We had been using 5,000 tablets every 6 weeks, which is a great deal.

They decided that it was a collection of various items where no further scientific evidence has been deduced that it really was a major contribution, and we discontinued Fiornal from our formulary. My pride was hurt, but I think that was the right thing to do.

Mr. GORDON. Now, assuming that there are several thousand different drugs on the market, would it also be fair to conclude as a corollary that except for the 400 drugs in your formulary, you consider the rest as perhaps duplicative or unnecessary?

Dr. CHERKASKY. I would think that with certain reservations the answer would be yes. The reservations would be that there are other parts of the country and there are other climates and areas where there may be other disease entities or problems which might call for drugs which we do not commonly stock, but with a very varied population, 400 ethical drugs cover 99 percent of our needs, and I would say to you that yes, most of the rest are duplicative, many of them noncontributory.

Mr. GORDON. Does the existence of so many unnecessary and duplicative drugs make rational drug therapy extremely difficult for the ordinary practicing physician?

Dr. CHERKASKY. I would say to you that there probably isn't an ordinary practicing physician, or even an extraordinary one, who knows what these drugs are for.

Mr. GORDON. Is it your opinion that from a public interest point of view a considerable amount of research man-hours, a very scarce resource, is being wasted in the development of unnecessary, duplicative or inferior drugs?

Dr. CHERKASKY. There is just no question about that. I don't mean to minimize the fact that sometimes even changing a drug so its dosage form would be more desirable is not a contribution, because it sometimes is, but again the ability to advertise and to capture a quick market, seduces the companies as well, and I think it is not constructive to allow talent that we could use to resolve some of our pressing problems, to be dealing with really noncritical areas of putting things together so they make a neater package and seem like a new drug when in fact they are not.

Mr. GORDON. Would it be fair to say that the large figures of money that the industry says it spends on research exaggerate the benefits accruing to the public?

Dr. CHERKASKY. Well, I don't know how they produce their figures, but to the extent that some of that money is spent for manipulative research I don't think it is constructive.

Senator HATFIELD. Doctor, let me make an observation first and then pose a question. I have had opportunities since these hearings started to talk to a goodly number of physicians, and I am convinced that there is a preponderance of practicing physicians today, each of whom is convinced in his own mind that there are certain preferences that he has for brand names, that he likes the freedom to prescribe brand names and not be forced to a purely generic system.

Let's assume that we established a national formulary of some kind. Let's assume that we could even restrict and reduce the impact of ad-

vertising as now carried on. How long do you estimate it would be before the preponderance of physicians would be willing to accept and use such formulary procedure? Or how long would they continue using their present base for prescription?

Dr. CHERKASKY. Well, of course, you are asking me to make a guess. Senator, I would say to you that if we could attribute to a formulary user status and being a good doctor, it wouldn't take long at all for doctors to accept it. When we instituted the formulary, we cut across many of the drug ordering habits of several thousand doctors, 800 or more at Montefiore, and more than that at Einstein College, and after a bit of adjustment, we have had not more than 1 percent requests outside the formulary. If we could establish that the superior physician was the one who was dealing with drugs by using a formulary, I think you would find doctors flocking to its use.

Senator HATFIELD. Plus a new approach in the educational format.

Dr. CHERKASKY. Yes.

Senator HATFIELD. The educational programs.

Dr. CHERKASKY. I think you have got to do the whole thing.

Senator HATFIELD. What would be the response, do you think, to such a proposal by way of cooperation of the American Medical Association and other medical groups?

Dr. CHERKASKY. Well, the American Medical Association has not dealt with this particular problem as constructively as I think that they should. Whether this has to do with the huge advertising revenues is speculation. I have no facts on this.

Senator HATFIELD. That would just be restricted to the journal.

Dr. CHERKASKY. Yes. It would seem to me that the American Medical Association has exactly the same interest which I express here, and that is to have all the drugs we need, but no more than we need, to have the doctor receive every bit of information about the drugs and their dangers. Organized medicine, if it has any responsibility to the public, cannot be satisfied with the method of education of the physician by drug advertising and detail men, that would be inconceivable. Of course, I would note that the American Medical Association sometimes does carry on activities that are inconceivable.

Mr. GORDON. Dr. Cherkasky, when a doctor practices in a hospital that has a formulary, doesn't that formulary place a limitation on his prescribing habits?

Dr. CHERKASKY. Yes. Well, obviously there is. One of the interesting byproducts has been that because we have a formulary which covers so many beds, the drug companies are very anxious to get their drugs in that formulary, and it gives us another competitive tool to get better prices.

We get the drug that we need, but it becomes very important to the drug company, for they recognize that there are going to be followups on this. The doctors in training having used these drugs in this formulary will tend to move in that direction when they got out and practice.

Senator NELSON. No witness before the committee and no member of the committee has suggested a compulsory national formulary. So I don't want anybody to be misled into thinking that the adoption of a compulsory national formulary has been advocated. We have discussed a national compendium, and I would like at a later time to ask you something about that.

May I interrupt simply to say I have to go to the floor of the Senate. They are going to vote at 12, and there is a bill for which I have to participate in a very brief colloquy. We will recess until 12:40. That will give everybody time for lunch, and we will resume your testimony at that time and hear the next witness after that.

(Whereupon the subcommittee recessed at 11:45 a.m. to reconvene at 12:40 p.m. the same day.)

AFTERNOON SESSION

Senator NELSON. We will resume the hearing. Dr. Cherkasky, I don't remember exactly where you left off in your testimony, but you may resume from wherever it was.

STATEMENT OF DR. MARTIN CHERKASKY ET AL.—Resumed

Dr. CHERKASKY. If it is all right with you, Senator, I just will paraphrase some of the material so we won't have to go through all these words.

Senator NELSON. Fine.

Dr. CHERKASKY. I want to talk a little bit about our expenditures in our use of generic drugs. We spent over a half million dollars on drugs in 1966, and despite the fact that we have a commitment to purchase generic drugs whenever they are suitable, we spent only $67,000, or 12 percent of our total expenditures on a generic basis.

One of the things, however, which is pointed up very excitingly by this fact is that while only 12 percent of our purchasing dollar went for generic drugs, it provided 40 percent of all the medication we used. If anybody wants to talk about the kinds of savings that are inherent in generic drug purchasing, this is a very apt demonstration.

Senator NELSON. Have you had any experience in your hospital to demonstrate that this 40 percent of the drugs which are purchased generically are inferior in any way to brand-name drugs that are used in the hospital?

Dr. CHERKASKY. Absolutely not, Senator Nelson. We would never compromise with the safety and security of our patients for a fiscal savings.

Senator NELSON. Now, when you see that they can be purchased generically, as I understand it, you let competitive bidding?

Dr. CHERKASKY. That is right.

Senator NELSON. You let all your bids in generic terms, and then all companies can bid whether or not they are producing a generic or a brand name; is that correct?

Dr. CHERKASKY. Right. What we do, however, is, we try to be selective about the companies that we allow to bid, trying to reassure ourselves that they produce quality drugs. One of the things that is interesting as well is that if we had purchased these $67,000 by the available brand names, it would have cost us $200,000.

We have at Montefiore a group practice unit with a variety of programs. One of them is a comprehensive group practice program with the Teamsters and Management Hospitalization Trust Fund. Part of the coverage for this group of 3,500 people is drugs, and we were able, because we had this group, to arrange for them to purchase drugs at

somewhat less than the going cost, just to take a few of them, meprobamate, a generic, we checked with the pharmacies and they gave us this information, that for a walk-in customer they would charge him $1.95 for 30 tablets. Our Teamster patient gets it for $1.45, and we provide it to our OPD patients at the hospital for $1.20. Of course, if we went to buy the brand name, Equinal, it would cost $2.75.

Reserpine is $1.75 as compared to $4.95 for the Serpasil which is the brand name. However, we give this drug to patients in the outpatient department in Montefiore Hospital for 35 cents, and that includes, by the way, our handling charges.

Senator NELSON. Does the hospital make a profit?

Dr. CHERKASKY. No; we try not to make a profit on that.

Senator NELSON. But you do cover all your costs?

Dr. CHERKASKY. We cover all our costs. We are going to try to work out an arrangement with the union people whereby we will provide the drugs directly from the hospital pharmacy because, as you can see, the savings even on the better price we can get them from the local pharmacies is huge. Tetracycline $1.95 to the walk-in customer, $1.25 for the union from the same pharmacy, and 60 cents at our outpatient department.

Senator NELSON. I assume that one of the reasons you can furnish it more cheaply is that you get a better price on your purchase.

Dr. CHERKASKY. Than the pharmacist does.

Senator NELSON. Than the retail pharmacist does.

Dr. CHERKASKY. That is right; and that is what is brought out, by the way, on the next page. We purchase the first drug, dioctyl sodium sulfosuccinate, $156, but the blue book for the same drug, $1,080 for 25,000 tablets, represents a huge difference between the generic name and the cost of the trade name to the neighborhood pharmacy, as opposed to our own cost at the hospital.

Senator NELSON. So, as I understand it, you are buying a generic product here and paying $156.25 for 25,000 tablets. That is the cost to the hospital.

Dr. CHERKASKY. Cost to us, 25,000 under the brand name will cost the pharmacy $1,080.

Senator NELSON. Where does this figure come from?

Dr. CHERKASKY. This is the blue book. This is the stated figure. We don't know about the exact arrangement between the pharmacy and the manufacturing company, but this is the stated listed price.

Senator NELSON. Is the generic bought from a generic house or is it a generic from——

Dr. CHERKASKY. I couldn't tell you about this one, but we buy either from a generic house or from one of the major companies which produces generic. Because we are very uncertain about the quality of the generic drugs, we will not buy from every generic house, and in fact, we carry on a kind of an independent inspection system, which is a very poor way to do it.

We don't believe that we have the manpower to do the proper kind of an inspection, but we feel more secure if we go into a plant to make sure that, at least as far as we can see, it has modern equipment and instrumentation, and so forth. And, of course, this really raises what is clearly one of the critical points.

The FDA must have the kind of manpower and program to enable me at Montefiore to purchase any drug from any place which is

licensed, with security. I shouldn't have to wonder about whether the inspection or quality control is good or whether their labeling is proper. This should be policed in a much more rigorous and effective way than it now is.

Now, I cast no reflections on the FDA. I don't believe that they have anywhere near the kind of manpower that they need for the kind of job that needs to be done, and I think that that is one of the very important things that has to be pushed.

It is interesting. I asked our pharmacist, why don't you use that huge list which the armed services uses. It is called "Responsible Prospective Contractors," as defined in Armed Services Procurement Regulations, part 9, revision 11. This is on page 11. I said why don't you use the same firm; there are hundreds of them.

He pointed out to me that this would not be sufficiently secure because the armed services can order a huge order of a single item with rigid specifications, that the particular drug house might be able to meet, but for small orders at another time and of multiple preparations, we could not be secure that they, in fact, were maintaining the level of control that we think is necessary.

Senator NELSON. I wouldn't think that it could necessarily be assumed that the quality control of a small company is better if it is handling a large order than if it is handling a small order.

Dr. CHERKASKY. No.

Senator NELSON. The second point I would like to make is that the Defense Supply does make small orders.

I have looked at contracts amounting to no more than $25,000 or $26,000, which wouldn't be considered a tremendous contract.

So, I wouldn't accept on its face, at least, the argument of your pharmacist that a company can produce a mass of drugs and have good quality control, but couldn't produce a small quantity and have good quality control.

Dr. CHERKASKY. I would think that you are absolutely correct. I think it really has to do with the matter of our sense of security, Senator.

Obviously if they can produce a massive order of good quality, you can produce a drug of good quality, but I think that we ought to be relieved from this sense of insecurity which is fostered all the time.

I don't mean to imply that, in fact, they don't produce good drugs, because we do buy substantial amounts of generic drugs from small generic houses which we have assured ourselves are good manufacturing concerns.

Some of the errors that we talk about in quality control don't apply only to the small houses. In fact, it seems to me, a more serious breach when serious quality control has been found in the major houses, as evidenced by citations last year of Squibb and Abbott for drugs manufactured without satisfactory controls. When you say this about a company like Squibb, that is shocking.

I would like to read a quote that we took from the report to the President on medical care costs. It states that:

> Brand name prescribing raises the cost of drugs not only to patients but also to the taxpayer when drug costs are covered by public programs. There is considerable sentiment in Congress to require or encourage generic purchasing or prescribing of drugs under all federally financed programs. Before such legislation becomes feasible, however, doubts about the therapeutic equivalence of drugs

with the same generic name must be erased. A major study should be undertaken of the most frequently prescribed drugs to determine the efficacy of brand-name products and their supposed generic equivalents.

And also, Senator Nelson, there is the point that you made earlier about the statement of the president of Schering about Meticorten and prednisone. There is really no evidence that that statement has any validity, and I think that in some official way, that must be imprinted upon the minds of the doctors in this country.

Mr. GORDON. Doctor, how about antibiotics which are batch tested?

Dr. CHERKASKY. I would have no question about that.

Mr. GORDON. Would you recommend batch testing for all drugs?

Dr. CHERKASKY. I am not really technically competent enough to tell you exactly what the process should be, but I am certain that there are technically competent people, our pharmacologists and others who could prescribe a method of testing or control which would provide me with the security that I feel that I require, so that while I can't give you the technical answer to that question, but I don't think it is a serious technical problem.

Senator NELSON. On this question of the careful testing of drugs, better investigations to determine generic equivalency and so forth, which is an important issue, I notice that in the testimony from the representatives of the companies and in their advertising they keep referring to generic drugs versus brand-name drugs without making it very clear that as a matter of fact, a large number of brand-name companies make generic drugs. So if you are talking about generic drugs you are talking about generic drugs made by——

Dr. CHERKASKY. Everybody.

Senator NELSON (continuing). Everybody. Next we take a look at prednisone, for example, in the Medical Letter. For all practical purposes many of the 22 drugs there are generic products. These firms were licensed by Schering to manufacture prednisone.

Dr. CHERKASKY. Right.

Senator NELSON. Some of them decided to sell to a certain market where it isn't necessary to advertise and establish a brand name, so they don't sell under a brand name. It is prednisone.

Some of them decide to go into the retail market and compete and therefore they spend money to popularize their brand name. But all that brand is, I take it, is their generic prednisone with their brand name added; is that not correct?

Dr. CHERKASKY. Identical, absolutely, sir. This is what the trouble is. It is really misleading advertising.

Senator NELSON. So, the real question here is for the FDA to expand its inspection, chemical testing, quality control, and clinical testing of brand-name drugs made by brand-name companies, generic-name drugs made by brand companies, and generic drugs made by generic companies.

We are talking about the whole drug field, and it shouldn't be isolated as though there was something perfect about all drugs made by brand-name companies and something suspect about all drugs made by companies that only make generic drugs; is that not correct?

Dr. CHERKASKY. Not only is that correct, Senator, but I would say to you that the responsibility with regard to the great drug houses is greater because of the confidence we have vested in them.

You know we tend to be a little more concerned about the smaller companies and tend to take it for granted that when we deal with a "large company," we are secure about the quality controls. We have to recognize that in both the great brand and great pharmaceutical houses and the smaller one, much needs to be done to secure the safety and the potency of the drugs.

Senator NELSON. One of the things that concerns me as chairman of the subcommittee is the assumption that is made by so many people in the medical field that if it is a generic drug, especially one produced by a generic house, it is assumed that there is something suspect about its quality.

The FDA's own tests of 4,600 drugs demonstrated that, with respect to the brand-name drugs, there was a 1 percentage greater miscalculation either over or under potency than there was with generic drugs. That is a rather bothersome statistic to me when you consider that the assumption is made throughout the profession that somehow generics are suspect, and brand names are accepted when in the only tests available in recent years the generics came out slightly better off on this test of potency than the brand names.

Dr. CHERKASKY. Well, I don't think this is accidental. I think that there has been a deliberate attempt, successful, to raise serious question about the generic drugs and the not-so-well-known drug manufacturers, which has made the doctor and the public insecure and I think what you are in a position to do is to establish the security of the physician and the public with regard to drugs, no matter who makes them.

Senator NELSON. Do you think it is feasible and worthwhile for the FDA to commence a program of taking the most frequently prescribed categories of drugs and contracting in one way or another with distinguished hospitals and laboratories to do clinical and chemical testing, so that the medical profession, on the basis of these studies, can have confidence in all drugs on the market? Do you think this is a feasible project?

Dr. CHERKASKY. I think it is feasible, it is reasonable, and I happen to believe it is long overdue and absolutely essential that it be done, Senator. I think that if we take this one step, we will move quite a way to rationalizing the whole drug situation. In any way I could I would support that kind of activity on the part of the Federal Government and the FDA. It is essential.

Senator NELSON. And do you see it as practical for them?

Dr. CHERKASKY. Yes.

Senator NELSON. There would be no problem, for example, for your hospital to participate in that kind of a program of double-blind testing in order to come up with clinical evidence?

Dr. CHERKASKY. I think you would find that every one of the very large number of great institutions and medical schools that we have in this country would be willing and clearly able to undertake these kinds of studies and to settle the questions definitively. I would like very much to see that done.

Senator NELSON. What page are you on?

Dr. CHERKASKY. Page 13, the story of David Bird in the New York Times on July 24. He is reporting what had happened at the previous day. Drugstore owners decided not to comply with the city of New

York's orders that generic drugs be substituted for more expensive brand-name drugs in prescriptions for medicaid patients.

The city had decided that they were going to ask pharmacists to fill them in this way. The pharmacists refused to do this, and he goes on to say:

"If it is effective" this move on the part of the pharmacists, "could at least double the cost of drugs in the medicaid program, which draws on Federal, State, and city funds to pay health costs for the needy."

With the huge amounts of money that Federal, State, and local governments are spending for medical care, hospital care, and doctor's care, which are going to continue to soar, we clearly must do what we can in the drug field and in every field to control these costs as much as possible.

I then go on in my prepared statement to note the use of the formulary and the pharmacy committee in the education of the doctor. The point that I make is that the hospital really is, in many ways, the best institution to continue the education of the doctor after he leaves his medical school and his residency training. Unfortunately a good many hospitals have no really significant educational programs. Unfortunately a goodly number of doctors, particularly in urban areas, do not have hospital appointments. It may startle you, Senator, to know that one-third of all the doctors in New York City have no hospital affiliation.

Senator NELSON. On that figure, is it necessary that they all do? It occurs to me—say, opthalmologists——

Dr. CHERKASKY. I would say to you that we are talking about practicing doctors. No practicing doctor can continue to be a good practicing doctor if he doesn't continue his education, and while it is theoretically possible to continue education in other ways than belonging to a hospital, it is not practically possible.

I would say that if a doctor who has not been related to a hospital over some period of time after he has left his medical school, it would be quite miraculous if he continued to be a first-class physician.

Senator NELSON. Are you saying hospital affiliation?

Dr. CHERKASKY. Being a part of the staff of a hospital, working in some hospital, in some capacity.

Senator NELSON. Do you mean by that a doctor who has patients who go to a hospital and are treated by them while they are there?

Dr. CHERKASKY. Attendance at the hospital is part care of the patient and part educational experience. A doctor who is on the staff of a hospital, for example, like ours brings his patients in and he treats them there. But he also participates in the educational program of the interns, the residents, the medical students, and his own. When you find that there are one-third of the doctors who haven't got this kind of a relationship with any hospital, and mind you, many of the hospitals don't have much of an educational program, that even that bare minimum is not available to a huge number of doctors in New York City, and I am sure that this is true in many urban areas, and is a very serious problem. This relates itself to the drug situation because if he is part of our hospital, with a formulary, and with a pharmacy committee, and with a drug newsletter, he is exposed to an educational process.

Of course this hospital relationship really transcends the matter

of drugs alone. It has to do with the whole problem of continuing education of the physician.

Then I go on to note in my prepared statement that one of the things that needs to be done is that the FDA and the medical schools and teaching hospitals and responsible drug manufacturers ought to get together to take this mass, this huge mass of data and numbers of drugs and bring it down to some kind of manageable level and provide simplified, clear data, and arrange for the doctor to have easy access to proper information. I talk about closed-circuit television, but we must use all kinds of methods. We talked about this earlier, some new method of providing a continual education for the physician with regard to drugs and drug usages.

Senator NELSON. How do you suppose that a closed-circuit television system would work in educating the doctor?

Dr. CHERKASKY. Well, for example, if we had something like this in the city of New York, and if we get some of the better medical schools and hospitals together, we could run a seminar daily or three times a week, in which we would talk about the drugs, what drugs are out, what drugs are best used.

For example, we had a discussion at lunch, we decided that even though we had 400 ethical drugs in our formulary, most doctors only use 25, 30, or 35 drugs.

It is an illusion to believe that the doctor has at his disposal all those thousands of drugs. He can't make use of them because he doesn't understand how to make use of them. We could, by use of closed-circuit television, have programs from week to week about different disease entities, and then talk about the drugs related to those diseases, which ones are available, and which ones are the sound ones.

We must, not only in drug therapy, but in connection with the entire continuing education of the physician, develop some kind of creative mechanisms of communication to keep them abreast.

Senator NELSON. You are thinking then that you would have a program to be given at certain regular time intervals?

Dr. CHERKASKY. Yes.

Senator NELSON. During the day, so many days a week?

Dr. CHERKASKY. Right.

Senator NELSON. Some announcement of what the subject matter was to be?

Dr. CHERKASKY. Right.

Senator NELSON. The doctor could set aside some time in his office and get the benefit of this current information on some subject?

Dr. CHERKASKY. There are all kinds of educational devices that we could use. For example, the doctor could probably call up at his request information having to do with drugs of certain kinds. I think we have got to think through a body of material and a method of communication sounder than what we have now.

Senator NELSON. Doctors and pharmacologists have testified before the committee that there ought to be a national compendium which would have the approval of the FDA and which would list all drugs by generic name and brand name, list the purpose and clinical use of the drug, and list the known side effects so that any doctor could open up the compendium, start with the generic name, and select whatever

company's product he wished to buy. There would then be an official compendium that was reliable and approved by the FDA which doctors all over the country could use. Do you think that this is a useful concept?

Dr. CHERKASKY. Absolutely. I think again, it is one of the essential things that we should have done before and that we ought to do now. It is sound in my view.

I then wind up my prepared statement with the notation that I talked with Senator Hatfield, that in medical schools we ought to examine how we are preparing the doctor to deal with the problems of drugs and that a lot of thought ought to be given to the body of information necessary and how we would get it into the medical curriculum.

I would like to sum up that the medical care expenditures as we know, are rising at an accelerated rate. The drug costs are a significant component in this rise. To moderate and control this trend, there must be maximum use of generic prescribing.

However, we must be absolutely secure about the potency and safety of every drug by any manufacturer. The model of the hospital formulary system must be expanded to include Government-financed programs, and techniques for expansion and improvement of continuing education for physicians must be developed and perfected.

Thank you, Senator.

Mr. GORDON. On page 16 of your statement you say:

> Stories are told about doctors in even great teaching institutions who have been so bemused by the confusing array of drugs that, dissatisfied with the effect of one drug upon the patient's condition, they switched to what they thought was another drug—when in fact, they were prescribing the very same drug by some other fetching title.

Isn't this one of the consequences of the use of brand names?

Dr. CHERKASKY. This is. That couldn't possibly happen with generic names. This actually happened.

I won't identify the institution. One of the great institutions in the city of New York, before they developed a formulary, and the doctor, a very good doctor, very well trained, just got caught up by the multiplicity of different names, and he thought he was prescribing another drug because the names are, you know, so different and so attractive.

Mr. GORDON. So the use of trade names or brand names involves certain dangers?

Dr. CHERKASKY. It certainly does.

Senator NELSON. We have had testimony from other distinguished witnesses on this exact point, confirming what you say at this stage in your testimony.

Mr. GORDON. Does the use of hospital formularies have any effect on the prescribing habits of a physician in his private practice?

Dr. CHERKASKY. We believe that it does. We haven't studied this, and I think that this is one of the things that we ought to take a look at and we will try to do so. It clearly must affect doctors prescribing practices.

The doctors who are at Montefiore who spend a considerable part of their time there, who get to learn to use this particular formulary, you would have to expect that this will have a significant effect. They are not very likely to use different drugs outside the hospital.

What is more, many of their patients at one time or another go through the hospital, and for those same patients they are almost

certain to continue the same kind of drugs that we have within our formulary. The answer is I think the formulary is a good educational tool that is a useful one and does have meanings beyond the hospital as far as the doctor's practice is concerned.

Mr. GORDON. Now, one other question. Is it your opinion that the competition fostered by the use of a formulary accounts for the lower prices to the hospital?

Dr. CHERKASKY. I would think that this is very certainly an effect. I think I mentioned it before, that getting into our formulary becomes very important, and I think that has helped us in our dealing with the pharmaceutical houses on price, the fact that we do have a very limited and restricted formulary.

Senator NELSON. Thank you very much, Dr. Cherkasky. You have been very kind to take all this time in your testimony. It will be of great value to the subcommittee. We appreciate your coming today.

Dr. CHERKASKY. Thank you for having me come, Senator.

(The prepared statement and supplemental information submitted by Dr. Cherkasky follow:)

STATEMENT OF DR. MARTIN CHERKASKY

I appear before you today on my own behalf as Director of Montefiore Hospital and Medical Center in New York City and on behalf of the Greater New York Hospital Association.

Montefiore Hospital and Medical Center is one of the large teaching hospitals in the city. As of July 1 we had 766 beds rendering treatment in all major clinical areas with the exception of obstetrics.

All of our chiefs of service are on full time and are salaried, and we have over 100 other full-time physicians. There are over 800 attending physicians all of whom are board eligible and/or certified in one or several areas of specialization.

In 1966, 226,404 days of care were given to almost 12,800 patients. Our operating expenses for 1966, amounted to more than $19 million. As of July 1, 1967, our research program amounted to $6.8 million of which $6.6 million came from the Federal Government. Montefiore Hospital and Medical Center is a primary teaching affiliate hospital for the Albert Einstein College of Medicine in the Bronx of which I am Acting Chairman of the Department of Preventive Medicine and Community Health. Third and fourth year medical students serve clinical clerkships and subinternships, respectively, at Montefiore as part of their medical school education. As of July 1, we had 69 interns, 248 residents and 20 fellows participating in an active medical education program.

We had an affiliation contract, since 1962, with the City of New York for professional services at the Morrisania Municipal Hospital, a 402-bed institution. Our house staff rotates through Morrisania as part of their program.

In addition, over 32,000 persons in the community receive their total medical care on a prepaid basis from the Montefiore Medical Group a group practice unit owned and operated by the hospital and affiliated with the Health Insurance Plan of Greater New York.

The Greater New York Hospital Association represents 124 institutions: 81 non-profit voluntary hospitals, 18 non-profit voluntary homes, and 25 municipal institutions for a total of approximately 55,000 beds. This group of hospitals and homes represented by the Greater New York Hospital Association is the largest organized urban group of hospitals in the country.

Since my last two testimonies at the Kefauver Drug hearing in 1961 and 1962 in support of S. 1552 and H.R. 6245, it appears to me that we are still faced with substantially the same problems. While the FDA under Dr. Goddard has become a much more effective instrument, there are still grave defects in the ethical drugs field.

I think it is only fair for me to tell you what I, as a physician, as a hospital administrator, and as one deeply concerned with the overall problem of medical care would like to see happen in the field of prescription drugs. First of all whatever regulation we institute must encourage the kind of sound research

and development needed to devise the cures for the many serious disease problems which plague us.

I would like to feel secure for our hospitals and all of our doctors that when a drug is ordered, it will be of the quality, purity, potency and safety that it is purported to be.

I would like to see drug costs brought down to a reasonable level with reasonable profits for the manufacturer and dispensing pharmacist—not only to curb exaggerated costs, but to prepare for tomorrow when new developments and inflationary trends will make all drug and medical care costs go up.

The costs of medical care are increasing at a faster rate every year, with no let-up in sight. We are currently spending about 6 percent of the G.N.P. for health care and 1966's health expenditures amounted to $43 billion, compared to $3.6 billion in 1928. The percent increase in Medical Care in the Consumer Price Index, from 1947–49 to 1961 was greater than that for any other major group in the Index; a 61 percent increase for medical care compared to 48 percent for transportation, 10 percent for clothing and 21 percent for food. The various components of medical care have been increasing, however, at different rates. Between 1946 and 1962 there has been an over 250 percent increase in hospital cost per patient day. During 1966, the costs of hospital care have escalated at an almost unbelievable rate of 16.5 percent as reported by the Department of Health, Education, and Welfare, in a recent report to the President on Medical Care Prices. It looks now as if our costs at Montefiore may increase almost 20 percent during 1967. All elements of medical care cost must be carefully scrutinized. Drugs represent an important part of hospital costs and a major item in medical care expenditures. At Montefiore Hospital, where in 1962 our pharmacy filled 169,492 prescriptions (inpatient and outpatient), accounting for drug expenditure of $326,610 or 2.7 percent of the total hospital budget, in 1966 we filled 220,111 prescriptions, accounting for $550,000 for drug expenditures or 3 percent of our budget. According to the United Hospital Fund, reporting on Voluntary Non-Profit Hospitals in the city, in 1965, $12,140,710 was spent by member hospitals on pharmaceuticals.

According to the recent H.E.W. Report to the President on Medical Care Prices, persons aged 65 and over spend 2½ times as much as do other age groups; and it is important to remember that Medicare does not provide coverage of prescription drugs except in the hospitals.

One of the ways hospitals and an increasing number of consumer groups have found effective in helping to reduce drug costs and maintain high quality and standards of care is by use of a Formulary System such as that at Montefiore Hospital and Medical Center (Exhibit #1).

According to a PHS study project on the Audit of Pharmaceutical Services in Hospitals (published in 1964 by the American Society of Hospital Pharmacists, Mirror to Hospital Pharmacy) a Formulary System is defined as a:

> "method whereby the medical staff of a hospital, working through a Pharmacy and Therapeutics Committee which it appoints, evaluates, appraises, and selects from among the numerous medicinal agents available those that are considered most useful in patient care, together with the pharmaceutical preparations in which they may be administered most effectively. Drugs compiled in this manner, then, comprise the hospital's formulary. Thus, the hospital formulary is a compilation of pharmaceuticals which reflects the clinical judgment of the medical staff. Continuous provision is necessary to maintain an up-to-date formulary."

According to this study, over 50 percent of the nation's hospitals operate under a formulary system and an additional 25 percent of chief pharmacists would like to operate under such a system. Thus, three out of four hospitals either now employ the formulary system, or would like to employ it. These figures are probably higher today, in that this study was conducted before the availability of the American Hospital Formulary Service in 1958. In addition, about three out of four hospitals with pharmacists have a pharmacy committee.

From a study conducted by Dr. Charlotte Muller as reported in the January 16, 1966 issue of Hospitals, pages 97–102:

> "A questionaire was sent to all short-term general hospitals in New York City with 104 of the 117 responding, accounting for 89 percent of the general hospitals and 96 percent of the short-term beds in the City. Of the responding hospitals 89 percent had a formulary, 7 percent were developing one

and 4 percent had no formulary at all. In three-quarters of the hospitals, the formulary was developed by a committee usually a standing committee of the medical staff."

The report of the Governor's Committee on Hospitals Costs (New York State) 1965, to which I was a consultant, stated that:

"The most effective technique for controlling the cost of drugs to hospital patients and for assuring the highest standards of prescribing is a well-organized and efficiently run hospital drug formulary system."

The Committee recommended that:

(f) "Those hospitals in the State that have pharmacies but do not have effective formulary systems should be required to initiate them."

(g) "The State Board of Social Welfare should make payment for the care of public charges to hosiptals contingent upon the existence of effective drug formulary systems and generic prescribing programs in such hospitals."

In addition, the (Folsom) Report stated that:

"The use of formularies and generic dispensing among hospitals in New York is widespread. Among 240 hospitals responding to a survey made by the State Hospital Association on behalf of the Governor's Committee all but 11 had pharmacy committees, all but 24 had established formularies and all but 69 used generic dispensing of drugs. It now needs to be made universal."

Montefiore Hospital and Medical Center utilizes a joint formulary developed by a strong and active pharmacy committee. This committee is composed of several full-time chiefs of service, full-time attending physicians, our chief pharmacist and a representative from administration. Clinical services represented on this committee include anesthesiology, cardiology, dermatology, gastrointestinal medicine, neoplastic medicine, obstetrics and gynecology, pediatrics, and psychiatry. The committee makes all decisions with respect to additions and/or deletions to the formulary. All requests for new drugs and those not in the formulary are carefully screened for approval by the appropriate chief of service and the committee. The committee meets on a formal basis once a month.

In addition, the adverse drug reaction committee is a subcommittee of the pharmacy committee and meets every two weeks. All adverse drug reactions are reported and followed up. If necessary, intensive studies are conducted to determine the cause of the action if it is not immediately determinable.

The Montefiore Formulary is a joint formulary, utilized by five hospitals in the Bronx, with 3440 beds, representing close to 90 percent of the municipal hospital beds and almost one-third of all the beds in the Bronx. There are many advantages to such a formulary. The physician is not burdened by having to make a decision among hundreds of available competitive drugs, rational drug therapy is insured and costs are reduced. With about 400 ethical drugs in our formulary, the use of drugs in the hospital outside the formulary represents only about 1 percent of total usage. All drugs are listed generically. Brand names are also listed but that is all that is given. A cross-reference to the appropriate generic equivalent contains the additional information: drug category, available dosage forms, and so forth. That drugs are listed generically encourages our physicians to prescribe in that manner. When physicians, however, prescribe for a brand-name drug, there is an understanding that the pharmacy may substitute the equivalent generic drug if it is available. We will not make any substitutions unless we are sure that both drugs are therapeutically equivalent. All generic drugs that we stock in our pharmacy are therapeutically equivalent to brand-name drugs. We are assured of this via our active pharmacy committee composed of experts in clinical medicine and pharmacology.

In summary, then the use of the formulary assures us of quality, serves as an educational device and saves us money.

The formulary contains about 550 drugs of which about 400 are the so-called "ethical drugs."

We spent $550,000 for drugs at Montefiore Hospital during 1966, despite a commitment to the purchase of generic drugs whenever they are suitable and whenever we are secure about the standard of preparation. Only $67,000, about 12 percent of our total expenditure, were on a generic basis. Let me note however a point which dramatically points up the financial meaning in generic drug purchasing. This 12 percent of our total purchasing for drugs provided 40 percent of all the medication we made available to our patients. When drugs have reached the stage where they can be purchased generically, we usually find that the cost

of the same drug under its brand name has also dropped. Despite that, the $67,000 worth of drugs purchased generically would have cost approximately $200,000 under its brand or trade name.

Even purchasing under the trade name can produce extraordinary variations. One of the effects of having a formulary particularly a formulary which is tightly observed and which covers the large number of beds I noted as covered by the Montefiore Formulary, is that the drug companies are very anxious to have their drug included among the only 400 we make available through our formulary—and therefore give us better prices. In addition, mass purchasing such as is done by the city of New York can produce tremendous savings in brand-name drugs. A prime area of concern must be the man who needs to fill a prescription for himself or his family. It is clear that the drug costs for individuals depend upon the auspices under which these drugs are purchased. We presently have underway a pilot program in group practice with 1,000 families representing 3,500 people of the Teamster Joint Council Number 16 and Management Hospitalization Trust Fund. This program is the most comprehensive program of group practice ever put together in this country, to my knowledge. It includes complete coverage for all drugs. We have arranged this so that the doctor in the group can issue any prescription he wishes and it is filled by certain local pharmacies. I have here listed a comparison of a few drugs comparing what the walk in customer pays at the retail pharmacy; what the member of this comprehensive group practice unit, designated TCP pays; and what we charge at the Montefiore Hospital pharmacy for the outpatients we care for—for the same drug.

PRICES CHARGED TO REGULAR RETAIL WALK-IN CUSTOMERS AND MONTEFIORE OPD

	Walk-in customer at retail pharmacy	TCP in retail	Montefiore OPD
Meprobamate, 400 mg., No. 30 (generic)	$1.95	$1.45	[1] $1.20
Equanil (or Miltown), 400 mg., No. 30 (brand)	2.75	----------	----------
Reserpine, 0.25 mg., No. 100 (generic)	1.75	2.25	.35
Serpasil, 0.25 mg., No. 100 (brand)	4.95	----------	----------
Tetracycline, 250 mg., No. 12	1.95	1.25	.60
Dilantin, 100 mg., No. 100	2.25	2.00	.75

[1] 0.04 tablet.

We are all familiar with the enormous savings available in the purchase of generic names as opposed to brand names. I will just give a few examples:

COMPARISON: TRADE NAME/GENERIC COST

Generic name	Trade name	Unit	Cost to hospital		Cost to community pharmacy
			Generic	Trade	
Dioctyl sod. sulfosucc., 100 mg. (capsules)	Colace	25,000	$156.25	----------	$1,080.00
Reserpine 0.25 mg. (tablets)	Serpasil	1,000	3.50	$33.58	39.50
Theophylline compound (tablets)	Tedral	25,000	67.50	----------	600.00

One of the obstacles to the purchasing of generic drugs rather than trade name drugs at every opportunity has do with the questions which have been frequently raised about the quality of generic drug manufacture as opposed to the quality of manufacture by the great drug houses. Recent publications have indicated that there are approximately the same number of drugs recalled from both sets of manufacturers. I must however note that most physicians and I suspect most lay people feel more secure with a drug either generic or trade name which has been produced by a great manufacturing company such as Merck, Squibb or one of the other large producers. This is for two reasons:

(1) There is a widespread view that huge organizations have a greater capacity for maintaining quality control and a corollary concern that

(2) despite the great improvement of the FDA under Dr. Goddard, there is insufficient control of drug manufacturing and labelling in smaller, less well-known companies.

In our own institution where we purchase from local manufacturers of generic drugs we have instituted our own inspection system. We use the form attached as Exhibit No. 2. We do not feel secure with it. When I raised with my pharma-

cist the question: Why can't we use the list of "'Responsible prospective contractors' with respect to drugs and medical supplies as defined in the Armed Services Procurement Regulations, Part 9, June 1965, Rev. 11"—saying, what's good enough for the armed forces with their high standards should certainly be good enuogh for us, my pharmacist demurred noting that the armed forces could come along with a huge order and rigid specifications and while the generic house would be capable of producing this large quantity of drug with these standards, it did not necessarily follow that small orders of a variety of drugs would be provided of an equaly high standard. It is quite clear that in view of the increasing amounts of public and private funds expended for drugs, we must pursue to the limit the huge savings possible in the use of generic drugs. To do this, however, there must be an absolute security that every drug produced by every drug manufacturer, large or small, generic or trade name, must have met a high set of standards, fully policed by an FDA with the kinds of manpower and resources it would take to do this job.

It seems strange indeed to me that I can walk into any supermarket or grocery store and pick up a can of food without the slightest thought crossing my mind "is it safe?". The same kind of security both for health and economic reasons must be extended to every nook and cranny of the drug industry. I am enclosing as Exhibit No. 2 the inspection reports which we use at Montefiore Hospital.

The need to be asured about the safety of generic drugs is sharply pointed up by the following:

> "The HEW report to the President on Medical Care Costs states: Brand names prescribing raises the cost of drugs not only to patients but also to the taxpayer when drug costs are covered by public programs. There is considerable sentiment in Congress to require or encourage generic purchasing or prescribing of drugs under all Federally financed programs. Before such legislation becomes feasible, however, doubts about the therapeutic equivalance of drugs with the same generic name must be erased. A major study should be undertaken of the most frequently prescribed drugs to determine the efficacy of brand-name products and their supposed generic equivalents".

That there is a need for the Federal Government to mandate the use of generic drugs wherever possible is highlighted by a news story by David Bird in the July 24, 1967 issue of the New York Times:

> "Drugstore owners decided at a stormy meeting yesterday not to comply with the city's orders that generic drugs be substituted for more expensive brand-name drugs in prescriptions for medicaid patients.
>
> "If it is effective, the move could at least double the cost of drugs in the Medicaid program, which draws on Federal, state and city funds to pay health costs for the needy".

Since we are here because we are interested in the health of the American people and therefore we are interested in making sound drugs available at fair costs, we must consider the continuing education of the physician as it relates to drugs. Much of the physician education about drugs comes through the drug industry which currently spends about $3,000 per doctor per year in advertising to the medical profession. I am afraid I have misused the word education for that term could hardly be applied to much of the journal advertising, the mass of mail, and the blandishments of the detail men who bombard the busy doctor. It is unreasonable to expect the doctor to be able to discriminate between the valuable and the specious. All of us are impressed by things in print, particularly in living color. The problem relates to the continuing education of the physician at a time of rapid change in medicine and medical therapeutics. Advertising and detail men by definition are biased and yet for many doctors they represent one of the major organized and readily available sources of drug information. How many physicians have the time to read and evaluate the myriad of articles—some good and some poor—about new drugs. The carefully tailored drug company releases help him. But can we allow this critical area of physician education to be monopolized by the self-service interests represented by the drug companies.

In hospitals such as ours the doctor not only cares for his patients, but is involved in an extensive educational program with medical rounds, conferences, teaching of interns, residents and medical students. In this educational process

the pharmacy committee and its formulary as well as a pharmacy bulletin (Exhibit No. 3) and our adverse drug committee all combine to equip the physician to make better use of drugs, old and new. It enables him to stay abreast of the most recent advances and modalities of treatment including effective and rational drug therapy. In view of this, I cannot stress enough the importance of every physician having a hospital appointment. This is a necessity; the hospital is, and will continue to be, the focal point for medical care and the physician without hospital privileges is going to be lost, and the hospital without an educational program is failing both the doctor and the community. In New York City alone there are about 6,500 physicians, more than ⅓ of the 17,000 practicing physicians in the city, without hospital privileges—this represents a menace to the community's health.

As I noted above, a pharmacy committee has important meaning for doctor education. It is also responsible for maintenance of an up-to-date formulary on drug therapy, periodic examination of drugs, regular review of new innovations in drugs, therapy, and review of requests for additions and/or deletions to the formulary to prevent unnecessary duplication of the same basic drug or its combinations and review of adverse drug reactions. These advisory and educational functions do represent some of the major areas of concern for the pharmacy committee.

In addition to these functions and the adverse drug reaction committee, (a subcommittee of the pharmacy committee) we are constantly evaluating drugs being used. Currently, a special committee is studying all of our antibiotics and will come up with recommendations relating to additions, deletions, new dosage, forms, and so forth. This type of activity insures us that we are using the best drug therapy possible.

Our physicians are also kept abreast of recent developments via our pharmacy bulletin (Exhibit No. 3). This is issued quarterly and contains information on drug therapy, drugs, adverse drug reactions, additions and deletions to the formulary, pharmacy committee notes, and investigational drugs.

While the hospital is or can be a major educational force for the physician, it is quite clear that this alone will not provide all the physicians in our country with the kind of secure drug information that they require. Under the cancer, heart disease and stroke programs we will have an opportunity among other things to provide community-wide educational programs. There should be no limit on the imagination and creativity exercised to help keep the doctor abreast of all that goes on in medicine and pharmacology. We will probably have to arrange that every doctor in his office will have access to closed-circuit television which will be utilized by the medical schools and teaching hospitals in cooperation with the FDA and responsible drug manufacturers to bring him factual, reasonably simplified, data which will clear away the confusion. Stories are told about doctors in even great teaching institutions who have been so bemused by the confusing array of drugs that, dissatisfied with the effect of one drug upon the patient's condition, they switched to what they thought was another drug—when in fact they were prescribing the very same drug by some other fetching title.

Medical education is undergoing and requires a thorough re-examination for many reasons. I would hope that in the restructuring of the new curriculum, recognition would be given to this dilemma the practicing physician faces with respect to drugs and arm the prospective doctor with more knowledge and information to deal with this. The Department of Pharmacology of Albany Medical College developed a drug advertising evaluation project which helped the students to learn how to cope with pharmaceutical advertising pressures, the detail men, and other such forces.

To sum up, the medical care expenditures are rising at an accelerated rate. Drug costs are a significant component in this rise. To moderate and control this trend, there must be maximum use of generic prescribing; we must be absolutely secure about the potency and safety of every drug by any manufacturer; the model of the hospital formulary system must be expanded to include Government financed programs, and techniques for expansion and improvement of continuing education for physicians must be developed and perfected.

EXHIBIT 2[1]

MONTEFIORE HOSPITAL & MEDICAL CENTER

Inspection report of the

_____
Name of company

_____
Date

_____
Inspector

I. General Information:
A. Name of company: _____
B. Address: _____
(Street)
_____
(City) (Zone) (State)
C. Type of ownership: _____
D. Name of owner(s): _____
E. Location of plant:
1. Part of city: _____
2. Appearance of surrounding neighborhood: _____
_____
_____
F. Brief description of plant:
1. Number of buildings: _____
2. Approximate size: _____
3. General appearance of buildings: _____
_____
_____
4. If located within another building, describe briefly:
_____
_____
_____
G. List name and title of person interviewed: _____
_____

II. Information of physical plant:
A. Floor:
1. General appearance: _____
2. Maintenance (Wet-pickup, waxed, etc.) _____
3. Use of disinfectants: _____
B. Walls:
1. General appearance: _____
2. Maintenance: (with or without disinfectant:) _____
C. Ceiling:
1. Height: _____
2. General appearance: _____
D. Lighting:
1. Type: _____
2. Adequacy: _____
E. Ventilation (Number of windows and size, fans, air conditioning):
_____
_____
F. Over-all maintenance:
1. Dust control system: _____
2. Dust (On top of cabinets, around radiators, etc.): _____
_____
3. General appearance: _____
4. Is there a planned program of vermin control? (Yes___No___)
If so, elaborate briefly_____
_____
G. List name and title of person interviewed:
_____

[1] Exhibit 1, Montefiore Hospital and Medical Center Formulary System, has been retained in committee files.

III. Information on personnel facilities:
- A. Type of clothing:_____
- B. Is clothing supplied by company?_____
- C. Where applicable, are personnel supplied with safety glasses, safety shoes, masks, etc.?_____
- D. Are washing and lavatory facilities adequate and conveniently located? _____
- E. Are separate eating facilities provided?_____
- F. List name and title of person interviewed:_____

IV. Commercial information:
- A. Products manufactured:
  1. List representative items by trade and official names:_____
  2. Attach price list, catalog, samples, circulars, literature, etc.
  3. Does company repackage items under its own label?_____
     - a. If so, what is the percentage in respect to total output? _____
     - b. Name representative sources of such items:_____
     - c. Are these items routed through Control prior to and after repackaging?_____
  4. Are items packaged to be sold under another company's name? _____
     - a. If so, what is the percentage in respect to total output? _____
- B. Sales:
  1. Does company have a sales force? (List approximate no.)____
  2. Does company sell mainly to
     - (1) Wholesalers?_____
     - (2) Physicians_____
     - (3) Direct Pharmacy Accounts?_____
  3. Professional relations:
     - a. Who receives and handles complaints concerning quality of products? How often?_____
  4. Return goods:
     - a. Is there a definite policy concerning return goods?____ If yes, attach copy of statement.
     - b. Are return goods:
       - (1) Reprocessed?_____
       - (2) Repacked?_____
       - (3) Discarded?_____
  5. List name and title of person interviewed:_____

V. Professional information:
- A. Raw materials:
  1. List major sources from which company receives these:____

	Yes	No
2. Does company have procurement specifications at least equal to official (U.S.P. and N.F.) requirements?	_____	_____
3. Are raw materials pretested before use?	_____	_____
4. Are materials quarantined before release?	_____	_____
5. Are control samples of raw materials retained? How long?_____	_____	_____
6. Are facilities available for reprocessing of raw materials?	_____	_____
7. Are specific identification markings used?	_____	_____
8. Are materials stored properly? (Containers, Temperature)	_____	_____
9. Are adequate records kept?	_____	_____

V. Professional information—Continued

B. Manufacturing plant:

1. Equipment:

a. Type and make of equipment (Tablet machines, homogenizers, etc.)_____

_____

_____

_____

_____

	Yes	No
(1) Properly located?	____	____
(2) Adequate for required operations?	____	____
(3) Constructed to facilitate cleaning?	____	____
(4) Properly maintained?	____	____

2. Personnel:

a. List number of employees:_____

b. Percentage of Professional Employees:_____

c. List name, education and experience of the head of the manufacturing operation:_____

_____

_____

_____

d. List qualifications of all other professional employees in the manufacturing operation: (i.e., B.Sc. Pharmacy, B.Sc. Chemistry, etc.) (Use back of page, if necessary):

3. Are manufacturing operations controlled by: (Determine by following a specific item during manufacturing)

	Yes	No
a. Use of suitable batch numbering system	____	____
b. Preparation of formula or batch records	____	____
c. Checking of ingredients (Identity, weight, measure)	____	____
d. Maintaining identity during processing	____	____
e. Checking yield against theory	____	____
f. Checking quality during processing	____	____
g. Adequate sampling and testing	____	____
h. Compliance with specifications	____	____
i. Maintaining of appropriate records and samples	____	____

C. Packaging operations:

(Determine by following a specific item during packaging)

1. Does company use only new containers?	____	____
2. Are packaging and finishing procedures controlled by establishment of specifications	____	____
3. A formal procedure providing for the inspection and issue of packaging materials including labels and labeling	____	____
4. Provisions for proper disposition of unused labels	____	____
5. Use of suitable batch, lot, or control numbers	____	____
6. Maintaining identity before and during packaging	____	____
7. Checking yield against theory	____	____
8. Sampling and checking	____	____
9. Provision for release by quality control	____	____
10. Maintaining of adequate records and samples	____	____

(a) List name and title of person interviewed_____

_____

V. Professional information—Continued

D. Control laboratory:

(Determine by checking on a specific product supplied by the hospital Pharmacist)

	Yes	No
1. Does the company utilize outside control facilities?	------	------
2. Does company have a quality control laboratory	------	------
a. List number of employees _____		
b. Percentage of professional employees: _____		
c. List name, education, and experience of head of the Control Laboratory: _____		
_____		
d. List qualifications of all other professional employees (i.e. B.Sc. Pharmacy, B.Sc. Chemistry, etc.) (Use back of page if necessary) _____		
3. Does the control laboratory receive or collect samples and regulate the release of materials from:		
	Yes	No
a. Receiving Department (Raw Materials)	------	------
b. Manufacturing Department	------	------
In-Process goods	------	------
Finished Preparations	------	------
4. Does the control laboratory have the final authority to reject items which do not comply with specifications? If so, are these items		
a. Reprocessed? (By authority of_____)	------	------
b. Repacked? (By authority of _____)	------	------
c. Discarded? (By authority of _____)	------	------
5. Are stability data on finished items awaiting shipment periodically collected and reviewed by the control laboratory?	------	------
6. If tests are performed by an outside laboratory, does the company have a policy to spotcheck tests?	------	------
7. If analytical control is performed by company itself, does the head of control laboratory check his use of "Dummy" products?	------	------
8. List name and title of person interviewed: _____		
_____		

VI. Inspector's Comments:

A. Do inspector's recommend this company as a supplier of competitive Pharmaceutical products for use by J.M.C.H. Yes _____ No _____

B. In the inspector's opinion, is a return visit indicated? Yes _____ No _____

[SIGNATURE] _____
(Name)

_____
(Title)

_____
(Date)

EXHIBIT 3

[From the Montefiore Hospital and Medical Center Pharmacy Bulletin, vol. 5, April 1967]

INVESTIGATIONAL DRUGS

Investigational drugs at Montefiore Hospital can be divided into two groups. The first group consists of drugs which are approved by the Food and Drug Administration (FDA) for the use intended by the investigator and which are on the market but which are not in the hospital formulary. Before using such a drug, it is only necessary to complete the Request and Approval for Investi-

gational Drug, F.D.A. Approved, Form PH–1210, obtainable in the pharmacy, have it signed by the Chief of the Division to which the investigator belongs and to forward the form to the pharmacy. The pharmacy will then acquire the drug and notify the investigator if and when it is available.

The second group of drugs consists of compounds which are either not approved by the FDA for marketing and general use, or which are approved by the FDA, but not for the purpose for which the investigator intends to use it. To obtain permission for the use of such a drug it is necessary to complete the Request and Approval for Investigational Drug, Non-F.D.A. Approved, Form PH–1228, which is also obtainable from the pharmacy. This form first has to be signed by the investigator and then by the Chief of the Division to which the investigator belongs. The properly completed and signed Form PH–1228 must be then forwarded to the Chairman of the Research Drug Subcommittee. The application should be accompanied with as much informative material, in the form of reprints or information supplied by the sponsoring drug company, as possible.

The completed applications are promptly reviewed by the Research Drug Subcommittee and if the use of the drug is approved, then the investigator is notified by the Office of the Director that he can proceed with the use of the drug. (In the past, in the vast majority of instances, applications have been approved by this committee.)

It should be emphasized that only those drugs can be employed for experimental use for which proper application has been made by the sponsoring drug company or agency with the FDA. In the case of drugs that have been synthesized in a research laboratory and not by a drug company, the individual who synthesized the compound can also be the sponsor.

(NOTE.—Additions or deletions to the Hospital Formulary will be found on the last few pages of the Bulletin. Please cut out and insert the pages in the front of your formulary.)

Under no circumstances may a drug which has not been approved by the FDA for experimental use or by the Research Drug Subcommittee be employed for investigational purposes at Montefiore Hospital & Medical Center.

FRANCIS F. FOLDES, M.D.,
Chairman, Research Drug Subcommittee.

The procedure also requires that consent be obtained from a patient or his representative. Consent forms are available from the Pharmacy. They should be made out in duplicate, the original should be placed with the patient's chart and the duplicate serving as the physician's copy for his personal records. If for some reason the physician feels that it is not feasible to obtain consent or, in his professional judgement, contrary to the best interest of these patients, a formal statement (using Form OD–1158, available in the pharmacy) must be submitted to the Chairman of the Research Drug Subcommittee stating the reason for this decision.

The procedure concerning patient consent is required by the Food and Drug Administration. This procedure should be adhered to for it protects the physician and the hospital as well as the patient if a question of liability arises.

The Pharmacy Department is responsible for packaging, labeling and distributing the drug in accordance with the requirements arranged with the investigator and only to other authorized physicians. We are happy to assist physicians with details involved in double blind studies and in many cases maintain the codes for these studies. Since the pharmacy is now open 24 hours a day, it is valuable to have this information in a central location should an emergency arise. We will, of course, maintain records of the distribution of the drug for the investigator, and provide the nurses with basic information concerning the drug since such information is not available in any of the general reference books.

The Research Drug Subcommittee will allow an investigator to maintain his own supply of a drug only in special cases provided that it has assurance that adequate controls will be maintained. We would like to discourage physicians from this practice, if for no other reason than that the pharmacy will invariably receive a call from a nursing unit requesting an additional supply of a research drug which is not available in the pharmacy and the physician cannot be located. In many instances the course of therapy is then interrupted.

ADVERSE DRUG REACTIONS

An adverse drug reaction committee was formed in December 1965 at Montefiore Hospital and Medical Center.

Dr. Milton Reisch was appointed as principal reporter for this program in August, 1966. Due to his efforts the number as well as the quality of the reports have improved. However, it is still felt that we are probably receiving only a fraction of the adverse drug reactions occurring in the hospital. We would like to encourage everyone's participation in the program. If a reaction is suspected, it is only necessary to complete an Adverse Drug Reaction Notice Card available on all nursing units (ordered from the Storeroom) and send it to the pharmacy. The following is a summary of the past 15 months that the program has been in operation.

There have been approximately 16,000 admissions to the hospital in the past 15 months. 197 reactions were reported in 164 patients during this period.

The majority of the reactions were caused by the following groups:

	Cases	Percent
Antibiotics	46	23.3
Antimicrobial	7	3.6
Antituberculous	12	6.1
Radiographic preparations	19	9.6
Sedatives	15	7.6
Hormones	10	5.1
Tranquilizers	8	4.1
Diuretics	5	2.5
Total	122	61.9

In only six of of these cases, the patient had a previous history of a drug reaction.

Penicillin and semi-synthetic penicillins accounted for twenty-five reactions—54.3% of total antibiotics—12.6% of total reactions.

11 patients with gastrointestinal disease had 7.2% of reactions—66% of these reactions were due to antibacterials and radiographic preparations.

The neurology and psychiatric services reported 9.2% of the reactions. Antibiotics, phenothiazines and antiepileptic drugs accounted for 50% of the reactions in this group (14 cases).

The pulmonary service reported 17.7% of the reactions. Antibiotics, antibacterials, antitubercular drugs accounted for 100% of the reactions (9 cases).

The genitourinary service reported 5.9% of the reactions. Antibiotics and antibacterials accounted for 100 % of the reactions (9 cases).

The diagnostic radiology department reported 15.1% of the reactions (23 cases)— 60% were due to intravenous pyelography.

The cardiovascular section had 14.4% of the reactions (22 cases)—45% of reactions were caused by sedatives and hypnotics. Diuretics were responsible for 20% of the reactions.

9 patients had at least two reactions
1 patient had three reactions
1 patient had five reactions
1 patient had eight reactions
72 reactions were cutaneous in response
4 reactions were due to moniliasis and cryptococcosis
2 reactions of ototoxicity were noted-kanamycin and streptomycin
2 reactions of gastrointestinal bleeding due to aspirin
3 reactions of thrombocytopenia due to thiazides
4 anaphylactic reactions—one due to mercuhydrin; two due to penicillin; one due to ACTH

There were four deaths related to drug reaction. Three were due to hospital acquired reactions.

PHARMACY DEPARTMENT PROVIDES 24 HOUR SERVICE

Effective April 2, 1967 the Pharmacy Department will be open 24 hours a day seven days a week. This will enable us to provide complete pharmacy service around the clock.

Because the tube room is closed from midnight to 8 A.M., a pharmacy messenger will be stationed in the department to pick up and deliver orders during this time.

SHORTAGE OF SERUM ALBUMIN CONTINUES

It is still difficult to purchase 25% Normal Serum Albumin (Human) Salt Poor. A limited supply of 20 ml. vials has been obtained by the pharmacy. These will be issued in place of the 50 ml. vials until further notice.

PHARMACY COMMITTEE NOTES

1. Fuorosemide (Lasix) tablets 40 mg. and Ethacrynic Acid (Edecrin) tablet 25 mg., 50 mg. and 50 mg. vials for I.V. use only have been added to the formulary. These diuretics have shown to provide good results. However, they are potent diuretics and are likely to result in potassium depletion. The following brief summaries of these preparations are therefore provided:

Furosemide (*Lasix*)	*Ethacrynic acid* (*Edecrin*)
Site of action: Mainly on distal tubules; inhibits Na and water reabsorption in both the loop and the ascending limb of the loop of Henle and possibly in the proximal tubule.	On the ascending limb of the loop of Henle and on the proximal and distal portions of the tubule.
Onset and duration of action: Within one hour. Peak effect in 1–2 hours. Duration of 6–8 hours.	Within 30 minutes after oral dose, 15 minutes after I.V. injection. Peak effect in 2 hours. Duration 6–8 hours.
Dosage: Usual initial dose is 40 to 80 mg. for adults given in a single dose. If diuresis is inadequate, a 2nd dose is given 6–8 hours later; maintenance dose is then given once or twice a day.	*Oral*: The smallest effective dose should be utilized, usually 50 mg.–100 mg. for adults given after meal. To determine smallest effective dose: 1st day: 50 mg., p.c. 2nd day: Depending on response increase to 50 mg. twice daily p.c. 3rd day: 100 mg. in the morning and 50 mg. to 100 mg. the following afternoon or evening meal, depending on response to the morning dose. *Maintenance dose*: 50–200 mg./day continuously or intermittently—alternate days or more prolonged rest periods. *I.V.* 50 mg. for the average adult.

Both of these drugs are powerful diuretic agents, having a rapid onset of action. If not properly used they can lead to excessive diuresis with water and electrolyte depletion.

Careful medical supervision is required of the patient. The physician should be aware of the dosage requirements, precautions, warnings and contraindications so as to prescribe these drugs effectively and safely. Such additional information is available in our pharmacy.

2. Fibrinolysin and desoxyribonuclease combined (Bovine) Elase was approved for the formulary. This preparation will replace Varidase Jelly which was deleted.

In a recent review of proteolytic enzymes by "The Medical Letter," they concluded that "the clinical value of systemic proteolytic enzymes has not been established. Despite the absence of definite evidence, it is possible that topical application of a preparation such as Elase may be useful in the treatment of some wounds."

The committee pointed out that such preparations do not replace good nursing care and that enzyme preparations can cause irritation of the skin.

ADVERSE DRUG REACTION COMMITTEE NOTES

1. Reports indicate that 5% of the total population show some sensitivity to Tetracycline and 10% to Penicillin.

2. Reaction reviewed concerning Novocaine indicated that when given intravenously it should not be administered faster than 1 mg./Kg./min. and should generally be given in isotonic sodium chloride injection or 5% dextrose injection.

3. Thiazide compounds should be administered with caution to patients who show elevated Urea Nitrogen (BUN).

4. Patients on tranquilizers may experience faintness due to the development of orthostatic hypotension. The blood pressure of these patients should be checked in a sitting or standing position. If low, the tranquilizers should be discontinued, or the patient kept in bed.

The following is an addendum (as of April 1, 1967) of all additions or deletions to the Formulary since October 1, 1966.

New drugs

1. Auralgan Ear Drops 15 ml.
2. Chlordantoin Cream (Sporostacin)
3. Ethacrynic Acid (Edecrin), Tablets-Capsule shaped, 25 mg., 50 mg.; Injection–for I.v. use 50 mg. vial.
4. Fibrinolysin and Desoxyribonucleas Combined-Bovine (Elase Ointment) 30 Gm. tubes
5. Furosemide (Lasix) 40 mg. tablets
6. Hyperphos-oral
7. Imphos-intravenous
8. Medroxyprogesterone Acetate (Depo-Provera) Inj.
9. Polymyxin B (Aerosporin) Otic Solution 10 ml.
10. Pseudoephedrine HCl (Sudafed) Syrup, 10 ml.

New dosage forms

1. Amitriptyline HCl (Elavil) 50 mg. tablets.
2. Ampicillin: injection, 500 mg. vial; Capsule, 500 mg.; Suspension, 250 mg./5 ml.
3. Atropine Sulfate Ophthamlic Ointment 1%.
4. Bethanechol Chloride 25 mg. tablets.
5. Chloroprocaine HCL (Nesacaine) 3%.
6. Dexamethasone Elixir 0.5 mg./5 ml.
7. Echothiophate (Phospholine Iodide) 0.25%.
8. Methenamine Mandelate 1 Gm. tablets.
9. Methenamine Suspension 500 mg./5 ml. Note: Replaces the 250 mg./5 ml.
10. Methotrexate Sodium Inj. 5 mg. vial.
11. Penicillin G. Potassium 250 mg. tablets.
12. Penicillin, Potassium Phenoxymethyl–250 mg. tablets.
13. Perphenazine (Trilafon) 16 mg. tablets.
14. Trifluoperazine (Stelazine) 10 mg. tab.

Drugs available for special departments only

1. Sparteine Sulfate Inj. 150 mg. ampul; OB–GYN Service.
2. Isoxsuprine (Vasodilan), Injection 5–mg./ml., 2 ml. ampul; OB–GYN Service.
3. X-Prep, Radiology Service of requesting hospitals only.
4. Hydroxyzine (Vistaril), Injection–25 mg. disposable syringe; Neurosurgery Service.

Deletions

1. Streptokinase - Streptodornase (Varidase) Jelly. Note: Replaced by Elase Ointment.
2. Ampicillin Suspension, 125 mg./5 ml. Note: Replaced by 250 gm./5 ml.
3. Methenamine Suspension 250 mg./5 ml. Note: Replaced by 500 mg./5 ml.

Please cut along dotted line, fold in half and place in front of your Formulary. Do not discard previous addendum.

New pages for the Formulary replacing the addendum will be available by the end of April.

Pharmacy Bulletin—Published quarterly as a service to the Medical Staff of Montefiore Hospital and Medical Center by the Pharmacy Department.

Appreciation is expressed to Dr. Francis Foldes and Dr. Milton Reisch for their assistance in the preparation of this issue of the Pharmacy Bulletin.

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Louis Kalaboke, B.S., Supervisor.
Zina Fediay, M.Sc., Supervisor.

Senator NELSON. Our next witness is Dr. Calvin M. Kunin, associate professor of preventive medicine and medicine, University of Virginia School of Medicine. Doctor, your statement will be placed in full in the record, including your professional credentials. You may proceed to summarize your statement and, if you don't mind, I may occasionally

interrupt with questions. The committee appreciates very much your taking the time to come here today, and your patience in waiting so long to appear before the committee.

STATEMENT OF DR. CALVIN M. KUNIN, ASSOCIATE PROFESSOR OF PREVENTIVE MEDICINE AND MEDICINE, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE, CHARLOTTESVILLE, VA.

Dr. KUNIN. Thank you, Senator Nelson. I will begin my testimony literally from the text, and then summarize parts of it. I would appreciate it if you would interrupt from time to time, for illustrations.

Before I begin my testimony, I would like to state clearly that the views which I shall present are my own and in no way represent those of the University of Virginia School of Medicine, where I am employed.

My qualifications include the following educational background and experience: A.B., Columbia College, 1949, M.D., Cornell Medical College, 1953. Intern in medicine, the New York Hospital, 1953–54. Senior assistant surgeon, U.S. PHS assigned to the Communicable Disease Center, 1954–56. Assistant resident in medicine, Peter Bent Brigham Hospital, Boston, Mass., 1956–57. Research associate, Thorndike Memorial Laboratory, Harvard Service, Boston City Hospital working under Dr. Maxwell Finland. Assistant professor of preventive medicine and medicine, University of Virginia School of Medicine, 1959. Promoted to associate professor, 1964, and to become chairman and professor of preventive medicine, effective September 15, 1967.

I am certified by the American Board of Internal Medicine and the American Board of Microbiology.

My fields of special interest include internal medicine, infectious disease, epidemiology, and, specifically, pharmacologic aspects of antimocrobial chemotherapy. I make no pretense of being an economist or a sociologist, but will try to present my views as a clinical investigator and teacher.

You have presented me with an outline of general questions to be discussed with some latitude to present opinions on other topics and personal experiences. I will follow your outline: (1) Views concerning drugs under generic names as against brand names:

I would take very much the position of the preceding witness, in which we feel that generic names are much to be preferred in teaching brand names. This is the only way to present a systematic approach to pharmacology to the medical students.

I give some examples here of how one would use penicillins and teach these drugs with generic names, such as benzyl penicillin, aminobenzyl penicillin, phenoxymethyl penicillin, dimethoxyphenyl penicillin, oxacillin, and so forth, and then a series of different brand names which have no real relevance to the student's interest in the chemical structure, for example, what would Wycillin, Polycillin, Pen-V-K, Staphcillin, Prostaphlin and Tegopen, and many more, depending upon the names of firms selling them mean? The same could be said for tetracyline derivatives on the market now with more than 20 brand names.

Mr. Gordon asked me to list some of these names. I just sat down and took about 5 minutes to collect them. These are all tetracylines. They are variations on the same theme, and essentially the same therapeutic agent: Terramycin, Aureomycin, Declomycin, Rhondomycin, Achromycin, Tetrex, Sumycin, Panmycin, Tetracyn. They are all essentially the same preparation. So there are variations on the theme, but basically they have the same pharmacological properties. This multiplicity of brand names is a source of confusion to students and practitioners and makes it exceedingly difficult to know exactly what they are using and the relative cost to the patient, as has been pointed out before.

Senator NELSON. May I interrupt?

Dr. KUNIN. Sure.

Senator NELSON. This is as appropriate a place as any. I just asked Dr. Cherkasky about the question of establishing a national compendium. I don't know whether you were listening.

Dr. KUNIN. Yes, I was.

Senator NELSON. Then I need not repeat what I mean by a national compendium. Would you find that a useful compendium to have for the practicing physician?

Dr. KUNIN. I think it is good in principle, but I believe it depends on how it is executed in practice. For example, I can visualize where a compendium would be so large that it would be impossible for any physician to really find it useful in his hands.

On the other hand we have, for example, an extremely good textbook of pharmacology, which would have to be very slightly expanded to include the drug names. This is the textbook by Drs. Goodman and Gillman, which essentially is a textbook of medicine, so to speak. It is such a marvelous and well-written document, that I would say that I would approve the thought of a compendium in principle, but I would like to see how it is constructed in actual practice, before I would blanketly say, this is the answer, the solution to our problems.

Senator NELSON. I am not exactly sure how it ought to be compiled, although I would assume that if there were to be a national compendium, the distinguished authorities in the field of drugs and the practice of medicine would be used as consultants and advisers in determining the scope, size, and nature of the compendium, and at least to my mind it ought to include something like quarterly inserts.

It ought to have the approval of the FDA in order to be certain that the information in it would be based upon the best medical information available. I assume that the FDA will, some time in the not too distant future, engage in an extensive program for quality control and clinical testing to determine the therapeutic value of drugs, so that the compendium would include this kind of information.

This kind of compendium would be available to the substantial number of physicians in this country who do not work in a hospital with a hospital formulary system. This is the kind of thing I am posing as a question. Do you have any observations about that?

Dr. KUNIN. I am in favor of this, certainly, and I believe that if conducted under the conditions that you outline, it would be a very valuable instrument. It certainly would be much more valuable than the Physicians' Desk Reference, which is essentially a compendium of brand names. I think it would be very valuable in that respect.

I would like to make one comment, however, in relation to Dr. Cherkasky's concepts of who is testing all of the generic drugs in mass programs all over the country. I think that there should be certainly a good deal of this kind of testing, and that testing is being done. But to extend it to every single generic preparation simply to do it, to speak when one can perhaps satisfy many of these questions by chemical analysis alone may be overwhelming. It may not be necessary.

Senator NELSON. I don't know that he was suggesting that. I had asked him whether it would be feasible to take the most often prescribed drugs and start a program of clinical testing. I think it is correct that if there are 40 or 50 versions of a particular drug, 40 or 50 manufactured by that many different companies, that you would have to select a few of this number for clinical and chemical testing, and then probably conclude that if the rest of them come within the range of those that have passed the tests, until proven otherwise, it is likely that they are equivalent.

Dr. KUNIN. That is quite reasonable, sir.

Mr. GORDON. Are you assuming, Doctor, that if certain drugs are chemically the same, they will have about the same therapeutic effect?

Dr. KUNIN. This would be correct, assuming that the formulations that are used in the mixers are the same. There is the classical story with the tetracyclines which I alluded to in my text, in the story of the gilded antibiotics. Here different corporations used different methods of manufacturing these drugs. It turned out that the excipients that were used; that is, the materials to make up the capsules actually were inhibitory to the final product, so that although they all contained tetracycline, the presence of calcium and magnesium salts was detrimental. Actually this whole story even became worse when it was found that one company, which had done quite a good job of putting in a good excipient to enhance absorption of their product and it later turned out that this particular excipient in the presence of moisture and heat turned the product into a toxic substance which then was quite dangerous.

So that one cannot ignore, you might say, the pharmacist's art here in terms of how the drug is compounded and one cannot use potency alone.

On the other hand, it is quite easy to state what type of excipient should be used, and this could be characterized very nicely, so I see no major problem here.

Senator NELSON. Dr. Miller of the USP testified here. I don't have the exact quotation but the impression he left with me was that if all products listed in the U.S. Pharmacopeia meet USP standards for dissolution time, potency, purity, et cetera, they are clinically equivalent and for any drug included in the USP there is no evidence to the contrary.

Is that your judgment?

Dr. KUNIN. Yes, that is right.

One learns of many of these things retrospectively. For example, the companies that work with the tetracyclines did this in all good faith. It was only in retrospect that one learned that certain problems were encountered, so that one can only go in good faith and on the basis of his best information. I believe that under those conditions I would agree completely.

I next summarize this section essentially as saying yes, I do think generic names are worthwhile and in the process of teaching medical students, in talks that I might give to physicians about the country, I always use the generic term.

Now, I include a remark here concerning Dr. Burack's book, "Handbook of Prescription Drugs," and note that I do quarrel with him about a few technical points, which always occurs in the medical world, and find that this book is really not the compendium that you are referring to.

I find that it is very useful in terms of costs, and I agree with the thesis that he presents in the book.

Senator NELSON. I believe he states in his book that it is not intended to be a comprehensive compendium.

Dr. KUNIN. That is right.

Senator NELSON. It was intended so the layman could understand it.

Dr. KUNIN. That is right.

Senator NELSON. And it is not the final word on the subject.

Dr. KUNIN. Yes. I find this to be a valuable book in those terms.

Senator NELSON. I might add that I have received a letter from a very distinguished professor at a fine school of medicine. He said he was very pleased with the book and wished that such a book had been available when he started out as a practicing physician.

Dr. KUNIN. Well, I make the point in my text that Dr. Burack is primarily concerned with the interest of the patient and the cost of drugs to him, and that most physicians are equally concerned about cost and that the lists such as these are very helpful.

The practicing physician, however, and I include myself here, is troubled by what the commercial pharmacist might do with his carefully worded generic prescription. How can the physician be certain that the pharmacist will always give the patient the least expensive preparation, or even that he will carry it in stock?

It is entirely possible that the pharmacist may charge prime prices for a low cost generic preparation. This problem is minimized, of course, in the large hospitals armed with a formulary system and conscientious pharmacists and by agencies which make bulk purchases, but what about the corner drugstore?

I believe this point is very important, because this is one of the points that physicians have raised with me in conversations.

We are very conscientious about prescribing generic drugs, but what does it really mean in terms of the patient?

Senator NELSON. To use the example of prednisone, if a doctor numbers himself among the 10,000 physicians who read the Medical Letter, couldn't he very well prescribe prednisone and then select the company whose product he prefers for his patient?

Dr. KUNIN. Sure.

Senator NELSON. Now, isn't it also true that the pharmacist is at quite a disadvantage here in that he can't stock everything, and so if the doctors are prescribing an expensive drug, there are 22 prednisones, and if the doctors are prescribing one that costs $17.90, and that is what comes in on the prescription, then under the law he is not permitted, in 40 States, to substitute?

Dr. KUNIN. That is right.

Senator NELSON. To substitute a generic for a brand name?

Dr. KUNIN. That is right.

Senator NELSON. Then isn't it likely that he stocks what the doctors are prescribing and that it is not the pharmacist's fault at all if a patient receives a high priced drug; it is the doctor's fault?

Dr. KUNIN. Well, I would like to offer my own personal solution to this problem. I believe that this is particularly suitable in an area such as ours, which is more rural, and perhaps does not have the large hospitals playing such an important role, I propose here that there be a meeting by a subcommittee of each medical society, each county medical society, with a similar group of pharmacists in the locality, and that these individuals go over the problem of what the physicians are prescribing in their area, and what the pharmacist's problem is in terms of his inventory, and that together they can prepare a formulary which would be perhaps somewhat broader than the ones that one would see in a more restricted hospital pharmacy, but would in such a way meet the needs of the patient, and that this be accompanied by a price list for that locality for the physician in the area.

Now, I started at this point because I believe that one should also always try to give the individuals in a free enterprise situation the opportunity to get together and to try to work out something that is reasonable for their locality, and so I suggest this particular mechanism.

I am not aware of this ever having been tried, but I think that it ought to be.

Senator NELSON. Is it your feeling that the county medical society, particularly in places where there isn't a hospital with a good formulary, could itself with the pharmacists develop a formulary of the most commonly prescribed drugs in the practice in that area?

Dr. KUNIN. That is right. They can, of course, model from the formulary of large institutions. This would be very valuable to them but it would be good to have a dialog between the physicians and the pharmacists so that, for example, if the physicians in the area feel that all prescriptions should have the generic name on the label, unless stated otherwise in the prescription, this could be an agreed to arrangement. They could also decide when they say generic prednisone, this is what they mean.

When they say prednisone, they mean generic drug, so that there is some meaning here across the board, so that the physician doesn't have to sit down with a large reference text or the Medical Letter. He knows that he has confidence in the subcommittee that have worked this out for him.

Senator NELSON. It sounds like a very creative suggestion, but the pharmacist has no control over what the doctor is going to prescribe, and if the doctor prescribes the generic name, the pharmacist may in some 40 States substitute a brand name?

Dr. KUNIN. That is right.

Senator NELSON. I would guess that often when a doctor prescribes a lower priced generic, since he is one of the rare doctors who does so, the pharmacist doesn't stock the drug generically and has to give the patient a brand name.

Dr. KUNIN. That is right.

Senator NELSON. So if they if they got together and it was understood that among these most commonly used drugs covering 80 or

90 percent of the cases, doctors would like to have generics in stock that you might very well solve some problems.

Dr. KUNIN. That is right. The physician in a sense is in a vacuum away from the pharmacist and the pharmacist in a vacuum away from the physician. They must talk to each other. They must straighten this out together.

Now, the second portion of this deals with the advertising and promotion of drugs, with which I, like every witness here, am very concerned. I will state this as dramatically as I can. One has to be blind, deaf, and dumb, to lock his office if he wishes to avoid being deluged with direct mail advertising, visits by detail men, and more recently heavy promotion in "throwaway" unsolicited journals which, for the most part, serve as advertising vehicles. One can read in the financial sections of the newspapers about the success of these throwaway journals, which, in my opinion, are taking a tremendous toll in trying to take over medical education. Booths are set up in hospitals and agents of drug firms walk the floors.

I have no objection to ethical promotion of products, but the matter is out of hand.

I cite an instance here in which we tried to teach some students certain facets of the diagnosis of infectious disease, illustrating a particularly difficult diagnostic problem.

We had a break for a few minutes, and the students were in the hall and saw one of the detail men who roam the halls of hospitals, and they chatted with him about this problem. He had a very simple solution: "Why don't you use my drug?" The answer is: "Don't think, Doctor. Just use our drug. It will solve all your problems."

When the students came back they essentially said, "What kind of a teacher are you? You are telling us to do all this work and all this complicated reasoning when all we had to do is use drug X and we would have solved our problem."

This is the antithesis of good education, and I think this practice is to be deplored.

I call this the hall medical school.

Now, there are techniques to combat this. In our institution, as well as others, a section of the pharmacology course deals with therapeutics in which the students do go through a large number of advertisements and very carefully go over the claims. They have very little difficulty in seeing through these claims under minimum guidance.

I have an example here, if you would like. May I present this, sir?

Senator NELSON. Yes.

Dr. KUNIN. This is an example. It is called:

A case for Keflin, Sodium Cephalothin.

Temperature down in twenty-four hours; patient free of infection after 8 days.

Patient was 51-year-old male with past history of heart disease, alcoholism, and anemia of unknown etiology.

This is the advertisement.

Temperature spiked to 103° F. on third day after admission to hospital for impending delirium tremens. WBC count was 19,800, and clinical findings were consistent with pneumonia of the right lower lobe. Temperature dropped to 101° F. after one day's penicillin therapy, but patient became hypotensive and more toxic. The BUN rose from 70 to 111 mg./100 ml. Treatment was begun with Keflin (1 Gm. I.V. q. 4 h.) and large doses of corticosteroids.

One day later, temperature had dropped and blood pressure was controllable with pressors and corticosteroids. Patient was more responsive but still dis-

oriented. BUN was 96. Dosage of pressors, antibiotic, and steroids was gradually reduced as the patient slowly and progressively improved.

Keflin discontinued on twelfth hospital day. Patient continued in hospital for evaluation of anemia.

Now, this is supposed to be a case for this particular drug.

Senator NELSON. Is this an ad?

Dr. KUNIN. This is an ad.

Senator NELSON. In what publication?

Dr. KUNIN. This you will find in any medical journal. This comes in all of them. This could be in the JAMA.

Senator NELSON. AMA has run this ad?

Dr. KUNIN. Oh, yes. Actually, I believe I took this one from the overseas edition of Lancet which is now published in the United States and filled with American advertisements.

Now, what is wrong with this advertisement? What is wrong is that we never are told what was wrong with the patient. They don't describe the fact that the patient had a sputum examination that was stained for certain bacteria which could well explain what he had. They don't tell us about blood cultures that would have been necessary for diagnosis. It is quite probable that the penicillin was working quite effectively and they just simply changed to another drug which did the same thing.

The effect of corticosteroids are dramatic and one does not know what role they played here.

We really don't know anything about this patient that we should know in terms of rational therapeutic practice.

This is an example of "don't think; use our drug."

(The advertisement referred to follows:)

A CASE FOR KEFLIN® (SODIUM CEPHALOTHIN)

Temperature down in twenty-four hours; patient free of infection after eight days*

Patient was 52-year-old male with past history of heart disease, alcoholism, and anemia of unknown etiology. Temperature spiked to 103°F. on third day after admission to hospital for impending delirium tremens. WBC count was 19,800, and clinical findings were consistent with pneumonia of the right lower lobe. Temperature dropped to 101°F. after one day's penicilin therapy, but patient became hypotensive and more toxic. The BUN rose from 70 to 111 mg./100 ml. Treatment was begun with Keflin (1 Gm. I.V.q. 4 h.) and large doses of corticosteroids.

One day later, temperature had dropped and blood pressure was controllable with pressors and corticosteroids. Patient was more responsive but still disoriented. BUN was 96. Dosage of pressors, antibiotic, and steroids was gradually reduced as the patient slowly and progressively improved.

Keflin discontinued on twelfth hospital day. Patient continued in hospital for evaluation of anemia.

Keflin is potent enough for the most severe susceptible infections: respiratory tract, urinary tract, surgical wounds, soft tissue, skin, bone, or blood. Keflin has proved to be outstandingly effective in a wide range of severe infections located in a variety of sites. Its *broad spectrum* covers virtually all gram-positive organisms; a great majority of gram-negative organisms are moderately susceptible, with the I.V. route affording maximum concentration. The *bactericidal action* of Keflin helps assure rapid, decisive patient response. This is especially important when host response is poor, as in debilitated patients. Keflin is active against both penicillin-sensitive and penicillinase-producing staphylococci. It is often effective when other antibiotics fail.

*Case history on file with the Lilly Research Laboratories.
This case, of course, does not typify every aspect of therapy with Keflin. For further information on indications, precautions, and adverse reactions, see accompanying text.

Keflin is especially useful in patients with reduced kidney function. Keflin has demonstrated a remarkably low toxicity. It may be used even when dehydration, oliguria, or other factors suggest the possibility of reduced renal function—a condition in which many other antibiotics are contraindicated. However, total daily dosages for such cases are proportionately less than those recommended for patients with normal renal function.

A cumulative report of 487 patients; many were seriously ill or hospitalized with respiratory-pulmonary infections or infections of the urinary or gastro-intestinal tract, skin and soft tissues (including postoperative wound infections), bone, or blood.

	Percent
Satisfactory	73
Equivocal	9
Failure	18

References: 1. Anderson, K. N., and Petersdorf, R. G.: Antimicrob. Agents & Chemother., p. 724, 1962. 2. Flux, M., Riley, H. D., Jr., and Bracken, E. C.: Antimicrob. Agents & Chemother., p. 254, 1963. 3. Griffith, R. S., and Black, H. R.: J.A.M.A., *189:* 823, 1964. 4. Heitler, M. S., *et al.:* Antimicrob. Agents & Chemother., p. 261, 1963. 5. Herrell, W. E., Balows, A., and Becker, J.: Clin. Pharmacol. & Therap., *4:* 709, 1963. 6. Holloway, W. J., and Scott, E. G.: Antimicrob. Agents & Chemother., p. 251, 1964. 7. Philson, J. R., Clancy, C. F., and Alexander, J. D.: Antimicrob. Agents & Chemother., p. 267, 1963. 8. Sidell, S., *et al.:* Arch. Int. Med., *112:* 21, 1963. 9. Walters, E. W., Romansky, M. J., and Johnson, A. C.: Antimicrob. Agents & Chemother., p. 247, 1963.

LILLY.

Senator NELSON. Why would a distinguished journal such as the Journal of the American Medical Association run an ad that on its face is incomplete and misleading?

Dr. KUNIN. I am not privy to their point of view, sir; and want to try to explain their position. I think that they might want to testify as to why they would run an ad of that kind.

Senator NELSON. But that ad appears regularly in a number of the medical journals?

Dr. KUNIN. Well, this one is a little unusual, I must say, the case report, is so poorly documented. Usually the statements are more overall.

I can give you another example. This would be more characteristic in terms of hyperbole. This one deals with Erythrocin, and the statement says:

After 15 years
Recent studies show it clinically effective in 94.8 percent of patients with everyday bacterial infections
with no known toxic effects on bone, blood, vital organs or teeth

"Erythrocin" or Erythromycin, which is the trade name.

Now, what are these? Is this the drug of choice? What should the physician do to diagnose these everyday infections?

It is essentially meaningless. This is more typical. That is a general statement rather than a specific case. It is easy to pick on the poor specific case as I did a few moments ago, but I think this is equally poor.

Senator NELSON. Where was that ad run?

Dr. KUNIN. This one was from one of the disposable journals, probably, what is it——

Mr. GORDON. Medical World News.

Dr. KUNIN. Medical World News, yes.

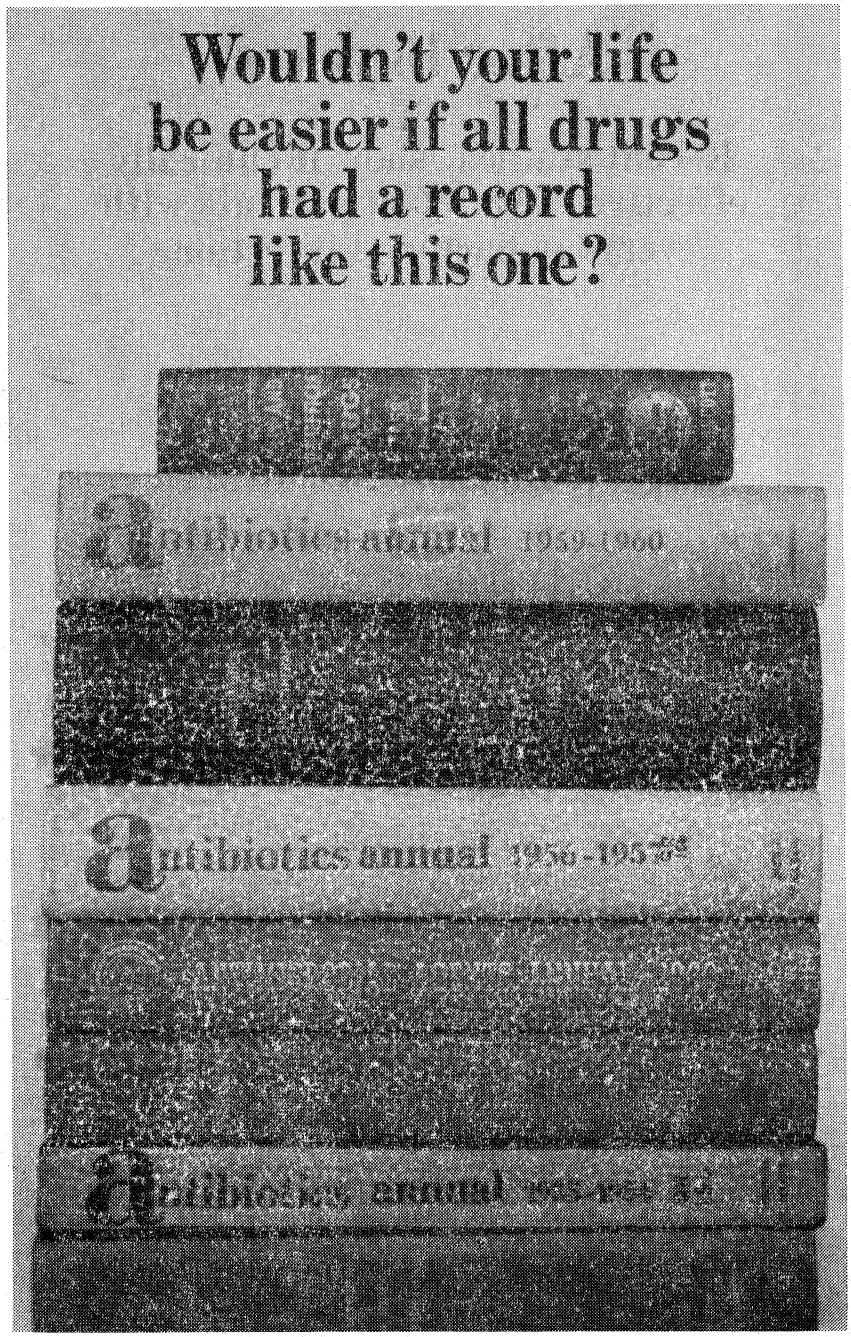
Senator NELSON. That is part of the continuing education of the physician, I take it.

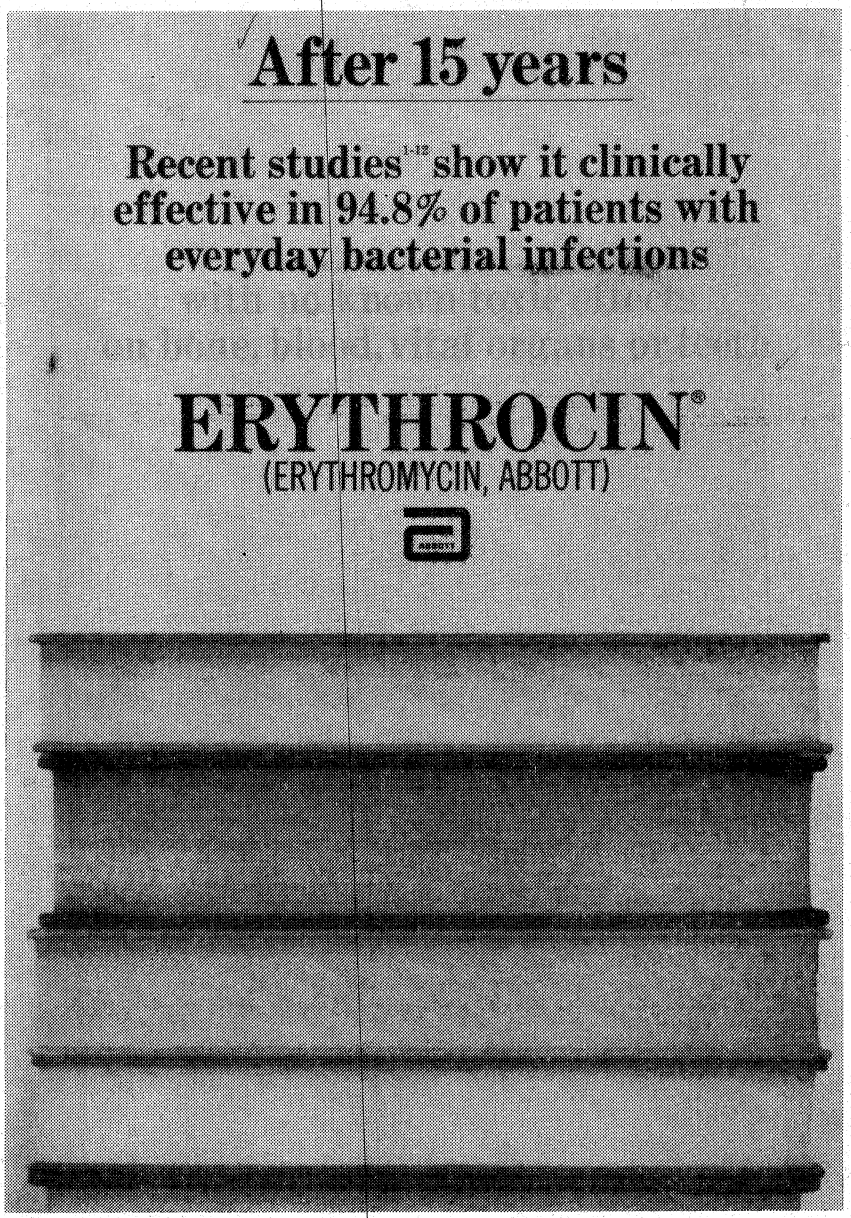
Dr. KUNIN. Yes, sir.

Mr. GORDON. May we have a copy of that?

Dr. KUNIN. Yes.

(The advertisement referred to follows:)


Wouldn't your life
be easier if all drugs
had a record
like this one?
Antibiotics annual 1959-1960
Antibiotics annual 1956-1957


After 15 years
Recent studies[1-12] show it clinically effective in 94.8% of patients with everyday bacterial infections
ERYTHROCIN®
(ERYTHROMYCIN, ABBOTT)

Senator NELSON. In discussing the question of the advertising and promotion of drugs, is it your view that someone, perhaps the FDA, ought to more carefully supervise and approve the claims of drug ads appearing in medical journals and elsewhere?

Dr. KUNIN. Yes, I believe so.

Now, it is my understanding that there are two mechanisms. One is the Federal Trade Commission's role here, and the Food and Drug Administration's role, and I have difficulty in distinguishing between whose responsibility belongs where. It is my understanding that the Food and Drug Administration is able to examine these advertisements and see that they follow to the letter the package insert.

Senator NELSON. The committee counsel informs me that the Federal Trade Commission deals with over-the-counter drugs.

Dr. KUNIN. Pardon me, sir?

Senator NELSON. Exclusively.

Dr. KUNIN. O.K.

Senator NELSON. Aspirin is aspirin, you know.

Dr. KUNIN. Right.

Senator NELSON. If you read Time magazine, you can find out.

Dr. KUNIN. There is a committee that has been set up by the National Academy of Sciences, which is dealing with review of drugs for efficacy, those drugs licensed from 1938 to 1962, I believe. A considerable length of time has been spent analyzing this problem, and their report, of course, is not ready yet, but I believe that this is a tremendous effort and a step in the right direction. Thus there is a major effort being undertaken. Of course, this was begun by Dr. Goddard and the Food and Drug Administration in conjunction with the National Academy of Sciences.

Mr. GORDON. This deals with efficacy?

Dr. KUNIN. Yes, sir.

Mr. GORDON. But not relative efficacy?

Dr. KUNIN. That is right.

Now, this next section of my text deals with relative efficacy, especially of antibiotics.

It is certainly true that antibiotics differ in relative efficacy for various infections. The subject, however, is very complex because of the great variety of disease states which must be treated and the large number of good drugs that are available. And I want to point out here that an agent may be the drug of choice under one circumstance while another drug be the secondary agent, but in another circumstance the second agent may be the primary drug. I cite Rocky Mountain spotted fever, for example, where one would use tetracycline whereas in pneumococcal pneumonia one would prefer to use penicillin, so that tetracycline would be a secondary drug for pneumonia but a primary drug for Rocky Mountain spotted fever. One has to relate it to specific disease efficacy.

This is covered in textbooks of pharmacology and the AMA new book "New Drugs" which makes an effort in this direction.

One of the factors that play a very important role in the hospital should be emphasized. This is the problem of antibiotic sensitivity testing.

This laboratory test will be misleading if one does not know how to interpret it properly, and one requires a fair amount of sophistication

to interpret these tests properly. For example, if we did a sensitivity test for a pneumococcus, which is an agent which causes pneumonia, against 20 different antibiotics, we might find that all 20 work perfectly well in the sensitivity test. We know from our clinical experience, however, that penicillin is the drug of choice so the sensitivity test in this case is not applicable.

In another situation we might find, for example, with a staphylococcus that this agent is sensitive to many drugs but we know from our clinical experience that only few drugs are really the drugs of choice, so that sensitivity testing in our hospitals, must be almost like a formulary system. We have to reduce the number of drugs that we would use for testing, so that they are appropriate.

Now, I will give you an example of this.

In an advertisement for methacycline, a tetracycline, this is called Rondomycin, the advertisement states:

> Intense activity where infection strikes most often.

It talks about in vitro susceptibility tests in the test tube. One of the points it makes is that it has intense activity against Staph. aureus, which is the first organism they list. Now, this is not the drug of choice against staphylococcus. This drug is a second line preparation in this area, and we would generally not use or even test our staphylococci against this particular drug or any related drug, and yet the advertisement implied that this might be a firstline drug. I think this is misleading.

(The advertisement referred to follows:)

Intense activity where infection strikes most often

demonstrated by
Protective dose$_{50}$ (PD_{50}) tests[1]
Intense activity against *Staph. aureus, Str. pyogenes, D. pneumoniae* in comparative studies.

In vitro susceptibility studies[2]
Of 271 cultured organisms from isolates of patients with respiratory tract infections, 260 were sensitive to Rondomycin.

Clinical results[2]
Over 90% success rate in respiratory-tract bacterial infections in 331 patients studied.

Activity across a truly broad spectrum

Therapeutic blood levels that last 24 to 36 hours after the final dose

150 mg. q.i.d. and 300 mg. b.i.d. dosage schedules are equally dependable

Good toleration with minimal risk of photodynamic reactions

Contraindicated: In individuals hypersensitive to methacycline.
Warning: In the presence of renal dysfunction, reduce usual oral dosage and consider serum level determinations to avoid liver damage.
Discoloration of developing teeth may occur although such toothstaining has not been reported with methacycline to date.
In certain hypersensitive individuals treated with methacycline, exposure to direct sunlight may precipitate a photodynamic reaction. Such reactions have not been reported with Rondomycin to date. In individuals with a history of photo-allergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.
Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. If such super-infections are encountered, Rondomycin should be discontinued and replaced by appropriate therapy. Before treatment of gonorrhea, if concomitant syphilis is suspected, a darkfield examination should be made of any lesion and serological tests for syphilis should be made monthly for at least three months afterwards. Increased intracranial pressure has occurred occasionally in infants treated with methacycline but has disappeared promptly and without sequelae, once therapy was discontinued.
Adverse Reactions: Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis, dermatitis, and allergic reactions may occur rarely. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.
Supply: Rondomycin (methacycline) is available as 150 mg. capsules containing 150 mg. methacycline HCl equivalent to 140 mg. of base and 300 mg. capsules containing 300 mg. of methacycline HCl equivalent to 280 mg. of base.
Rondomycin syrup contains 75 mg. per 5 cc. of methacycline HCl equivalent to 70 mg. per 5 cc. of base.
More detailed professional information available on request.

References: 1. Research data on file, Medical Department, Pfizer Laboratories. 2. Clinical data submitted to F.D.A. Available to physicians on request, Medical Department, Pfizer Laboratories.

Science for the world's well-being®

Pfizer *Since 1849*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc. New York, N.Y. 10017

new **Rondomycin®**
methacycline
adds depth to true broad-spectrum activity

Dr. KUNIN. Now, one of the best advertising devices of all is to be able to put one's own company sensitivity testing into a hospital, and supply you with the little pads that will go on the wards with the brand names showing how sensitive this particular drug is. Very often there are two drugs that are essentially the same, but the brand name catches on.

If I were trying to advertise a drug, this is the way I would do it, and I think the companies are very clever in trying to do this type of promotion, but I think this is to be deplored, also.

Now, the fourth item here deals with problems with continuing education of physicians. I believe that the drug companies must be given a great deal of credit for trying to support continuing education for physicians. Some of these meetings are well attended. They use a soft sell, and they are not obnoxious.

I think that one company that does it very well is Lederle. which sponsors a good number of excellent sessions of this kind with a minimum amount of fanfare.

Nevertheless, I believe one must remember that a physician earns an adequate income, and the courses are not so expensive as to be better funded by medical societies, hospitals, and medical schools without direct support by drug firms. I have no objection to the firms supporting hospitals and medical education, indeed, they must and should be more generous, but I would urge that this be done by general institutional grants that really amounts to something, rather than the little frills of a sporadic meeting.

The problem of continuing education is one of the major responsibilities of medical schools. At the University of Virginia this is a serious area. We have an assistant dean who is in charge. He was in practice for many years and knows the physicians and their problems. We are making a good effort in this area.

I think this should be supported by unobligated funds from both the Government and from industry.

I would like to go back a minute to one part of advertising that I left out. I think this should be brought about. This is on page 5 at the top.

This is about the detail man.

He often does serve a useful purpose and these are very pleasant people. We always try to talk to them and see what their pitch is, and sometimes they are very helpful. But sometimes they go a little far, and some of these little gimmicks are annoying. There are presents that are useless, like calendars that have their drug names on it, executive pointers and so forth, steak parties for house officers, gifts of books and medical bags to graduating students, and trips to the big city, including wives of medical students. This seems to be going much too far.

I think what the companies are trying to do, and they are perfectly deliberate, is try to find favor with the people who are going to be the individuals who are going to prescribe their products in the future.

But this is a little bit, I think, too much.

I wanted to just emphasize that that point was not left out in the verbal testimony.

The last section deals with so-called fixed combinations of antimicrobial agents. I point out that use of combinations of drugs is an old story in medicine. It was part of the mystique of medical care and

is still used over the world. In some instances there are good reasons to use combined preparations.

In the world of antibiotics, combinations are used to broaden the coverage in individuals when you don't know what you are dealing with and it is an emergency situation. Another use is to delay the emergence of resistance to one of the drugs. This is commonly used in tuberculosis, or to achieve an effect, a so-called synergistic effect, when the effect of the combinaton is greater than the addition of the properties of the two agents.

Actually, however, except in tuberculosis and one form of heart disease, use of drugs in combinations are really not essential.

Senator NELSON. When Dr. Miller, representing the USP testified here he said that the USP does not list any combination drugs in the belief that since drugs administered separately give the physician greater control, there is no good reason for listing combination drugs.

You say basically the same thing except in reference to cases in tuberculosis and rare infections of the heart where combinations are of value; is that correct?

Dr. KUNIN. Well, we must make a distinction between the combined use of drugs and the fixed combination of a drug in one package.

Senator NELSON. I was referring to the fixed combination. Is that what you are talking about?

Dr. KUNIN. In tuberculosis they don't use the fixed combination. I am sorry if I implied that. There are drugs used in combination, but they are used separately. There is no fixed combination there, necessarily.

Senator NELSON. Do you see any value in the fixed combination drugs appearing in one capsule?

Dr. KUNIN. No.

Senator NELSON. For any disease that you know of?

Dr. KUNIN. No. I will give you an example from an advertisement if you wish. Urobiotic—by the way, it took me only 10 minutes to pull these out. These are available so easily in all the medical journals that one doesn't have to work hard to find these examples.

Here is one called Urobiotic, which is a combination of oxytetracycline, a tetracycline derivative, which is an excellent drug, glucosamine, which is simply an excipient and a sulfonamide, and a material to turn the urine red. The dose of oxytetracycline is very low, 125 milligrams. This is lower than we would customarily use. It does have sulfonamide, 250 milligrams. It might work. But this would be an unnecessary combination, perhaps not as effective as the tetracycline Terramycin component all by itself, and so I think this is an example of a fixed combination that has no place in the market.

(The advertisement referred to follows:)

In the treatment of genitourinary tract infections, when the need arises for antimicrobial and analgesic action consider

Urobiotic®

Each capsule contains: Terramycin® (oxytetracycline as the HCl), 125 mg. with glucosamine HCl; sulfamethizole, 250 mg.; phenazopyridine HCl, 50 mg.

Product Information

Actions: Urobiotic is a product designed for use specifically in urinary tract infections.

Terramycin® (oxytetracycline) is a widely used antibiotic with clinically proved activity against gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain protozoa.

Sulfamethizole is a chemotherapeutic agent active against a number of important gram-positive and gram-negative bacteria.

Phenazopyridine is an orally absorbed agent which produces prompt and effective local analgesia in the urinary tract.

Indications: Urobiotic is indicated in the therapy of a number of genitourinary infections caused by susceptible organisms. These infections include the following: pyelonephritis, pyelitis, ureteritis, cystitis, prostatitis, and urethritis. Both antibacterial components are active against the most common urinary pathogens, including *Escherichia coli, Pseudomonas aeruginosa, Aerobacter aerogenes, Streptococcus faecalis, Streptococcus hemolyticus, and Micrococcus pyogenes.* Urobiotic is particularly useful in the treatment of infections caused by bacteria more sensitive to the combination than to either component alone. The combination is also of value in those cases with mixed infections, and in those instances where identification of the causative organism is pending laboratory isolation.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to any of its components.

This drug, because of the sulfonamide component, should not be used in patients with a history of sulfonamide sensitivities, in pregnant females at term, in premature infants, or in newborn infants during the first week of life.

Warnings: Reduce usual oral dosage and consider serum level determinations in patients with impaired renal function, to prevent possible liver toxicity.

Oxytetracycline, which is one of the ingredients of Urobiotic, may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans. Use of oxytetracycline during the last trimester of pregnancy, neonatal period and early childhood may cause discoloration of developing teeth. This effect occurs mostly during long-term use of the drug, but it has also been observed in usual short-treatment courses.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight which may also be produced by other tetracycline derivatives. Should such a reaction occur and in individuals with a history of such reactions, exposure to direct sunlight should be avoided and the drug should be discontinued at first evidence of reaction.

NOTE: Photoallergic reactions to Terramycin (oxytetracycline) are exceedingly rare and phototoxic reactions are not believed to occur.

Because of its sulfonamide content, this drug should be used only after critical appraisal in patients with liver damage, renal damage, urinary obstruction, or blood dyscrasias. Deaths have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, and other blood dyscrasias associated with sulfonamide administration. When used intermittently, or for a prolonged period, blood counts and liver and kidney function tests should be performed.

Precautions: As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate specific therapy should be instituted.

Increased intracranial pressure with bulging fontanelles has been observed occasionally in infants receiving therapeutic doses of oxytetracycline.

Although the mechanism for this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

This drug should be used with caution in persons having histories of significant allergies and/or asthma.

Adverse Reactions: Nausea, diarrhea, glossitis, stomatitis, proctitis, vaginitis and dermatitis, as well as reactions of an allergic nature, may occur during oxytetracycline therapy, but are rare. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As in all sulfonamide therapy, the following reactions may occur: nausea, vomiting, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, injection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria. The dosage should be decreased or the drug withdrawn, depending upon the severity of the reaction.

Dosage: In adults, 1-2 capsules q.i.d. is suggested. In children under 100 lbs., 1 capsule q.i.d.; in children under 60 lbs., 1 capsule t.i.d. In acute urinary tract infections, therapy should be continued for a minimum of seven days or until bacteriologic cure occurs.

To aid absorption of the drug, it should be given at least one hour before or two hours after eating. Aluminum hydroxide gel given with antibiotics has been shown to decrease their absorption and is contraindicated.

Supply: Urobiotic Capsules: bottles of 50.

More detailed professional information available on request.

Science for the world's well-being®

Pfizer *Since 1849*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
New York, New York 10017

Senator NELSON. Isn't it correct that most of the fixed combinations are more expensive than if the drugs included were prescribed separately?

Dr. KUNIN. It is my understanding that that is correct although I have not looked into that specifically.

Mr. GORDON. Then, why do doctors prescribe them?

Dr. KUNIN. I would suspect that this is related to the amount of advertising, the beautiful name Urobiotic, which is designed around the indication, the frustrations that one deals with in terms of individuals who may have infections or other disease stages in which one uses one drug or another and has difficulty with results.

In other instances, there may be a historical reason for a particular combination. The reason, perhaps, no longer exists, but the tradition may still continue.

Senator NELSON. But aren't additional fixed combinations still being placed on the market?

Dr. KUNIN. Sure.

Senator NELSON. Is there anybody of distinction in the field of medicine who argues that there is value to fixed combinations?

Dr. KUNIN. Not to my knowledge, sir, not to my knowledge. I know of no one in the field of antimicrobial therapy who you might say is academically concerned with the problem who would feel that a fixed combination would be essential or really required or needed.

Senator NELSON. Then aren't you really saying that the doctor who prescribes such a combination doesn't know really what he is doing?

Dr. KUNIN. No. What I am saying is that the doctor who prescribes it doesn't believe perhaps what I say or what my colleagues might say. He may have his own reasons and perhaps he should have his day to present his position here. I see no personal reason to do this.

Senator NELSON. Well, if you state that you are not aware of anybody of any distinction in the medical profession who claims that there is any value to a fixed combination, can you then think of any reason for a doctor to prescribe one?

Dr. KUNIN. Well, I would suppose that it is a reflection once again of advertising, of detail men pressing certain products, of our failure in the field of postgraduate medical education.

Senator NELSON. Are you saying that the doctor really doesn't know what he is doing when he is prescribing? Are you implying a failure of education in the field of drugs? Is that so hard for you to say? I think it is a very sad commentary on the medical profession, and I would like to have a doctor of your distinction say it more directly than say it is a failure of——

Dr. KUNIN. I would like to dilate on that point, because if a physician finds that a particular fixed combination that he is using works, and many of these are effective agents, he may say, "This is an effective agent which in my experience works perfectly well."

What we are really saying is not that this agent does not work well or isn't effective essentially. What we are saying is that the combination is really no greater than one with more potent ingredients, and that it would be wiser in practice to use one drug. It does not mean that he is using a drug which will hurt his patient necessarily. It means that he is using something more complicated when he could use something more simple.

Now, lawyers sometimes use big words when they could use a little word, so it is the same sort of a thing in many respects.

Senator NELSON. But they don't charge more for big words than for little words. The fact is that the patient's pocketbook is affected. I don't know if it is true of all drugs, but those that I have seen that are in fixed combinations cost more than its components would cost if purchased separately.

Dr. KUNIN. Yes.

Senator NELSON. And previous witnesses from schools of pharmacy and medical schools have said exactly the same thing. I think it is a rather sad commentary on the gullibility of the medical profession that they will prescribe drugs in fixed combination which pharmacological authorities say are not any better than separately administered drugs, but do cost the patients more.

Dr. KUNIN. Sure.

Senator NELSON. That is a matter of importance to the people of this country, and I think it is about time that the doctors woke up.

Dr. KUNIN. I agree with you.

Mr. GORDON. Isn't it also correct that when you use a fixed combination, you lack flexibility in varying the amounts to be used?

Dr. KUNIN. Oh, sure.

Mr. GORDON. There are certain disadvantages both to the patient and the doctor; isn't that correct?

Dr. KUNIN. Oh, sure. I list these disadvantages here. I am not trying to be a weasel here, Senator. What I am trying to do, though, is put this in the perspective of how the physician would look at it in the sense that if he has had a good experience with a particular preparation, and there are individuals who I might personally disagree with who would say, "I have had such good experience with the combination of penicillin and sulfur for earaches," that this becomes a part of the common teaching among certain groups of physicians.

Now, I might stand up and say that I think this is nonsense and that you could use one drug, but there is a large body of, we might say, folklore or medical practice that is accustomed to this way of doing things, and that one shouldn't, I don't believe, accuse the physician of directly trying to hurt the patient or his pocketbook, but trying to follow a practice which has been part of the American medical scene for a long time.

So I think one has to have a more dispassionate view, so to speak, of this, and to try to change this practice, but not in the punitive way, necessarily, by saying that physicians don't know what they are doing. They know what they are doing, but they are doing it in a different way.

It is, perhaps, not the best way, but it is an effective way in their type of practice.

Now, I agree with you in principle, but I don't think it is wise to make blanket statements that physicians are not doing or are not desiring to do what is best for their patients.

Senator NELSON. I don't think anybody has said that here, although several witnesses have said that they think that many of the doctors are not well informed about the drugs that they are using.

Dr. KUNIN. That is true.

Senator NELSON. And I think that this is probably the case.

Dr. KUNIN. That is right.

Senator NELSON. In the March 16, 1967, issue of the New England Journal of Medicine a letter from you was printed. You make a very interesting point, and I would like to have the letter printed in the record at this point. I would like to have you look at it, refresh your memory, and extemporaneously give us your comments about it.

(The letter referred to follows:)

NEW ENGLAND JOURNAL OF MEDICINE,
March 16, 1967.

PRICE FACTOR IN RELATION TO DRUGS

To the Editor: The price of the drug is virtually never stated in advertisements from pharmaceutical houses. Informed laymen are particularly annoyed by this, and in some recent books and popular magazine articles, physicians have been, perhaps, unjustly, accused of lack of concern for the costs that the patient must bear. This is of course, only a half-truth since most physicians, particularly those in private practice, are deeply concerned with such matters. A series of recent experiences in treatment of bacterial meningitis with ampicillin brought patient costs to mind once again. It seems of particular importance now that *Time* magazine, in a recent issue, has seen fit to report the value of this drug to the general public.

The advocates of the use of ampicillin have presented convincing evidence that this drug is effective, when used alone in the treatment of meningitis due to the pneumococcus, meningococcus and *Hucmophilus influenzae*, and that it is as good as or better than other forms of therapy. I have no argument with the use of the drug, particularly in cases in which the offending organism cannot be definitely characterized in stained specimens of spinal fluid, and when 1 of the 3 organisms listed above is probably the responsible etiologic agent. I am concerned with the relative cost of ampicillin versus penicillin G, however, and would advocate a switch of therapy to the latter, less expensive drug, once the bacteriology laboratory has reported the pneumococcus or meningococcus to be present. I believe that most clinicians would agree, including those who have performed the valuable studies with ampicillin.

The cost to the patient in our hospital for penicillin G is $0.25 per 1,000,000 units (600 mg.—supplied in vials containing 20,000,000 units), as compared to $3.00 per 500 mg. of ampicillin for parenteral administration. Projecting this to a ten-day course of parenteral therapy, the cost for an adult receiving 1,000,000 units of penicillin every two hours would be $30, and that for ampicillin given as 1 gm. every four hours would be $360. Many clinicians would use even larger dose of the latter drug, particularly in the early stage of treatment. Costs will vary among hospitals and dose schedules in children, but the order of magnitude of the difference between penicillin G and ampicillin will probably be about the same. I believe that the facts clearly speak for themselves.

CALVIN M. KUNIN, M.D.,
Associate Professor, Department of Preventive Medicine, University of Virginia School of Medicine.
CHARLOTTESVILLE, VA.

Dr. KUNIN. Well, this concerns the treatment of meningitis with a new penicillin, Ampcillin, and I think that here we have had a wonderful addition to our medical armamentarium, the addition of this new particular penicillin, because of its great breadth of activity and its effectiveness in this particular form of disease. It does help the physician very often when he has to treat meningitis, which is a serious disease and which may be due to any one of three common organisms. This drug alone will often be quite effective.

Now, the problem arises in that this drug is very, very much more expensive than, say penicillin G alone, and all I point out here is that once the physician does actually have the diagnosis perhaps in a day or two, he can then stop the more expensive drug and go on to a very much less expensive agent for the same therapeutic purpose.

Senator NELSON. Why? Is one of them a specific drug for one of the causative agents?

Dr. KUNIN. That is right. One is more broad and one is more specific.

Senator NELSON. The broad one is the expensive one?

Dr. KUNIN. That is right; so that if one uses his diagnostic laboratory facilities, he may in 24 to 48 hours find out what the true offending agent is. Under those conditions he may decide that it is better to use the broader agent because it still has what he wants, or he may find that he has a fairly simple organism that is treated with a much less expensive agent, in which case he can switch his drugs to the less expensive agent.

This emphasizes the importance, actually, of going back to this advertisement and to my section with the students, about why it is so important to try to find out exactly what is causing the infection or the problem, so that one might use the most specific and least expensive drug, rather than say, "The patient is sick, therefore, I use a drug."

Senator NELSON. You cite an instance of prescribing each of these two drugs over a certain period of time.

Dr. KUNIN. Yes. If one uses 10 days of therapy, I calculated from going down to our hospital pharmacist, the relative price would be $30 for, say, penicillin G, which is fairly cheap and available, versus $360 in our particular hospital formulary for the other preparation. Now, this is in no way saying that the other drug is not valuable and not worthwhile and we should not continue to have it. It is really to emphasize the problem of trying to make the diagnosis so one can use the less expensive drug under the conditions that will permit him to do so. That is why it is so important for the student to learn, you might say, the natural history of disease and diagnosis rather than blind therapy.

Mr. GORDON. I would like to ask you about Pentids, which is the Squibb version of penicillin G. Now, I notice that it is a big seller and it is about six or seven times more expensive than the generic.

As you know, all antibiotics are batch tested. Can you give any good reasons why Pentids should be prescribed by a doctor rather than a generic penicillin?

Dr. KUNIN. No; I have no reason to prescribe this over a generic penicillin. It is the buffered variety. This is probably the buffered penicillin G.

Except, perhaps, as I may have mentioned to you, the fact I believe that there is a formulation for a liquid oral form which is very nice for young children.

Mr. GORDON. I am talking about the tablets.

Dr. KUNIN. In the case of the tablets they are probably essentially identical so far as I know. They have the same amount of the same drug and if it is buffered penicillin G, it is fine.

Mr. GORDON. But the doctor prescribes it simply because it is the name made familiar to him by advertising and promotion?

Dr. KUNIN. Sure. This is a reflection of the tremendous effect of heavy promotion of drugs on the practice of physicians.

Senator NELSON. I think that is all the questions we have, Dr. Kunin. We appreciate very much your taking the time to give us your very valuable testimony. It will be very helpful to the record that the subcommittee is compiling.

Dr. KUNIN. Thank you very much.

(The prepared statement and supplemental information submitted by Dr. Kunin follows:)

STATEMENT OF DR. CALVIN M. KUNIN

Senator Nelson, members of the subcommittee, staff and guests: Before I begin my testimony, I would like to state clearly that the views which I shall present are my own and in no way represent those of the University of Virginia School of Medicine, where I am employed.

My qualifications include the following educational background and experience:

A.B., Columbia College, 1949.

M.D., Cornell Medical College, 1953.

Intern in Medicine, The New York Hospital, 1953–54.

Senior Assistant Surgeon, U.S.P.H.S. assigned to the Communicable Disease Center, 1954–56.

Assistant Resident in Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts, 1956–57.

Research Associate, Thorndike Memorial Laboratory, Harvard Service, Boston City Hospital working under Dr. Maxwell Finland.

Assistant Professor of Preventive Medicine and Medicine, University of Virginia School of Medicine, 1959. Promoted to associate professor, 1964, and to become chairman and professor of Preventive Medicine, effective September 15, 1967.

I am certified by the American Board of Internal Medicine and the American Board of Microbiology.

My fields of special interest include internal medicine, infectious disease, epidemiology and specifically, pharmacologic aspects of antimicrobial chemotherapy. I make no pretense of being an economist or a sociologist, but will try to present my views as a clinical investigator and teacher.

You have presented me with an outline of general questions to be discussed with some latitude to present opinions on other topics and personal experiences. I will follow your outline:

(1) Views concerning drugs under generic names as against brand names

In general, I prefer characterization of drugs by their generic rather than brand names. This is certainly essential in teaching a systematic approach to drug usage to medical students and to people in allied health professions. The relation of drug structure to function is exceedingly important. Generic names usually render themselves much more readily to classification than do brand names. For example, among penicillins it is much easier to discuss the pharmacologic differences between generic names such as: benzyl penicillin, aminobenzyl penicillin, phenoxymethyl penicillin, dimethoxyphenyl penicillin, oxacillin and cloxacillin than the multiple brand names for each of these which would be, for example, Wycillin, Polycillin, Pen–V–K, Staphcillin, Prostaphlin and Tegopen and many, many more, depending upon the names of firms selling them. There are only five tetracycline derivatives on the market, but more than 20 different brand names for them.

This multiplicity of brand names is a source of confusion to students and practitioners and makes it exceedingly difficult to know exactly what they are using and the relative cost to the patient. It is not uncommon to see the same drug advertised by different manufacturers to be a superior product to itself.

About 10 years ago, the competition among purveyors of tetracycline was so intense that various excipients were added, each purporting to give higher blood levels. These "gilded" antibiotics were shown by a number of investigators to be essentially the same and although the noise in this area has quieted somewhat, much of the advertising energy has been directed to long acting preparations which really are not very much, if any more, effective. All of these promotional schemes did not increase the physician's therapeutic armamentarium, but led to much confusion. Small variations on such themes appear to be designed to keep the companies one step ahead of the clinical investigators who require time to catch up with them by careful comparative studies.

Thus, from the point of view of clarity of expression and understanding, generic names are preferred over brand names and I attempt to use only generic terminology in all my lectures and conferences and talks with practitioners. It is of great aid in the ideal hospital formulary in keeping drug inventories minimal and less expensive to the patient.

I have read carefully Dr. Richard Burack's book, Handbook of Prescription Drugs, and, although I might quarrel about a few technical points, and find his catalogue of drugs too incomplete for an adequate reference for physicians other than for cost, I agree with his general theses.

Dr. Burack is primarily concerned with the interest of the patient and the cost of drugs to him. Most physicians are equally concerned about cost and the lists supplied are very helpful, indeed. The practicing physician, however, and I include myself here, is troubled by what the commercial pharmacist might do with his carefully worded generic prescription. How can the physician be certain that the pharmacist will always give the patient the least expensive preparation, or even that he will carry it in stock? It is entirely possible that the pharmacist may charge prime prices for a low cost generic preparation. This problem is minimized, of course, in hospitals armed with a formulary system and conscientious pharmacists, and by agencies which make bulk purchases; but, what about the corner drugstore?

It would seem to me that this issue could be resolved, in part, by routine meetings between a committee of each county medical society with a counterpart committee from the local pharmacists. A semiofficial formulary with enough flexibility to meet special situations could be devised. Care would be taken that marginal manufacturers not be included. I would visualize that both generic and brand name preparations be available, but that the physician and pharmacists decide exactly where generic drugs may be included to best benefit patients. I believe that the physicians should then be supplied with a list of costs in his area so that he may prescribe wisely. In this way, it is hoped, that confidence between the two groups may be established and that the patient will also gain more confidence in the professions that guard his health.

This is the Monopoly Subcommittee of the Senate Small Business Committee and I may seem to have overstepped my bounds by presenting you with what might appear to be collusion between physician and pharmacist; although this is not my intent. I would like to see some force from the private sector protect the patient's pocketbook from overzealous promotion of drug firms, and enable the pharmacist to maintain a smaller inventory.

(2) *The advertising and promotion of drugs and their impact upon medical practice*

One has to be blind, deaf and dumb and to lock his office if he wishes to avoid being deluged with direct mail advertising, journal advertising, visits by detail men and more recently heavy promotion in "throwaway" unsolicited journals which, for the most part, serve as advertising vehicles. Booths are set up in hospitals and agents of drug firms walk the floors. I have no objection to ethical promotion of products, but the matter seems almost out of hand.

I was particularly disturbed one day when my group was given the opportunity to spend time with a medical school class to teach careful diagnosis and management of patients with infectious disease. One of the patients we discussed had a rare, but complicated problem which required good clinical judgment and management. We were very pleased to present to the students the details of the evolution of the problem. We then had a class break for 30 minutes. When the students returned, some reported that they had discussed the problem with one of the detail men. He confidently promoted his product and the students then asked, "If so-and-so's drug is good, why do we have to bother about learning how to diagnose the patient's problem? We could just use that drug." This is, of course, the antithesis of good medical practice and almost undid our teaching effort. Sometimes I feel as though the detail man has more time allotted to him in the "hall medical school" than do teachers of infectious disease in the medical school curriculum. Similar problems are encountered in house officer training.

Medical student exercises in analyzing claims made in drug advertising are very enlightening to them and to their teachers. Such discussions are an important training ground for the future practitioner.

It would be wrong to blankedly condemn detail men. They are often helpful to physicians and simply doing as they are told. Their gimmicks, however, are disturbing. These include unnecessary and useless presents. Steak parties for house officers, gifts of books and medical bags to graduating students and trips to the big city including wives of medical students. This seems to be going much too far. The companies seem to be trying to make friends of impressionable medical students and house officers to open the future office doors to their detail men. A paper by Hagood and Owen, Virginia Medical Monthly *94:* 110–114, 1967 supporting this position, is attached.

(3) The relative efficacy of drugs, especially antibiotics

It is certainly true that antibiotics differ in relative efficacy for various infections. The subject, however, is very complex because of the great variety of disease states which must be treated and the large number of good drugs that are available. One drug can be more effective in a given situation than another while the reverse might be true under different circumstances. For example, penicillin would be preferable in pneumococcal pneumonia to tetracycline, whereas tetracycline might be preferable to penicillin in an infection of the urinary tract or in Rocky Mountain Spotted Fever.

This problem is well covered in good text books of pharmacology in the AMA's new book New Drugs, which is updated each year in the medical literature and as brought out in teaching conferences, lectures and seminars.

One factor that frequently governs choice of antibiotics, is antibiotic sensitivity testing. This laboratory test is usually helpful when properly conducted, but can be misleading. For example, pneumococci (the causative agent of many cases of pneumonia) are uniformly sensitive to penicillin G, the drug of choice. Erythromycin is available for those patients who are allergic to penicillin. No sensitivity test need be done, indeed if they were done, the physician might use an inferior agent. Similarly, in important staphylococcal infections, the drugs of choice are penicilling G for sensitive or one of the new enzyme resistent penicillins for resistent organisms. Patients allergic to penicillin could be given cephalothin or vancomycin. Accordingly, at the University of Virginia Hospital, we do sensitivity testing only for the drugs of choice. If we were to include all the available agents, an inferior drug which looks good in the test might be used and the patient suffer from poor or inadequate therapy.

Unfortunately, it has become a standard practice for certain drug firms to offer to donate sensitivity tests for their own brand of drugs, and to give the laboratory large supplies of report forms with the brand name listed. This often results in duplication, since the generic drug is already being tested, or to the most direct form of advertising of what may be an inappropriate agent. I believe that this practice should be stopped.

(4) Problems connected with continuing education of physicians

Many enlightened drug firms support continuing education programs for physicians. These are usually well attended and the "sell" is so soft as not to be obnoxious. Nevertheless, physicians earn adequate incomes and the courses are not so expensive as to be better funded by medical societies, hospitals and medical schools without the direct support by drug firms. I have no objection to the firms supporting hospitals and medical education, indeed, they must and should be more generous, but I would urge that this be done by general institutional grants that really amount to a sizeable contribution rather than to the frills of a sporadic meeting.

The problem of continuing education is one of the major responsibilities of medical schools. These efforts are now beginning to be well organized. I believe that unobligated funds from the drug firms and government would be of great help in their growth.

(5) Other aspects of this subject

I would like to take the rest of my time to decry the use of fixed combinations of antimicrobial agents.

The combined use of drugs has an ancient history which dates back to an age when therapeutic medicine was little better than witchcraft. Most of the old classic prescriptions which prescribed a variety of ingredients are no longer part of modern medical practice. Combined use of drugs are, however, sometimes of value and a case can be made for using them in antimicrobial therapy. These can be generally summarized as in cases of 1) desiring to broaden coverage in unkown infection, 2) delaying emergence of resistant bacteria to one of the drugs (this is commonly used in treatment of tuberculosis) and 3) achieving an effect not possible with a single agent, so-called synergism when the effect of the combination is greater than that achieved by the addition of the properties of the two agents.

Actually, except in tuberculosis and a rare form of infection of heart valves, combined use of drugs is of little value, except in desperate situations before the physician has adequate information about what bacterial infection is occurring and must use his clinical judgment.

A careful review of fixed branded combinations on the market, including combinations of penicillin and sulfomamides, penicilling and streptomycin, tetra-

cycline and antifungal agents and tetracycline and novobiocin, does not substantiate claims that the combination is superior to one of the agents used separately. These combinations are expensive, deny the physician flexibility in dosage, are primarily promotional devices and have the inherent problem that the patient undergoes the risk of serious adverse reaction to two or more drugs rather than to a single defined agent. The physician can not determine which component is causing trouble if a bad reaction is encountered. I personally believe that we would do much better without these preparations.

In summary, Mr. Chairman, I have tried to give you a brief and honest presentation of my personal views on some of the problems of drug usage in infectious disease. I may have seemed rather hard on the drug industry; I do not mean to subject them to harassment since they have made major contributions to good medical care and will continue to do so. I hope that they will not be overburdened with rules and regulations. I speak to them as a friend who finds some faults, but does so to be helpful. The physician's primary responsibility is to his patient; all other considerations must be secondary.

Thank you.

Enclosure.

[Reprint from Virginia Medical Monthly, vol. 94, pp. 110–114, February 1967]

THE IMAGE OF THE DRUG INDUSTRY, AS SEEN BY TOWN AND GOWN

William J. Hagood, Jr., M.D., Clover, Va., John A. Owen, Jr., M.D., Charlottesville, Va.

(Presented before the Public Relations Section of the Pharmaceutical Manufacturers Association, Sixth Annual Meeting, Hot Springs, Virginia, October 4–7, 1964.

(From the Division of Clinical Pharmacology, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville. Aided by Training Grant HE 5544 from the United States Public Health Service.)

Results of a questionnaire with regard to the pharmaceutical industry and products are presented

During the last years the pharmaceutical industry has repeatedly made headlines—not always to its advantage. Perhaps for this reason, the Public Relations Section of the Pharmaceutical Manufacturer's Association included in its 1964 convention program a panel discussion on the industry's image in the eyes of the physician. In preparing our independent presentations for this program we distributed two questionnaires: one to 200 general practitioners in the rural areas and small towns of Virginia and the other to the medical students, interns, and residents of the University of Virginia Medical Center. The contrasting responses from the two groups have given rise to some discussion and conclusions which may be of interest.

THE GENERAL PRACTITIONERS' QUESTIONNAIRE

There were five general questions on this list, as follows:

1. What is your impression of the pharmaceutical industry? Why do you have the opinion you have expressed?
2. What influences you to use a drug company's product? Why do you think the influences you have expressed are important?
3. Do you favor the continuing use of the medical service representatives or "detail men" by the drug companies? Why?
4. Do you think the cost of drugs is too high, too low, or about right? What would you suggest the pharmaceutical industry do to better inform the patients why drugs cost what they do?
5. What is your opinion of the apparently growing practice of physicians gaining a financial interest in pharmacies and drug distribution firms? Why do you have this opinion?

Of the 200 physicians queried, 80 (40%) responded; these 80 resided in 55 of Virginia's 99 counties and had practiced medicine from three to 61 years in offices located either in open rural country or in villages ranging in population up to 4200. In the following paragraphs, percentage figures will be based on the 80 responses.

In reply to the first question, 64 physicians (80%) affirmed that they have a good impression of the pharmaceutical industry, based primarily on the industry's extensive research programs and high ethical relations. Another 9% were non-commital. Only nine physicians (11%) actually criticized the industry because of exorbitant prices, pushy and garrulous detail men, or excessive advertising.

As reasons for using a specific company's product, 40% claimed to be guided mainly by previous results with the product, 33% by the positive influence of detail men, 28% by the over-all integrity of the company, 21% by medical journals, and 14% each cited the research behind the drug and the relative cost of the drug as being crucial to their decision. There were in all 17 reasons given, the least popular (1 physician, 1%) being the evaluation of the drug by the *Medical Letter*.

Regarding the utility of the detail man, 85% of general practitioners gave him a strong vote of confidence, because his new drug information was valuable to them and he could order drugs directly for dispensing physicians. The other 15% felt that in view of the abundant available literature his services could be eliminated and the resultant savings be passed on to the patient.

Questioned about drug prices 51% of general practitioners thought that they were "about right", and 45% thought that they were "too high"; none considered them "too low." Furthermore, 24% urged a better public relations attempt to help the layman understand why drugs cost what they do. However, one physician urged the opposite course; "reduce the cost instead of spending more money to tell the patient why drugs are expensive."

Finally, the general practitioners were definitely opposed (75%) to the practice of physicians gaining a financial interest in pharmacies and drug distribution firms.

THE MEDICAL CENTER QUESTIONNAIRE

Questions 1 and 2 required a listing of material gifts from drug companies and stock ownership in them. Questions 3–5 asked for a graded evaluation of the pharmaceutical industry on its (1) record in the development and testing of new drugs, (2) margin of profit in prescription drugs, and (3) performance in disseminating information about new drugs. Questions 6 and 7 tried to assess the impact of the new Food and Drug Administration regulations concerning clinical trials in terms of general awareness and reaction. In question 8, each person was asked to compare and rate the following over-all sources of comprehensive information about new drugs: faculty and house staff, scientific meetings, scientific articles, advertisement in medical journals, mail literature from drug companies, detail men, the "Physician's Desk Reference," the *Medical Letter* and drug inserts. Question 9 asked for a correct matching of both the generic names and the therapeutic effects to the trade names of twenty common drugs.

Question 10 was multiple choice: "The pharmaceutical industry could better serve the medical profession by (1) continuing just as it is; (2) cutting prices; (3) developing more new drugs at a faster rate; (4) sponsoring more post-graduate courses; (5) distributing more educational material; (6) changing its advertising policy as follows; (7) changing its drug development policy as follows; (8) changing its detail man program as follows; (9) changing its drug sample policy as follows; or (10) other." Question 11 asked each person to assign a grade rank to the following factors as strongly affecting his opinion (good or bad) of a specific drug company: "(1) advertisements; (2) experience with its products; (3) gifts and services to you; (4) research support; (5) assistance in post-graduate and medical educational programs; (6) detail men; and (7) others."

Returns from this questionnaire were scattered, ranging from a 7% response from the second-year class to a 30% response from the fourth-year class. There were 73 questionnaires completed and returned from the 384 persons polled, an over-all 19% response.

Almost everyone had received some sort of gift from one of the drug companies. Eli Lilly and Company had donated 57 pen lights, 46 medical bags, 45 percussion hammers, 35 stethoscopes, 30 pocket notebooks, 28 tuning forks, 19 pen knives, and 18 tape measures, as well as sundry other diagnostic aids, to the 73 persons polled. Burroughs Wellcome & Company had given 18 pocket notebooks, Ciba Pharmaceutical Company had distributed 11 subscriptions to the *Ciba Symposia*, and Wyeth Laboratories had given 10 pen lights. In all, 19 drug companies were listed as donors, some only once, of generally minor and inexpensive gifts.

Of the 73 polled, six owned stock in one or more drug companies and 58 of the non-owners considered such stock to be a good financial investment.

Most answers rated the pharmaceutical industry's record in development and testing of new drugs as good (41, or 56%), its marging of profit in prescription drugs as wide (35, or 48%), and its performance in disseminating information about new drugs as good (39, or 54%). Most of the other answers were equally divided between the two evaluations nearest the mode ("very good," and "fair").

Knowledge of the current Food and Drug Administration regulations regarding clinical drug trials seemed to be greater among residents than medical students: 26 out of 35 students had at most a vague cognizance of them; 17 out of 32 residents had a fairly good or exact knowledge. Most medical students felt they were "necessary and reasonable", but the residents were divided equally between this viewpoint and "necessary and unreasonable". In addition, five residents felt them to be "unnecessary and unreasonable", and three "highly commendable and long over-due".

The ratings of best sources of comprehensive information about new drugs are shown in Table I. The influence of faculty and house staff rises to a peak during the intern year and then progressively declines. Articles in medical journals appear to be the most consistently respected authority throughout, with the *Medical Letter* running a close second during the post-graduate period. Advertisements, mailed literature and the detail man are usually at the bottom of the list, although the latter performs better during senior residency years.

TABLE I.—Q.8. WHICH DO YOU BELIEVE TO BE THE BEST OVERALL SOURCE FOR COMPREHENSIVE INFORMATION ABOUT NEW DRUGS?

[Legend: M.S.—medical student; I.—intern; R.—resident. Numbers indicate years of training. Abbreviations for sources self-explanatory.]

M.S.2	M.S.3	M.S.4	I.	R.1	R.2	R.3	R.4
Insert	P.D.R.	Journ.	FacHS.	Journ.	Journ.	Journ.	Journ.
Journ.	Journ.	FacHS.	Journ.	MedLet	MedLet	MedLet	MedLet
FacHS.	FacHS.	P.D.R.	P.D.R.	FacHS.	FacHS.	Insert	Meets.
Meets.	MedLet	Insert	MedLet	Meets.	Insert	FacHS.	FacHS.
P.D.R.	Meets.	MedLet	Meets.	P.D.R.	P.D.R.	Detail	Detail
Ads.	Mail	Meets.	Insert	Insert	Meets.	P.D.R.	P.D.R.
	Insert	Mail	Ads	Ads	Mail	Meets.	
	Detail	Ads	Mail	Detail	Ads	Mail	
	Ads.	Detail.	Detail.	Mail.	Detail.	Ads.	

In the matching quiz, some generic names were almost as familiar as their corresponding trade names but there were some impressive discrepancies: 60 persons correctly described Elavil (Merck Sharpe and Dohme) as a mood elevator but only 14 of these knew that its generic name was amitriptyline; 60 persons knew the therapeutic action of Dulcolax (Geigy) but only 23 knew its generic name.

The last two questions produced the most spontaneous responses. The suggestions for the pharmaceutical industry are summarized in Table II. The same general sentiments are reflected in the responses to the last question, illustrated in Table III. The same three sources of dissatisfaction (detail men, advertisements, and gifts) are again apparent.

TABLE II.—*Q. 10. The drug industry could best serve the medical profession by*

Sponsoring more post-graduate courses	18
Distributing more educational material	18
Cutting prices	16
Changing its advertising policy	15
Changing its drug sample policy	15
Changing its detail man policy	14
Developing more new drugs at a faster rate	7
Changing its drug development policy	7
Continuing just as it is	5

TABLE III.—Q. 11. YOUR OPINION (GOOD OR BAD) OF A SPECIFIC DRUG COMPANY IS MOST STRONGLY AFFECTED BY

Factor	Total response	Favorable	Unfavorable	Either
Experience with products	57	9	12	1
Detail men	32	1	7	1
Advertisements	23	2	3	3
Personal gifts, etc	19	6	--	--
Postgraduate educational support	17	8	--	--
Research support	14	8	--	--

COMMENT

It would be imprudent to attempt multiple interpretations of the responses to two different questionnaires, distributed to two different and heterogenous groups, with such a variable percentage of replies. However, the following similarities deserve emphasis.

1. There is general appreciation for and satisfaction with the over-all performance of the pharmaceutical industry.

2. A feeling that drug costs are too high or profits too wide is evident in 45% of the answers from the general practitioners and in 48% of those from the Medical Center.

3. Most doctors judge a drug company by the efficacy of its products, with the activities of the detail man receiving second place in consideration.

In addition, one may ask what is the comparative efficacy of the three forms of advertising: direct mailing, medical journal ads, and the detail man? The physician has a built-in bias against them all, knowing that none is likely to give him what he wants: a carefully balanced comparison of the product vs. (a) older, simpler substances, (b) new products of competitors, and (c) no treatment at all. Also, to make best use of his limited reading time he gladly dispenses with all save the most authoritative sources of information. So it is unlikely that mail literature and journal advertising have any lasting impact; both could probably be curtailed completely without much effect on the practice of medicine.

This is true because in their absence the detail man could serve the same functions. Conversely it is hard to see how impersonal mailings and glossy advertisements could take the place of an ideal detail man; cheerful, helpful, disarmingly proprietary, willing to listen and happy to debate. Although the physician spends time with him, he spends it as he chooses; he can in effect carry on a conversation with a person, with a drug company, or with the entire pharmaceutical industry.

If the ideal detail man exists, he is clearly outnumbered by his imperfect brethren who reportedly interrupt the office routine, parrot steretoyped encomiums, hawk their wares in a truculent manner, and talk without listening. This confrontation destroys the one thing the physician wants: a chance to learn some valid information. Since the physician is unlikely to change his attitude, the pharmaceutical industry must become more information-oriented. The metamorphosis cannot occur spontaneously but requires active and vocal effort on the part of the physician. The following avenues of information have been worked out at many teaching medical centers:

1. A hospital policy for detail men requires that any "detail visit" (five minutes) to any physician be scheduled through a central office.

2. A similar policy encourages drug companies to work through a central office in arranging clinical trials of new drugs, thus bringing together the most promising drug and the best-qualified investigator.

3. Books, films or other educational material can be useful in both medical and post-graduate education; courses and lectureships, research fellowships and honoraria for visiting speakers have been deeply appreciated gifts from the pharmaceutical industry.

4. Occasionally the drug company may support an entire laboratory or clinical research area, where patients are hospitalized for study by all the newer techniques of clinical pharmacology.

Implicit in all of these programs is the presence of a professional persons or persons who maintains a liaison with the drug house representatives and arranges these collaborative efforts. At every opportunity such a person works toward one specific goal—to help bring the best information available from the drug houses to the physicians.

Whenever the physician works actively in cooperation with the pharmaceutical industry in these areas, he appreciates anew its scientific contributions and puts aside his built-in resistance to its commercial aspects. Thus these possible approaches to a closer working relationship, while sometimes apparently restrictive, cannot fail to increase the physician's appreciation of the industry—a reservoir of good will which is a powerful reality and capable of even greater enhancement. The medical profession and the pharmaceutical industry, working together, should bend themselves to that task.

(Whereupon, at 2 p.m., the subcommittee recessed, to reconvene at 10 a.m., Thursday, August 10, 1967.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, AUGUST 10, 1967

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Scott, Javits, and Hatfield.

Also present: Benjamin Gordon, staff economist; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The committee will come to order.

Our witness today is Dr. James L. Goddard, Commissioner of the Food and Drug Administration, U.S. Department of Health, Education, and Welfare.

Dr. Goddard, the committee is grateful that you were willing to come here today to give your constructive and valuable testimony. You may proceed in any way you see fit. I assume you have no objection to my interrupting from time to time with questions.

STATEMENT OF DR. JAMES L. GODDARD, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ARLINGTON, VA.; ACCOMPANIED BY WILLIAM W. GOODRICH, GENERAL COUNSEL; DR. HERBERT L. LEY, DIRECTOR, BUREAU OF MEDICINE; ALFRED BARNARD, DIRECTOR, BUREAU OF REGULATORY COMPLIANCE; AND DR. DANIEL BANES, ACTING DIRECTOR, DIVISION OF PHARMACEUTICAL SCIENCE

Dr. GODDARD. Not at all. We are pleased to be here today.

Accompanying me are William Goodrich, general counsel; Dr. Herbert Ley, Director of the Bureau of Medicine; Mr. Alfred Barnard, Director of the Bureau of Regulatory Compliance; and Dr. Daniel Banes, who heads our Division of Pharmaceutical Science.

We appreciate this opportunity to appear before you and comment on the drug questions this committee is considering. It has been several years since the Senate has considered in such depth the relationship between the pharmaceutical industry, those who prescribe and those who use drug products. Since this relationship—at this time, so closely bound together by new Federal and State health programs—is of principal interest to the Food and Drug Administration, my staff and I are most pleased to appear before you this morning.

As you, Senator Nelson, have indicated several times, one of the major interests of this committee is the pricing of drugs, the actual costs to the patient or the institutional purchasing agent of the life-protecting and lifesaving drugs available. While our agency does not have jurisdiction over prices, nor have we sought it, we are concerned primarily that the American consumer receive quality drugs. The operations of the Food and Drug Administration are geared toward assuring that all drugs are reliable. The administrative work of our agency, the review of data that comes into our medical and compliance bureaus, and our constant surveillance over the drug industry are aimed toward this goal. If all drugs are reliable, then there is a basis for price competition.

I would like to state, and later discuss briefly, the factors that must operate if we are to be sure that all marketed drugs are reliable:

1. There must be honest, soundly conceived, and well-executed research to establish a drug's safety and effectiveness for its intended use before it is marketed commercially.
2. There must be proper manufacturing, packaging, labeling, storing, and shipping of the drug. In short, there must be good manufacturing practice.
3. The existence of good manufacturing practice must be checked not only by the producing firm, but also by a separate impartial agency. The FDA is the impartial agency.
4. Users must have adequate, truthful information about the drugs they employ. Drug names should be as simple and useful as possible, drug labels and advertising should be honest, and summary information about the entire drug armamentarium should be readily available to every professional in the health team.

There is, of course, an additional safeguard which needs no elaboration from me, that is the continuing communication throughout the medical community of information about the results obtained with drugs in clinical practice.

The 1962 drug amendments to the Federal Food, Drug, and Cosmetic Act significantly expanded our agency's authority over drug commerce, and for the first time placed FDA in a position to require correction of a number of abuses that were then apparent.

Senator NELSON. May I interrupt just a moment? Does your agency supply directly to physicians any information, clinical or other, that is important?

Dr. GODDARD. We rarely do that, Senator. We have, I believe twice in the past year, sent a letter directly to physicians. This is a very costly procedure for us as an agency. These were unbudgeted costs and I think each letter ran approximately $40,000 in direct costs to the agency.

Now, there is, therefore, a limitation in dollar costs in direct communications.

Senator NELSON. Would you consider it of value for your agency to have more continuous direct contact with physicians?

Dr. GODDARD. Yes; I think it would be extremely valuable if we had a continuing contact and channel of communication. A two-way channel, by the way, would be most effective between the practicing physicians and the Food and Drug Administration. We would like

to be able to share more effectively information that we have about drugs and in turn, have physicians inform us about their experiences with the drugs that they are using on their patients.

Now, I have no question that as our data processing capabilities develop and as the communications linkages now being tentatively explored are developed that we can be involved much more directly with the practicing community. In some countries—Australia, England, for example—they do have much more frequent communications between the Government agency and the physician than we do. These are smaller countries with fewer physicians, of course.

Senator NELSON. Would it be feasible as some partial achievement of that objective of communication to regularly communicate with the president of the county medical societies, or that your communication be read at county medical society meetings, or that they duplicate it and send it to physicians, that sort of thing?

Dr. GODDARD. This is a possibility that we had discussed in the past. It is one that we have not used and need to explore further, Senator Nelson. There are 3,000 counties in the United States today and this should not be an excessive burden in communication costs for us. The only problem is whether the next step is actually taken to get information from the county medical society secretary to the members. I think in most instances we could count on that being done.

Senator NELSON. What kind of information did you send in the two letters?

Dr. GODDARD. Well, the letters that we have sent primarily are concerned with changes in labeling and adverse reactions to drugs. We have also caused other letters to be sent by firms with respect to their advertising. This was done under our direction, so in a sense, we caused a communication to occur then, too.

Senator NELSON. I think the idea of better communications is a good one. As a matter of fact, I did not know that you had sent the letter, but in 1 week's time, two physicians mentioned to me that for the first time during the course of their practice, they had heard directly from the Commissioner and they were very pleased to have received your communication.

Dr. GODDARD. We get a fair number of letters from physicians, Senator Nelson, who express their point of view about a given drug or about these letters sent to them and raise questions with us. That is fine, too. There is just the very beginning about some communication now between the Food and Drug Administration and the practicing community. We badly need to encourage that. We would welcome the more frequent direct communication, particularly on drug experience, from the practicing physicians.

In turn, we need to get information out to them and we will be exploring a variety of methods for doing this.

Mr. GORDON. Dr. Goddard, can you conceive of a communications network tying the FDA in with every doctor in the country?

Dr. GODDARD. I can if it is a network that is created for purposes other than communication only with the FDA. We did look into the possibility and had a number of meetings with A.T. & T. in early fall of last year, with the American Medical Association, PMA and others involved in these meetings to try to explore the use of the existing telephone network to get messages to doctors quickly when there was a

need for this. Such a capability does exist. The costs at that time were considered to be perhaps excessive. We are also exploring at the present time the possibility of a communication system using the phone, with a number listed here in Washington that physicians could call from, say, 9 in the morning until 10 at night and let us at FDA know their experiences with drugs. Hopefully, this sort of system could someday be expanded to provide information to the physicians upon their request. I would say in direct answer, yes, we do visualize the possibility someday, but no, the price of such a system would not be justified by our need to communicate, but rather, as the communications capability develops in the medical community, we wish to take advantage of it.

The 1962 drug amendments, as I said, significantly expanded our authority over drug commerce and put us in a position to require correction of a number of abuses that were then apparent.

For example, enactment of the 1962 law:

Required new drugs to be proved effective, as well as safe before marketing.

Provided better means for withholding or withdrawing approvals of new drugs.

Gave us authority for the first time to make complete inspection of factories making prescription drugs.

Required drugs to be produced under current good manufacturing practice.

Authorized us to establish simple, useful common or generic names for drugs.

Established an effective control over prescription drug advertising and placed it under FDA.

Extended batch certification to all antibiotics for humans.

The 1962 law also expressed the desire of Congress for more and better control of drugs being tested clinically on man, and required strengthening of revised regulations that FDA had proposed that same year.

Let me now discuss those four factors that must be present if our Nation is to have a good drug supply.

Senator NELSON. Is there any reason why batch certification of all drugs used on humans would not be feasible? Is there anything peculiar about antibiotics?

Dr. GODDARD. You recall antibiotics are used in what one would have to term lifesaving situations. The antibiotics developed largely after World War II in terms of the number that were being marketed, and it was felt that careful control had to be exercised because of the complex production process. Thus these controls were put into effect and batch-by-batch certification has been carried out now since 1962 for antibiotics. I believe that insulin batch-by-batch certification preceded that in 1941. These were the basis for batch certification.

Senator NELSON. Are there any other drugs that ought to be batch tested?

Dr. GODDARD. We did propose to Congress last year, Senator, that the Secretary of Health, Education, and Welfare be given the authority to extend batch certification to those drugs that were significant drugs or for which the health of the public might be more directly protected under such circumstances—such potent medications as corti-

costeroids, for example, were considered as potentially susceptible of this approach. This legislation was not acted on last year. It is something that is currently under study by the Food and Drug Administration along with other methods of helping to assure the quality of drugs in the marketplace.

Senator NELSON. Thank you.

Dr. GODDARD. Before 1938, drug research and investigation was predominately empirical; the law did not require conclusive establishment of either the safety or the efficacy of a drug before marketing. Many discoveries were fortuitous. In many instances serious side effects were discovered only after the receipt of complaints as the drug was distributed widely.

One of the most important provisions in the 1938 Food, Drug, and Cosmetic Act was a requirement that all new drugs be studied and evidence of their safety be submitted to this agency for approval before the products were shipped. Here we see a major step toward rational therapeutic science. This was a substantial improvement in scientific method as well as in the law. After 1938, the accumulation of at least some clinical data was necessary before a drug could be marketed. The Food and Drug Administration, in administering the law, could require the accumulation of preclinical and clinical data according to a reasonable protocol before allowing the drugs to be marketed. But again let me emphasize that approval of drugs under this 1938 act was only contingent upon a showing of safety—not a showing that the drug would be effective for all of the conditions for which it was to be offered. The 1962 amendments correct this deficiency by requiring a showing of effectiveness, as well as safety.

At present, no drug may be shipped across State lines for experimental use in man until certain requirements, which are set forth in our investigational new drug regulations, are met. Some of the key provisions of these regulations are:

The sponsor of an investigation shall prepare and present an acceptable plan for the investigation. The plan describes the drub, outlines the experimental procedure, and identifies the qualified person who will conduct the studies. It establishes mechanisms for monitoring the studies, reporting on their progress, keeping all investigators as well as the agency informed of any hazards that are discovered, and taking the needed steps to carry the investigations out in a way that would minimize the risks to subjects of the experiment. The subjects, incidentally, must consent to participate, except in certain well defined situations where obtaining consent is not feasible or is not in the interest of the patient.

Senator NELSON. Has this provision of the law been complied with consistently by those doing the testing?

Dr. GODDARD. This particular provision was implemented under the regulations that we issued last September, as I recall, and took effect July 1 of this year. This was debated rather extensively in the scientific community. We had a number of meetings with clinical investigators about the provisions of these regulations and modified them slightly in accord with and following these discussions. But we think we have followed the lines that Congress intended us to in the 1962 amendments.

Senator NELSON. Did the 1962 amendments require that patients

be informed if an experimental drug is going to be used in treating them?

Dr. GODDARD. Yes, except in those two instances.

Senator NELSON. In what two?

Dr. GODDARD. Where it was not feasible because of the state of the patient in terms of either his consciousness or awareness, and second, when it would be detrimental to the best interests of the patient.

Senator NELSON. Then those cases which we have read about where physicians actually either falsified the record, or didn't ask the patients, were clearly violations of the law?

Dr. GODDARD. They would have to be construed that way, sir. I would like to point out that in terms of physician investigators, the agency has had relatively few of these whose data has been falsified. This has only happened in a handful of cases, and we do have 25,000 investigators of record at this moment. So by and large, I would have to say that the physicians have conducted themselves in an exemplary fashion.

Senator NELSON. 25,000?

Dr. GODDARD. Yes, sir.

Senator NELSON. Full-time investigators?

Dr. GODDARD. No, sir. Not full time. You see, the firms, particularly in large pharmaceutical manufacturers, who sponsor much of the research, use large numbers of investigators, particularly in phase 3 investigations, when they are trying to test the drug under conditions of usual usage. They may go to 100 obstetricians and gynecologists to try a drug that would be particularly useful in their practice. Then there may not be occasion for that particular company or any other company to call upon that group of physicians for some time—several years or even longer. So there are a large number of persons whose names are on our files as active investigators, "active" in quotes.

Senator NELSON. You are not talking about investigators who review the work done by the physician who experimented with a new drug?

Dr. GODDARD. No, no.

Senator NELSON. I see.

Dr. GODDARD. They are clinical investigators.

The agency keeps current on investigators, either from reports or through inspection, requires that the studies be carried out according to a rational plan, requires modification of the plan if necessary, and occasionally orders the investigations discontinued if the plans were not adequate, were not being followed, or if the investigation produced evidence that it was unsafe to continue.

Currently, the Food and Drug Administration has 2,188 active investigational new drugs—IND's—on file, with an annual entry of new IND's running at a current rate of approxmiately 700. Thus, about a third of the IND's on file at any one time are new for the year; another quarter will be discontinued within the year.

The point which I wish to make here, Senator Nelson, is that with the IND procedure, FDA has a chance to follow drug research from the beginning; we are thus better able to react when the manufacturer requests that we approve commercial marketing of the new drug. The manufacturer requests such approval in an application which we call a New Drug Application, or simply an NDA. The NDA contains or

refers to all the evidence upon which the manufacturer bases his belief that the product is safe, and effective, and also contains copies of the labeling which he proposed to use in promoting and selling the product—the submission of this labeling and our approval of it have an important bearing on truthful advertising of prescription drugs as will be discussed shortly.

Senator NELSON. The New Drug Application does not involve the question of patent?

Dr. GODDARD. No, sir.

Senator NELSON. So this is a nonpatentable drug?

Dr. GODDARD. The drug itself may be in addition patented by the manufacturer. I believe the patent period is 17 years, which gives him commercial exclusivity.

Senator NELSON. Are most of the New Drug Applications drugs that are nonpatentable?

Dr. GODDARD. Of the NDA drugs in the past decade, as a rough estimate, 50 percent of them, I am told, would be drugs that are not patented. However, I must point out that the members of the industry have said to me in discussions that holding a valid NDA is as good or better than having a patent.

Senator NELSON. Why?

Dr. GODDARD. Because of the policy of the Food and Drug Administration. We do not make public the information submitted by a manufacturer with respect to the clinical studies, the preclinical animal studies, the toxicity data——

Senator NELSON. What is that now?

Dr. GODDARD. We do not make public any of the data submitted by the manufacturer in his NDA.

Senator NELSON. So if a nonpatentable drug goes on the market, and another company desires to manufacture it, it would have to make a chemical analysis of the drug, perform the animal and clinical testing that the law requires, and then present the New Drug Application to FDA for exactly the same drug that has been adequately tested before, is that correct?

Dr. GODDARD. That is correct.

Now, the timespan covered from the discovery of a chemical entity until its ultimate marketing, on the average, through the NDA procedure is about 7 years.

Senator NELSON. The timespan for what?

Dr. GODDARD. The discovery of the chemical entity, its testing in the laboratory and all the steps it has to go through right up to marketing with a valid NDA, is approximately 7 years. So you see if a company can get an NDA approved and get into the marketplace with a drug, their leadtime may be sufficiently great that they can capture a significant share of the market and hold it for a long period of time.

Senator NELSON. Well, the same applies if a drug is patented. Then for 17 years, if it is a good, valid patent, the manufacturer has exclusive control in this country over the sale and distribution of that drug; is that right?

Dr. GODDARD. That is correct, sir.

Senator NELSON. I assume that the circumstances are different between a New Drug Application and the requirement that any competitor go through the experimental process when a patent expires.

Dr. GODDARD. The difference there would be that there would be a body of established literature after 17 years that would permit the truncating of the New Drug Application. The individual firm then involved could submit a shortened NDA, a short form NDA, in essence, citing the world's literature with respect to clinical safety of the drug and so on. It would still have to submit, however, the manufacturing procedure, the quality controls, the labeling that is to be used and in some instances, even some clinical studies showing that the drug manufactured by that process would produce the effect that to be claimed. This is particularly true in the antibiotics field.

Senator NELSON. Did I understand you correctly that once the patent expires, Food and Drug does not require any manufacturer of the drug on which the patent has expired, to repeat through all the clinical testing.

Dr. GODDARD. Not all of it, no. As I say, some of the information to support an NDA that the manufacturer sends in can be drawn from the existing world literature. But there is still some duplication, Senator, make no mistake about this. Some of the toxicity studies would have to be repeated on animals and some of the clinical studies may have to be repeated—not in every instance, though.

Senator NELSON. Is there any reason for requiring any extensive testing of prednisone which has been on the market for 17 years and is being produced by 50 companies? Along comes a company which wants to produce the drug and if they meet the requirements of USP, is there any reason why they should go any further?

Dr. GODDARD. We think there is a reason they should submit a New Drug Application in order that we may control the labeling, the advertising that surrounds the drug, have knowledge of the manufacturing process that is going to be employed. We feel that the drug should come in under the NDA procedure.

Now, the part that Congress itself has never discussed, Senator, is whether or not this information that we hold in our files should be made public and thus avoid duplication of scientific effort and repetition of certain kinds of experiments. And it is not only for the drug that is now coming out of the patent protection status after 17 years. This holds true for those drugs that are not patented and thus could be marketed by additional firms at any time. In other words, those in which 17-year exclusivity is not involved.

Now, in most of those instances, the complete work has to be duplicated. All the clinical trials, additional subjects studied, all the preclinical animal data has to be duplicated. I think this is a question that Congress must examine, however, with respect to the policy of FDA. In the 1962 amendments, the language, the legislative history, shows no consideration of this at any time.

Senator NELSON. But there is no statute that sets out this requirement——

Dr. GODDARD. No, sir.

I think that with regard to a policy that has been in effect as long as this one has by the Food and Drug Administration, I would, as an administrator, be guilty of overturning what amounts to——

Senator NELSON. A bad rule.

Dr. GODDARD. I do not mind overturning a bad rule. But this is something that I think the Congress itself has to study. This is an established policy, it is an accepted policy. I think it needs debate and

discussion by the scientific community as well as the drug firms involved.

Senator NELSON. Well, speaking for a moment of a patented drug. The company that has the patent has gotten from the Congress 17 years of exclusive use, which is a good long time. Then, as the Commissioner is well aware, once a drug has occupied the market for 17 years, the habit of prescription is such that the original product most often dominates the market thereafter. They may reduce the price, but they have the advantage of having dominated the market, and of having had 17 years of experience with producing the drug. Is there any reason at all why, once a patent runs out, that the FDA should not then open up its files to reveal all of the information and background testing, instead of preserving an unfair competitive situation at great expense to the public? The Congress did not intend a patent to run beyond 17 years, but in effect, this kind of secrecy keeps small competitors who could not afford the testing out of the market. It just hampers competition unnecessarily.

What is the justification?

Dr. GODDARD. Mr. Goodrich, do you want to supplement my earlier remarks on this?

Mr. GOODRICH. Our concern, Senator, is not with the patent, but with the drug being safe and effective for the purposes for which it is offered. Now, through the drug procedures, there are fundamentals that the labeling be controlled and that there be established a system to keep us up to date on those drugs. It is a gross oversimplification to say that simply because the two drugs are the same by clinical test, they will have the same chance or you will get the same experience from them. Now, it is important to us——

Senator NELSON. That you get the same experience?

Mr. GOODRICH. You may get a report of an adverse effect from one drug that you do not get from another. It is very important to us, we think, that we get complete reporting of clinical experience with the drugs and the only way to do that is through the new drug procedures. Now, even with an unpatented drug, before the 17 years runs out, if the date is made available in the scientific literature, it is possible for other manufacturers to use that to obtain an effective approved New Drug Application.

Senator NELSON. You can't get a New Drug Application when there is an existing patent.

Mr. GOODRICH. No, I am speaking of the unpatented drug. With an existing patent, he might get an approved New Drug Application, but would not be allowed to market it because of the patent laws.

Senator NELSON. I do not think you have responded to me. Maybe I did not state the question very clearly. The question is what is the policy reason, at the expiration of 17 years of the patent, for the FDA not immediately making public all the information it has about the drug, including the experiments on the animals, experiments on human beings, and so forth. Why should that not become public information forthwith?

Dr. GODDARD. There is no reason why it should not be, but when the Congress passed the Freedom of Information Act, which provided that commercial and business information be exempted from public disclosure. There is a provision in the Criminal Code that prohibits

us from divulging information of this kind. Also, there is provisions in the Federal Food, Drug, and Cosmetic Act about trade secrets.

Now, these provisions collectively were the basis for the policy established some years ago. It has been followed. We have said in 1962, and repeat here again today, that if Congress wishes us to make that information available generally to other manufacturers, we are prepared to do that. But we think it was presented to us as business and commercial information and thus we have not made it generally available. We do, however, accept in New Drug Applications scientific data about these drugs which is reported in the open literature and allow other firms to rely on that.

Senator NELSON. Have you been advised by the Attorney General's office that it would be illegal for you at the expiration of a patent, when all legal protection is ended under the law, to disclose everything you know about a drug?

Mr. GOODRICH. We have not. We have asked them several times their interpretation of title 18, section 1905, I believe it is, how they interpret that. We have not received an awful lot of help from them.

Senator NELSON. You have not had an answer?

Dr. GODDARD. They have not told us that we could do it and in the recent Attorney General's manual on the Freedom of Information Act, there is a discussion of commercial and business information which covers this kind of information. That is an exception to the open disclosure.

Senator NELSON. You mean commercial and business information that the Government picks up from a business you are not permitted to reveal to his competitors?

Dr. GODDARD. Right.

That is what we are talking about here.

Senator NELSON. It is really not the same question where a patent is involved, is it?

Dr. GODDARD. I think it is broader than the patent policy. This is the very point.

Senator NELSON. This does not seem to me to be a very sound public policy position. The Congress gave a 17-year exclusive right of protection under a patent. I do not think anybody intended that such protection should continue beyond that time.

Let me ask you another question. You are much stricter then, under the requirements of the New Drug Application. Do I understand correctly that if company A makes a New Drug Application for a drug that is not patentable, is on the market for 4 or 5 years, is a good drug, and then another company wants to put it on to the market, you require company B to go through the same clinical testing that you required of company A; is that correct?

Mr. GOODRICH. We may or may not.

Dr. GODDARD. We may if the scientific literature does not provide a sufficient amount of information with respect to clinical studies. In that case, company B may be required to repeat, in effect, those studies carried out along the same lines by company A.

Senator NELSON. How often do you permit a company to submit a New Drug Application on the same chemical formula as one that is on file without requiring any clinical tests at all?

Mr. GOODRICH. It is very infrequently that we say no tests are necessary.

Senator NELSON. Clinical tests.

Dr. GODDARD. Very rarely.

Mr. GOODRICH. But we say in every instance, Senator, that you can refer to and use in your New Drug Application scientific data in the open published literature as part of the New Drug Application. We want to be sure that these drugs are safe and effective and we believe that as a general rule, there should be at least some clinical testing of all new drugs by whomever put them on the market.

Senator NELSON. Well, I understand the Commissioner to say that the New Drug Application is almost better than the patent.

Dr. GODDARD. That is what I am told, Senator.

Mr. GORDON. It is better.

Senator NELSON. Now, when company A makes a New Drug Application which meets the standards of clinical and other testing and you issue the New Drug Application, is there anything to prevent company A from licensing company B to produce that drug?

Dr. GODDARD. Company B would then have to provide proof that they had obtained such permission and also get an NDA approval by FDA. This would be done on the basis of incorporating by reference in their NDA the material submitted by company A.

Senator NELSON. So we are in the most unusual position where a private company has more authority to delegate the right to manufacture a drug than is exercised by the FDA?

Dr. GODDARD. Yes, sir; in a sense.

Senator NELSON. That is an incredible situation.

Dr. GODDARD. We hold the final approval authority. Now, that is a business arrangement, the licensing arrangement, over which I do not believe we should have any control. Now, we do, however, control the NDA that the second firm may get.

Senator NELSON. If you require that company B makes a New Drug Application for exactly the same compound for which an NDA has already been granted to company A, the basis for your position that there has to be some clinical testing is, I assume, the protection of the patient. Why is it that then company A, fine as it may be, which has no official public responsibility, can take the New Drug Application that the FDA gave them and license B, C, D, E; if you look at prednisone there are at least 22 companies that Schering licensed. You say you do not have any right to interfere in licensing. This is not a licensing question, it is a health question.

Dr. GODDARD. Oh, we do have the authority to make certain that the health of the public is being protected in this fashion. Each one of those 22 firms then has to get an NDA approved by FDA.

Senator NELSON. But you allow them, if I understand you correctly, Doctor, to incorporate the testing that was done by company A.

Dr. GODDARD. The clinical testing.

Senator NELSON. Yes.

Dr. GODDARD. The manufacturing controls and manufacturing procedures and submission of samples and the factory inspection, however, are carried out de novo. The labeling is also under our jurisdiction, and thus the advertising is controlled. The only thing that is omitted in that instance is the animal toxicity study and the clinical testing on humans.

Senator NELSON. But why can't you have confidence in company B taking a compound that is available to everybody in the market, and

without any clinical testing at all, produce tablets to go on the market—B, C, D, E, F, G, H, the whole series of companies—just because Schering, say, licensed them? You say, well, if Schering licensed them, they are able to incorporate Schering's clinical research into their application and that excuses them from going this long route, which you have testified takes as long as 7 years.

Dr. GODDARD. That is correct.

Senator NELSON. I do not get an answer that rings any music in my ears.

Dr. GODDARD. We are having trouble communicating, Senator.

What I are trying to say is we are protecting the public's health in that instance by making certain that the company is capable of producing the drug and producing it properly, with the right manufacturing controls, quality controls, under sanitary conditions, without contamination of the tablet. Now, we yield and say, yes , company A proved this drug to be safe and effective. We don't need any further proof than that because Schering, or company A, has on a business arrangement permitted all these other companies to use the clinical information they submitted.

Now, we accept that, just as we will accept use of the world's literature to prove safety and effectiveness for drugs that are not patented. It is the same situation, Senator.

In those instances——

Senator NELSON. Did you say same or strange.

Dr. GODDARD. Same.

Senator NELSON. I just wanted that in the record. Well, it is a strange situation to me. It seems to me that you have a situation where——

Dr. GODDARD. Well, I think I can see why you feel it is a strange situation. I also feel that there is some unnecessary duplication involved in these activities, and that is why the question comes up. I think properly that the question should be discussed by Congress in terms of the scientific community and the business community involved. Congress should get down to the issues involved here and see whether or not the interest of the public at large might better be served by a public policy which permitted disclosure of the clinical, the scientific information incorporated in New Drug Applications.

Senator JAVITS. Would the Senator yield?

Are you prevented in making that public now?

Dr. GODDARD. Senator Javits, we think we are. I as an administrator think the past policy of not revealing this type of information in effect binds me not to change the policy until there is proper discussion by Congress.

Senator JAVITS. Well, why do you say discussion? Do you want law by Congress, do you want a recital in the congressional report? What do you want?

Dr. GODDARD. I think it would require law in this instance—a change in the law.

Senator JAVITS. So though the law does not actually foreclose you, you still want affirmative law to release you, is that right?

Dr. GODDARD. That is correct, sir.

Senator JAVITS. Because you say the practice has been such that it makes you feel you cannot do it?

Suppose the President told you to do it? Would you have authority to do it under the law?

Dr. GODDARD. I would have to ask Mr. Goodrich, my general counsel.

Senator JAVITS. What about asking him, then?

Mr. GOODRICH. The recently passed Freedom of Information Act which you are, of course thoroughly familiar with, continues the exemption for commercial and business information from public disclosure. This is the policy that we have followed over the years and we propose to follow it from here in, up until the time that Congress changes the law.

If the President directed us to make commercial and business information available, this is an exemption from the disclosure which could be waived by Executive direction at that level.

Senator JAVITS. Well, I have been kind of browsing through your statement. You indicate that you would recommend that where firms are marketing the same compound, that is page 14; that is correct, is it not?

Dr. GODDARD. Yes.

Senator JAVITS. FDA would recommend that this be done and that is one of the things that can be recorded if we choose to espouse it as a recommendation of these hearings. Is that correct?

Mr. GOODRICH. We are recommending that that issue of policy be examined by the Congress and according to our position in the testimony, we believe that it might be very worthwhile to shift from an individual licensing situation to a rulemaking situation.

Senator JAVITS. One other thing you said that finds an echo in my mind. You said something about your authority with respect to advertising, a subject which we have heard a good deal at these hearings dealing with the alleged overwhelming volume and intensity of advertising as very much boosting costs. Yet I see you claim to be pretty powerless in this regard. Your statement says at the top of page 12:

> To say that our Agency has had some difficulty with claims made by many companies in drug advertising is to understate our experience of the past year or so.

Do you wish us to believe that you do not have enough authority? If so, where are you deficient in authority?

Dr. GODDARD. I was not raising the question of authority there, simply trying to cite the problems we have had with firms exceeding the permitted labeling and the difficulties we have had to get them to adopt the basic concept that drug advertising is educational and thus should be truthful, that it differs from advertising of motor vehicles and other items in our economy, that there is a special significance here. That is what I was trying to get at, Senator Javits.

Senator JAVITS. Well, do you have authority to enforce that?

Dr. GODDARD. Yes, and we are enforcing it now. We have proposed for adoption new regulations on drug advertising. September 1 is the final date for receipt of comments. These regulations are being studied by the pharmaceutical industry at the present time.

Senator JAVITS. Well, one would get the impression that you are being run by events and that you are not running them. You have the authority and yet you sort of give the feeling that your hands are tied. What are we to conclude?

Dr. GODDARD. Well, perhaps this is not properly stated, Senator. I have 10 men in the advertising division who have to review all drug advertising put out by the pharmaceutical industry. Now, as a matter of priority, we have tried to concentrate on new products entering the marketplace, to try to catch misleading promotional campaigns in the early days before the misinformation gets firmly implanted in the physician's mind. So, in terms of extent of coverage, we perhaps have not been as comprehensive as one could or might determine desirable. But we think we have the authority. In fact, we have been getting corrections of misleading advertising put out by pharmaceutical firms in the form of "Dear Doctor" letters mailed to every physician.

Senator JAVITS. But we are justified, then, in the impression that up to now you have been sort of overwhelmed by the problem and by these practices and you have not been able to do too much about them. You have gotten some corrections, you have amassed some "Dear Doctor" letters; you have a small staff, you are issuing regulations which are being considered, but really, the problem has inundated you? It has certainly been testified to us as if you did not have any power over it at all, and that things were just running wild.

Dr. GODDARD. Well, Senator, I think it is just a question of the volume that is involved. I am told the expenditures in drug advertising, in all forms of drug promotion, exceed $800 million a year. Now, we in truth can't review every ad in every journal. I do not think this would be desirable. What we have been trying to accomplish is, through our selective actions, to get the pharmaceutical manufacturers to exercise some leadership and to voluntarily see to it that their ads are honest, truthful, and provide the information as Congress intended, in fair balance.

Senator JAVITS. Well, now, you have not even issued adequate regulations to make them do that, let alone policing the authority that you have.

Dr. GODDARD. Senator, we think these regulations that are out now are more adequate than the ones that were issued in 1963. I personally thought the ones issued in 1963 were adequate in both the degree of detail they provided and in expressing what was intended. But, continually I heard the complaint from the firms that came into my office that the regulations were not explicit enough, they were not clear on what is meant by "in fair balance." So these new regulations are more detailed.

Senator JAVITS. Well, now, have you tried any enforcement against firms you thought were abusing the old regulations?

Dr. GODDARD. Yes; we have seized products in the marketplace in at least three instances in the past year. We have in other instances had the firm come in and we have sampled their product. In the event that they chose not to issue corrective letters and drop their misleading journal advertising, we have been prepared to go the other route of bringing the issue before the courts. So we have taken action of that nature.

Senator JAVITS. But you have obviously not taken enough action to have a material effect on the situation.

Dr. GODDARD. Senator, I may be an optimist, but I begin to feel that I am seeing some improvement in journal advertising. I look at these journals and I have greater difficulty in finding violative ads

just on quick inspection. I think that the firms have a desire to improve their advertising. They believe that we are going to enforce the law and the regulations that were put out under the law. And this has been an important factor.

The agency did not, from 1963 until 1966, take many actions on drug advertising.

Senator JAVITS. Well, now, with reference to the efforts at self-regulation, have you had any meetings of the whole industry where you laid down the law?

Dr. GODDARD. We have had meetings on self-regulation with representatives of the PMA, a committee that was appointed by their organization to discuss this. We have had meetings with individual companies. I have spoken to the entire membership of the PMA, as well as the Drug and Allied Products Guild and expressed my concern on this subject. We had a meeting of the advertising firms in New York that was attended by over 700 individuals last fall. We met in Chicago. I personally spoke before the midwest advertising group and people from the west and east coast were also in attendance. The ballroom was filled at that hotel. I think that the industry has had ample opportunity to learn from us what our position is.

Senator JAVITS. Under those circumstances, I request that you submit for the record your plan, including personnel and cost, that you feel would be required in order to really perform the duties vested in you by the law in respect of this matter.

Dr. GODDARD. I would be happy to do so.

(The information referred to, subsequently received, follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING THE PLAN FOR IMPLEMENTING MEDICAL ADVERTISING SECTIONS OF THE 1962 AMENDMENTS

The Division of Medical Advertising currently has a staff of eight full-time professional employees. It includes one Medical Officer, the Division Director; four PHS Scientific Associates, two physicians and two pharmacists assigned to FDA by PHS; two Food and Drug Officers; and one advertising analyst. The cost in fiscal year 1967 for this program, including the salaries and expenses of the professionals together with benefits and clerical support, was approximately $125,000.

The following is a list of some of the activities of the Division of Medical Advertising in fiscal year 1967:

Citations and hearings	7
Seizures (Lincocin, Lasix, Indoklon)	3
Prosecutions filed	3
Letters to firms regarding corrections, advisory opinions, etc	70
Meetings with firms on advertising matters	75
PDR and supplement monographs reviewed in fiscal year 1967	170
PDR and supplement monographs reviewed in fiscal year 1966	36
Participation by division personnel in public meetings, seminars, etc., on medical advertising	4
Drugs subject of "Dear Doctor" remedial letters issued by the drug sponsors at request of FDA	14

To accomplish the desired program in fiscal year 1969 would require a total staff of 13 physicians and 10 other professional health personnel. The cost of such a program, including clerical support, benefits and miscellaneous expenses, would require a funding of approximately $418,000.

In addition, it should be noted that the Division of Medical Advertising regularly uses as consultants Medical Officers of other areas of the Bureau of Medicine, especially those Medical Officers whose evaluations contribute to the approval of the NDA for the drug being advertised.

Senator JAVITS. That seems to me to lead to the key thing which our chairman has directed our discussion. It seems as if you have the authority to work out names for these drugs, so the public can buy generic drugs and be confident in purchasing drugs. Is this a field where you have inadequate staff and inadequate organization to do what needs to be done?

Dr. GODDARD. I believe we have an adequate staff in this area, Senator. We have been working with the USAN, U.S. Adopted Name Council. Last fall we did propose for adoption 27 names that they had recommended. We now have membership on the council, something that we did not have before so we have a voice in the actual selection of the generic name that is to be used.

Senator NELSON. What is the composition of the committee that selects the names?

Dr. GODDARD. A representative of the USP, a representative of the industry, a representative from the American Medical Association, a representative from the National Formulary, and an FDA representative.

Senator JAVITS. But the 1962 amendments, you say, authorized FDA to establish simple useful names for drugs. Now, people who have been in business, and I have very extensively as a lawyer, realize that when you have the muscle, it is a lot easier to get cooperation than when you have not. Has the FDA asserted this authority to fix the brand names itself in a wholesale way—that is, fix the names itself, if the industry did not? Twenty-seven certainly sounds like a real drop in the bucket.

Dr. GODDARD. We have not on the generic names. Now, every firm that brings a drug into the marketplace has to suggest a generic name at that same time. This has been done since 1962, but FDA as an agency has not exercised that authority and did not until last fall.

Senator JAVITS. Will you be good enough to give us also a memorandum as to what it will take to exercise that authority effectively so we get some action in this field which as one Senator, I feel is more important than anything else in this business. That is how competitive forces operate. If a fellow calls for a drug with a very simple name, it takes all the Romans out of the name business.

Thank you, Senator Nelson.

(The information referred to, subsequently received, follows:)

STATEMENT ON A PLAN OF ACTION BY FDA FOR IMPLEMENTING THE PROVISIONS OF THE 1962 AMENDMENTS WITH RESPECT TO ADOPTION OF OFFICIAL NAMES OF DRUGS

The United States Pharmacopeia (USP) and the American Pharmaceutical Association (APhA) through its publication of the National Formulary (NF) have been selecting nonproprietary names as the official names for drugs included in these compendia since well into the last century.

The Council on Pharmacy and Chemistry—later the Council on Drugs—of the American Medical Association (AMA) undertook in 1910 the selection of nonproprietary names for new drugs in collaboration with the respective sponsoring pharmaceutical firms. This served a useful function in that the inclusion of newly developed drugs in official compendia was often delayed for several years or they were never accepted as official drugs. On eventual acceptance of new drugs by these compendia, however, the nonproprietary names selected by the Council on Drugs of the AMA were usually adopted as official names. This mutual interest between these organizations led to the formation of an AMA–USP Nomenclature Committee in June 1961 and then to the United States Adopted Names (USAN) Council in January of 1964 for the purpose of selecting nonproprietary names.

The USAN Council, sponsored by the AMA, USP and APhA (publisher of the NF), negotiates with manufacturing firms in the selection of nonproprietary names for drugs which it is understood will be adopted as official names if the drugs are included in either compendia. On tentative selection by the Council of a nonproprietary name it is submitted for comment to collaborating organizations—FDA, WHO and the pharmacopeial commissions of the British, French and Nordic countries. By this procedure conflicts of the proposed names with existing nonproprietary names or trademarks may be revealed and avoided in the final selection. This collaboration, however, does not assure the selection of the same names by these organizations. Although the names adopted by the USAN Council do not have statutory recognition many of them eventually achieve this recognition by acceptance in official compendia and they have as a general rule been accepted as nonproprietary names in the approved labeling of drugs by FDA.

The 1962 drug amendments gave the Secretary authority to "designate an official name for any drug if he determines that such action is necessary or desirable in the interest of usefulness and simplicity." FDA has initiated action to assure the selection of names which are in fact simple and useful and to designate them as official by publication in the *Federal Register*.

On April 20, 1967, official names for 28 drugs were published in the *Federal Register*, following publication for comment in August 1966. These were names originally selected by the USAN Council. The list would probably have included others if there had been no question of their usefulness and simplicity.

In the fall of 1966 FDA approached the USAN Council in the interests of promoting the selection of simpler names which would be more useful to the health professions, in order that the names selected by the Council could routinely receive official recognition by publication in the *Federal Register*. This led to two important developments. The first was a revision of the existing guiding principles of the Council for the selection of names. This was accomplished by incorporating into them a number of guidelines recommended by FDA. The resulting "Guiding Principles ***" are published in the current (number 5) edition of "United States Adopted Names," and in the 1967 edition of "New Drugs Evaluated by the AMA Council on Drugs."

A second development was an agreement between the sponsors of the USAN Council (AMA, USP and APhA) and FDA whereby the latter would appoint a member to the Council and agree to accept any name on which the Council is unanimous as the established or official name. In the event that the USAN Council cannot reach a unanimous agreement on a name the Commissioner of the Food and Drug Administration reserves the right to select the official name. For the latter purpose it is the intention of the Commissioner to appoint a committee, expert in this area, to advise him should the occasion arise. The program under this agreement has been operative since June 24 of this year with Dr. Ralph G. Smith as the FDA representative on the Council. An intramural Advisory Committee on Drug Nomenclature is being appointed to assist Dr. Smith on any special nomenclature problems encountered in relation to USAN activities or otherwise. The publication of additional official names is currently in process and it is intended that such publications will be a continuing operation.

This arrangement promises to have merit in that FDA obtains the services of an experienced organization with established procedures for the selection of appropriate and available names while retaining its legal authority to make its own selection in case of disagreement. It is also advantageous to the USAN Council to the extent that the names which it unanimously selects will be accepted as legally official names.

Through our policy of cooperation with the USAN Council will result in gradual, periodic designations of official names, it has the overriding merit of using a recognized organization with established procedures and expertise in this area.

The Food and Drug Administration budget allots some $50,000 per year for this activity which is carried forward by a medical officer and support staff, aided by expert consultants.

Senator NELSON. When did Congress take the power away from the companies to formulate the generic name for the drugs they develop?

Mr. GOODRICH. Congress did not take the authority from the companies to formulate names. What it did in 1962 was to provide that

the agency could adopt established names in the interest of simplicity and usefulness. The step we took to implement that was to require soon after the passage of the law that each new drug application presented to us provide for an established name for the drug. Then, as Dr. Goddard said, last year we took a number of established names, adopted through this USAN committee, and adopted them as our own as simplified names. This is the only way those USAN names can be given legal effect, either by our adoption or by an adoption by the U.S. Pharmacopeia or the National Formulary.

Senator NELSON. Who has the authority to decide what the established name shall be?

Mr. GOODRICH. The ultimate authority rests in the agency. However, Congress did continue the practice of recognizing USP and National Formulary names as the established names unless we establish an established name as an agency name.

Senator NELSON. So the law historically was that the company that developed a drug provided the name which became the generic or established name; did it not?

Dr. GODDARD. That is correct.

Senator NELSON. Now, they still supply a generic or established name and it may or may not be accepted by USAN; is that correct?

Dr. GODDARD. That is correct. And it may or may not be accepted by FDA.

Mr. GOODRICH. And for us to make the USAN name binding, it would have to be adopted by the agency or by one of the official compendia.

Senator NELSON. You did not happen to bring along a list of generic names supplied by brand-name companies that are shorter than the brand names they created for themselves; did you?

Dr. GODDARD. That would be a very short list, Senator.

Senator NELSON. If company A gets its New Drug Application approved as submitted then it may license company B and several other companies. These other companies then just submit their New Drug Application and use the clinical evidence originally submitted by the licensing company, company A. That takes away several years of work?

Dr. GODDARD. Yes.

Senator NELSON. Maybe you could tell me how much of the 5 years that you say it takes from the beginning to the NDA approval really involves clinical testing on animals as against clinical testing on humans.

Now, we have the situation where company A might license 50 companies, some of them quite small. Each one of that 50, big or small, distinguished or unknown, may incorporate all of the experience of company A.

Along comes one of the biggest drug companies in America. Company A did not and will not license them. So they come in and produce a drug that meets all USP standards—dissolution rate, potency, purity, and so on. In fact, it meets them better than company A and all the others.

Yet it cannot put the drug on the market without going through that 5 years of research. Is there any evidence whatsoever to justify making this requirement of the large company and not of the other companies?

I do not quite grasp what you are protecting in the public interest by allowing this company to license freely. Its licensees have not done the clinical testing. On what grounds do you allow the licensees not to have clinical testing and yet you require tests from the biggest companies in America if they have not been licensed by the original company?

Dr. GODDARD. Senator, in the first instance, of the 25 companies, we do know that the drug, as they propose to produce it, has been proven to be safe and effective, because we have the manufacturing control data submitted to us in each of those instances.

Senator NELSON. Let's say there is just one supplier. All the firms are using exactly the same compound from the same source.

Dr. GODDARD. Right.

Senator NELSON. So the only question left is in the formulation of the tablet, is it not?

Dr. GODDARD. Yes.

Senator NELSON. If they all meet USP standards why decide that the drug of one of the biggest companies does not get a license when all the rest do?

Dr. GODDARD. Senator, in this instance, if company B's manufacturing process were identical with that of company A, I intellectually would not be able to defend any position here. I could not say that there is a lack of prior proof of safety and effectiveness. Now, the probability of the process being identical is, however, slight, I think. In that instance, then, with the variation in the manufacturing process, the Congress does require that we have proof of safety and effectiveness. The drug has to be demonstrated by the manufacturer to do that job.

Senator NELSON. But, doctor, you are undertaking what I think is a marvelous program. I want to commend you. You have done a great job in your position as Commissioner in behalf of the public interest without being unfair to private interests. You are undertaking a program now of clinical testing. You confront exactly the same question, because as I understand it, you will take a drug of which there are many versions on the market, and test a certain number of them. Then you will assume that if the rest meet proper standards, they will get the same clinical result.

Now, why can't you do that when company X comes in with a drug which meets all the chemical standards of the version of the drug that is on the market?

Dr. GODDARD. The burden is on the company in that instance, Senator Nelson. Also, we do feel that because of the Freedom of Information Act and past policies we would be turning business information over to these companies. And that has been our reason for not doing so. I am simply trying to raise before Congress the issue and say this needs to be discussed and our national policy on it examined. I do not happen to agree with it. I think in these instances that it is wasteful of scientific talent and that we ought to devise a better method of handling the problem than we currently have.

Now, maybe I am just a coward, Senator, because I am afraid to do this on our own initiative. But I have been advised by our General Counsel that we should not take this step and that it is something that the scientific community and Congress need to discuss along with the business community that is involved.

There is one further point. I mentioned before the difficulty in manufacturing process. A slightly different process might also give unanticipated toxic impurities in a drug, too, and thus the safety of the drug has to be checked in those situations. We are dealing with a very complicated issue here, Senator. It is one that I wish I could make extremely simple. But it is not one that I can make simple. Again, it is something that I feel needs adequate discussion here in the Senate and in the Congress.

Senator SCOTT. On that question, could I ask a question directed to that?

Senator NELSON. Surely.

Senator SCOTT. This is a general question right here, then, Doctor. Would the policing of clinical data furnished by an individual company in the public domain, in your judgment, encourage or discourage more research in private industry?

Dr. GODDARD. Senator, I am hard put to answer you on that. Some people have the opinion that it would discourage it. I would hope it would not. I tend to think it would not, because the firm that gets the drug into the marketplace first, as Senator Nelson pointed out earlier, has the marketing advantage in terms of intensive advertising, does tend, the record shows, to hold a competitive advantage in the continuing sale of that product through prescriptions written by physicians. So I do not think it would. But that is just a personal opinion.

Senator SCOTT. Not meaning to run ahead of your statement—I am anxious to hear the rest of your statement. You mentioned this on page 14. But just to close off the questions I have on that, let me just ask you, do you feel that this proposal that we are discussing would subsidize those companies who have not done substantial research in the drug field and would, therefore, if that is so, be equitable under our economy?

Is there not danger that you're subsidizing the companies not doing the research?

Dr. GODDARD. Well, I suppose theoretically, that would be correct. However, Senator, for those products developed from new research which are patented, there is a method available to the firm who chooses to go this route. They then have 17 years of exclusivity granted.

Senator SCOTT. Well, what, then, in your opinion would be the future role of the pharmaceutical companies in medical and pharmaceutical research if there were a requirement that the clinical data be put in the public domain?

Dr. GODDARD. I would hope their role would continue to be that of the primary producers of new drug products in our economy. This has been a very strong industry. I think it is today. I can't see that this would change.

Senator SCOTT. You do not think it would discourage the drug companies from doing a major part of the research?

Dr. GODDARD. Well, if their research produces a new product, one that is patentable, I think the economic awards under our system are very great and would continue to provide incentive to the firm. I think that is good, Senator.

Senator SCOTT. So long as the Government does not take it all back in taxes.

Dr. GODDARD. That is a different problem. That is out of my province.

Senator SCOTT. Thank you, Senator Nelson.

Senator NELSON. If I understand correctly, you said that about half the New Drug Applications were for patentable products?

Dr. GODDARD. That is an estimate we have made in the past decade; that about half of them are patentable.

Senator NELSON. Do the firms usually get a patent if the drug is patentable?

Dr. GODDARD. I assume they do. We do not know. The Patent Office has a serious backlog problem, too, Senator.

Senator NELSON. Under the law, all that is necessary is that the new drug be proven safe and efficacious; is that correct?

Dr. GODDARD. Those are the general requirements, and also that they will provide us information on their quality controls and provide good manufacturing practice, et cetera.

Senator NELSON. Then, what percentage of these nonpatentable new drugs are really just molecular manipulation or a fixed combination?

Senator SCOTT. Would you excuse me, that is how we got here as a result of molecular manipulation, is it not?

Dr. GODDARD. Yes, sir, we are products of RNA and DNA, going back to earliest forms of life.

Senator NELSON. The results you get by manipulating depends on who you are and what quality you have?

Dr. GODDARD. That is right.

Senator SCOTT. The process provides a good deal of amusement to the human race.

Dr. GODDARD. Though one can't take any given year as being completely representative, last year we approved 83 New Drug Applications. Fourteen of these were new products, Senator, really new chemical entities.

Senator SCOTT. Under the criteria used——

Senator NELSON. Fourteen of——

Dr. GODDARD. Eighty-two. So 69 of them were what have been called "me too's" or molecular manipulation.

Senator NELSON. They did nothing that some other drug already on the market did not do?

Dr. GODDARD. That is right. These 69 represent another tranquilizer, another new diuretic, et cetera.

Senator NELSON. No clinical superiority of those 69 over older drugs?

Dr. GODDARD. There would be differences in levels of clinical superiority.

Senator NELSON. How many of those 69 were fixed-combination drugs?

Dr. GODDARD. If I can refer to the record here, less than a third, I would say. I am guessing now. I would like to submit that for the record to be entirely accurate.

Senator NELSON. If you would.

(The information referred to, subsequently received, follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING THE NUMBER OF FIXED COMBINATIONS APPROVED FOR MARKETING IN FISCAL YEAR 1967

Of the 69 NDA's approved in fiscal year 1967 other than those for new single chemical entities, 11 were NDA's for combination products. Seven of these were

NDA's for new combination products; four for duplicates of combinations already marketed. Counting the latter four, 62 NDA's were approved for drugs which were, in effect, "me too" drugs.

Senator NELSON. We have a situation here where 69 out of 83 New Drug Applications last year were for drugs that added nothing for all practical purposes to the improvement of the health of the public?

Dr. GODDARD. I would be careful on that, Senator, because it is a little early to tell. You know, the time a drug is marketed——

Senator NELSON. There is nothing that you do know about it that would prove that it has different functions from any other drug. Otherwise, it would be patentable as something else.

Dr. GODDARD. Yes. We know the drugs we have approved are safe and effective for the conditions that they are intended to be used. Then we keep them under surveillance for the next couple of years—in fact from then on in the marketplace—to see if changes have to be made in labeling and if new problems develop. So I am hard pressed to be really responsive and say there is not anything really good in these drugs. One of those "me too's" may be a better drug in terms of having fewer side effects in the long run.

Senator NELSON. Do you think your clinical tests would not have demonstrated that?

Dr. GODDARD. In the number of people involved, side effects might not have shown up.

Senator NELSON. But anyway, the 69 had nothing new about them?

Dr. GODDARD. Nothing to jump up and down about.

Senator NELSON. So what we have really done with the process of New Drug Applications is to take products that are not patentable or whose patents have expired and then, by keeping secret the results of clinical testing, have guaranteed a monopoly or an extension of it. This has been done with no statute on the book that Congress very affirmatively passed. Is that correct?

Dr. GODDARD. (Nods affirmatively.)

Senator NELSON. You said that a third of these were fixed combinations.

Dr. GODDARD. I am guessing at that. I would have to get an accurate count.

Senator NELSON. We have had testimony from pharmacologists, professors, physicians, including Dr. Calvin Kunin on Tuesday, to the effect that there was no reason for using fixed combinations at all. I asked Dr. Kunin if doctors prescribe them because they did not know any better. He was not prepared to say that. He did say, however, that it meant a lack of education in the use of drugs. What's your judgment about fixed combinations?

Dr. GODDARD. Senator Nelson, I am in favor of a limited number of fixed combinations. I think they serve a useful purpose in the marketplace and they ought to be available for those physicians who view them as offering an advantage to their patients.

In the practice of medicine I did use fixed combinations myself. As a patient, there have been times I have enjoyed the advantages of fixed combinations, being able to take one drug instead of two. I think there is a rational place for combinations. I am not a distinguished pharmacologist and I do not pretend to be. But as a former practicing physician, I would have to say that I see a very real place for fixed com-

binations, ones that are rational, particularly in pediatric usage. There are some real advantages.

Senator NELSON. I am glad to have your observation.

Senator SCOTT. That is equivalent to saying it is easier to get one pill down a child instead of two; is that it?

Dr. GODDARD. Is that not right, Senator?

Senator SCOTT. Yes.

Senator NELSON. And, of course, if the patient suffers an adverse drug reaction, you do not know which drug caused it. That is one of the criticisms made and both pharmacologists and M.D.'s have said they think it was much better to administer them singly.

Dr. GODDARD. I submit that you cannot tell if you administer them singly, either. If you are giving a child three different medications during a day, I think it is difficult to sort out which might have produced the side effect. Side effects do not come on in every instance in a time relationship within a half hour of administering the drug. It may be a delayed reaction.

Take the common kinds of reactions you experience—urticaria, for instance. In urticaria, a reaction may not appear for several days after the drug has been initiated. So one is hard put to determine at times which drug has caused it. I did mention that there should be some rationality in the situation. We should not have subtherapeutic doses in these combinations. We should not have drugs that are not effective in the combinations. The combination itself should be proven to be an effective one. There are certain rules of science here that should prevail as well.

Senator NELSON. You have said in some limited circumstances, you approve of fixed combinations. But that is not the rule under which you issue a New Drug Application, is it? If it is effective and so forth, then it can be issued whether it has any additional value over——

Dr. GODDARD. That is correct.

Mr. GOODRICH. That was a judgment Congress made in 1932 in ruling out relative efficacy as a test for approving a drug.

Mr. GORDON. Dr. Goddard, I have a question on these NDA's. Suppose during clinical testing of a drug, somebody died as a result of taking the drug. Is such information made available?

Dr. GODDARD. Are you talking about a drug that is approved and in the marketplace now? Let's say four people have died during clinical testing of drug X which has now been approved by FDA.

Mr. GORDON. That is right.

Dr. GODDARD. The package insert would include the information that there had been four deaths reported.

Mr. GORDON. Suppose it was not approved in that particular form, what then?

Dr. GODDARD. If it involved the same chemical compound in a different form, there would have to be, as I understand it, a cautionary note, including that information.

Senator NELSON. You said that if there were deaths that seemed to be attributable to the drug and the drug was subsequently approved anyway, the package insert would have to contain the information?

Dr. GODDARD. Final labeling.

Senator NELSON. Who gets the package insert?

Dr. GODDARD. Usually the pharmacist. The physician quite often does not get it.

Senator NELSON. What good does it do the doctor, then?

Dr. GODDARD. This same information would have to appear in the advertising. So there would be not just one channel of attempting to get this information to the physician.

Now, I also have a fair degree of confidence that this kind of information would be the subject of a paper in a scientific journal, too.

Mr. Goodrich wishes to add something to this.

Mr. GOODRICH. We also have provision in the investigational new drug regulations that all investigators be kept advised as to any adverse reactions encountered by any other investigator. Let us say one out of 100 investigators encountered an adverse reaction. We require that that information be disseminated back to us and to all other investigators.

On the approved new drugs, every hazard that is relevant is a part of the final printed labeling and that provides the base line for all promotion. By promotion I mean the direct mailing, all the sampling, and all the promotions in the journal and other media.

Mr. GORDON. My understanding is that a large part of the clinical testing is paid for by the U.S. Government, either within Government institutions as in VA hospitals, PHS hospitals, Army, Navy, and so forth, or extramurally through Government grants.

Dr. GODDARD. Under our public information policies of the Government that is available, yes.

Mr. GORDON. Is that a recent development, or has that been the situation all along?

Dr. GODDARD. I am going to have to ask counsel that because I have not been on the scene that long.

Mr. GOODRICH. I am not exactly sure of the complete extent to which this information is available, but I do know that the results of the Government-supported research are generally made available to all comers.

Senator NELSON. That raises this question. If the Government, then, has done clinical testing on a new drug and finds that the results are good, will you allow the firm which submits the NDA on that drug to incorporate your research?

Mr. GOODRICH. Yes, if it is in the public domain, of course.

Senator NELSON. And you will approve their manufacturing of the drug without going the route of testing it on animals and human beings?

Mr. GOODRICH. If the data in the public domain already shows that it has been adequately tested, of course. All we are talking about, Senator, is turning over the business information supplied by one firm to another firm. Any information in the public domain can be incorporated in a New Drug Application and relied upon.

Senator NELSON. Supposing a drug in a New Drug Application has been on the market for 5 years with good clinical results. Company A applies for a New Drug Application on the same drug. Do you still require this applicant to go through the route of testing on animals and humans or do you let him incorporate the public knowledge?

Mr. GOODRICH. We let him incorporate the public knowledge. But we want to be sure what the drug is, how it is made, how it is con-

trolled from identity, strength, quality, and purity, how it is going to be labeled, how it is going to be controlled, and that it is indeed the drug that has been tested and has shown itself to be safe and effective.

Now, all that is in the literature does not necessarily mean that is all the knowledge about this drug.

Senator NELSON. But it is clear to me in any event—that when somebody licenses 25 other companies, the licensees do not really have to meet the same standard as somebody who applies for a New Drug Application for the same compound.

Mr. GOODRICH. They have to meet the same standard.

Senator NELSON. We went through that. If they all meet USP standards they are allowed to manufacture the drug because we assume the clinical results will be good. But the one new applicant is not automatically approved, because we assume that he has to prove safety and efficacy.

Mr. GOODRICH. We do not make any such assumptions. We make the decision on the basis of the data and the data is used to make that decision depending on whether it is in the public domain and all comers can use it or whether it is private business information in which the owner of that information controls its use. But we would not approve a new drug simply because a second company was licensed. We require the presentation of hard scientific data showing——

Senator NELSON. But you remember that you require from the licensed people that they meet standards of production and USP standards.

Mr. GOODRICH. We require the presentation of clinical data and this may take the form of incorporation of the previous clinical data on a business arrangement.

Senator NELSON. Does that improve the quality and the proof of the clinical value of that company's drug, whereas B can't incorporate the data and therefore he does not? That is nonsense.

Mr. GOODRICH. I do not agree with that, but since you are the chairman, I will have to.

Senator NELSON. You would be better off if you said there is no justification at all for allowing one company to license five companies, incorporate their clinical tests and then because the licensees incorporate the application of the original company, say that the proper standards are being met.

Senator SCOTT. I do not want you to feel you have to agree with Senator Nelson, because none of us——

Senator NELSON. None of us do.

Senator SCOTT. We have various degrees of blood pressure up here and each of us would require different medical treatment, probably.

Senator NELSON. My 6-year-old gives me arguments like this sometimes.

Senator SCOTT. I have found that sometimes the children are right.

Dr. GODDARD. The New Drug Application is evaluated by FDA scientists, medical officers, pharmacologists, chemists, who are now organized along team lines handling similar action drugs. We must reach a decision as to whether the usefulness of the drug outweighs its possible dangers. All the experimental data—both animal and human—are reviewed. During this past fiscal year—the year in which we

eliminated the so-called "NDA backlog"—the FDA's Bureau of Medicine approved 83 drugs for marketing; approximately 2 dozen of these are considered to be new chemical entities.

The discrepancies in this figure and the one I mentioned earlier, Senator Nelson, is that of the 24, 10 of them were different dosage forms of the same chemical entity, but under the rules, they have to get a new NDA for each form.

Senator NELSON. If the new drug is approved and there are a dozen other drugs on the market that perform the same function as far as you can tell, the company in its advertising can't claim that it has anything, can it?

Dr. GODDARD. Not unless they can substantiate that claim. In fact, that happens sometimes, Senator. A drug, let's say, for example, a tranquilizer produced by 28 different firms, may be advocated in the advertising for minor psychiatric illnesses, tension states, anxiety—we might find almost anything that tranquilizers are good for. Another company may come along and do some entirely different research which shows that children who have, let us say, enuresis, benefit by the use of tranquilizers. That would be the only firm that could make a claim of enuresis relief in that advertising, despite the fact that the other 28 in the market have the same chemical compound. That is another irrationality.

During this same fiscal year, Senator Nelson, we received a number of other NDA's and found them not approvable. Five times as many NDA's were found to be not approvable as were found to be approvable. If, however, two groups of applications, those for pentaerythrital tetranitrate—PETN's—and dipyrones—which represent special problems—are excluded from consideration and further discussion, three times as many applications were found to be not approvable as were found to be approvable. The majority of those rejected were found to be deficient in several aspects. Forty-five percent of these unapprovable NDA's did not have enough animal safety data—generally, considerably more animal data are required for commercial marketing than for clinical trial. Seventy-two percent of the unapprovable NDA's did not show adequate clinical safety when used in humans; 76 percent were lacking in clinical efficacy; component and composition data were not adequate in 30 percent and 41 percent of the NDA's returned, respectively. In 71 percent of these NDA's the application did not stipulate manufacturing controls which we felt would assure a quality drug product. Samples submitted were unacceptable in 46 percent of those returned. And in 53 percent of these NDA's we refused to allow proposed labeling.

We can anticipate a claim by PMA that these refusals were based on our medical bureau's subjective judgments—with which they disagree.

We are prepared to present any of these NDA's to the scientific community for its evaluation of our actions if PMA will obtain agreements from its members to release the files.

Mr. GORDON. Would you be prepared to conclude that the work submitted to support the NDA's is pretty sloppy?

Dr. GODDARD. What I would say is that it is the present level of submission is not an acceptable level and we intend to take steps to correct these deficiencies.

Senator NELSON. What kind of work are the PMA companies doing on the NDA's as compared to the work submitted by the non-PMA's?

Dr. GODDARD. We did this kind of analysis in preparation for the hearing because in a recent meeting, the president of the PMA said there were two drug industries. He raised the issue, so I thought it was a fair way to analyze this kind of data. I can submit the record if you wish, to comparable applications for each category. In general, the PMA did about as well as one would expect on a representative basis, except in two categories where the performance was indeed superior. That was with respect to composition and components, where their percentage of deficiencies were 29 and 23 percent, respectively. Now, in animal safety, PMA member firm submissions had deficiencies of 49 percent, clinical safety, 60 percent. Clinical efficacy, 56 percent.

Senator NELSON. These are deficiencies?

Dr. GODDARD. That is right, in the incompletes: Composition and components I mentioned earlier. In manufacturing they also did better, 46 percent; samples, 44 percent; and labeling, 51 percent.

Now, the number of incompletes in fiscal 1967 from PMA was 137 out of 258.

So PMA had 53 percent of all incompletes that year. Their overall percentage of performance was about 53 percent, about which one might expect. So you see, it is not a function of size.

Senator NELSON. They were not any better off than the others?

Dr. GODDARD. That is our evaluation and I am prepared to defend this before the scientific community by letting the scientists evaluate any 10, 20, or any number of applications we rejected as not being complete.

Senator SCOTT. Of those rejections how many would you think would be due to differences in interpretation between the FDA and industry scientists?

Dr. GODDARD. We, of course, Senator, feel we are correct in our judgment and are willing to place it on the line with the scientific community and let them be the final arbitrator.

Senator SCOTT. In your opinion, are industry scientists on the whole capable and well directed? What do you think?

Dr. GODDARD. Well, I must admit we have had considerable dialoge since I have been Commissioner with the industry scientists and I have explained about the quality of IND's and NDA's. I have asked industry scientists to review our IND requirements and suggest improvements. We have talked at meetings involving industry scientists about the quality of submissions and that quality had to be improved, that we were coming into a different era of drugs; therapeutic agents that were more potent, intended for longer term usage. I just do not find this to be an acceptable record of performance from the pharmaceutical industry. I am not differentiating between large and small and I am trying to be fair about this, Senator.

Too often the research offering in the IND's and NDA's seem to have been designed to get the drug to the market with the minimum data that the manufacturers think we will accept; they are not generally models of scientific planning and clinical execution to produce the evidence that will promptly admit drugs to the market on the basis of proven safety and effectiveness. This is the only conclusion I can draw to explain the large number of applications that are

seriously deficient, except for the few cases in which false data have been submitted to us.

Senator Nelson, I have not been satisfied with the research results presented to us. We have taken some steps to try to help industry improve the quality of its NDA submissions; it seems that still more steps are necessary. The high percentage of poor applications must be greatly reduced. There is no reason why a manufacturer cannot do the job properly the first time. Poor new drug studies and applications are wasteful economically; but much more important, they are wasteful of the very limited scientific talent and resources available for conducting and evaluating clinical trials. Such poor work delays the introduction into medical practice of valuable new therapeutic agents, and increases the cost of research with no benefit to the public.

We have taken a number of corrective steps such as:

Working with industry scientists to explain the requirements for good testing.

Outlining improved methods for organizing and submitting NDA's.

Terminating clinical trials where necessary, and in a few cases barring certain investigators from the privilege of participating in further trials.

We are inaugurating a further step that may be of some help; we are going to resort routinely to more formal procedures. Heretofore, we have usually advised firms informally of the deficiencies found in their NDA's and given them an opportunity to correct them. The result often has been a time-consuming series of phone calls, conferences, or memorandums, meetings.

Henceforth, we plan to file each application submitted—unless there are obvious gross deficiencies immediately apparent—and then make a formal decision on that application. This we believe is the procedure the law contemplates. If a manufacturer knows he may not be able to make continuing corrections in his submission, he will have a greater incentive to send us the best possible submission the first time. Further, where the situation warrants such action, our rejection of a poor NDA will be with prejudice to the resubmission of that particular document or its further use if the firm still wants that drug approved.

Senator SCOTT. Right there, doctor, when you say these will be rejected with prejudice, does that mean with prejudice also to those whom the drug might help if it is ultimately accepted?

How do you handle that?

Dr. GODDARD. You are talking about the patients who are being thus denied the benefit of the drug?

Senator SCOTT. Yes, sir.

Dr. GODDARD. Sir, I submit if we are not in a position to evaluate properly the material the manufacturer has submitted, if it is so poorly done, then there must be real doubt in our minds as to whether the patients will benefit. It may ultimately be proven that they will, but we cannot tell the future. We just have to have the proper kind of data.

Senator SCOTT. You are making the decision there?

Dr. GODDARD. Yes, sir. That is reason for administrative review, Senator, that is available in such instances and we have used this

upon a number of limited occasions in the past and the firms affected have chosen to have a hearing.

There is no question that the more stringent provisions of the Kefauver-Harris amendments were intended to require sponsors of new drugs to conduct more meaningful research which will lead to improvement in the drug supply. In many cases the improvement is already becoming evident. This is one of the beneficial results of the passage of the amendments by the unanimous vote of the Congress in 1962. And I might add that the improvement is taking place without damaging the industry as some of its spokesmen warned would happen—and occasionally still do. The drug industry is healthy, viable, and growing.

Mr. GORDON. Dr. Goddard, the material submitted, as I understand it, has to show only that the drug is more effective than nothing, than a placebo, and not more effective than another drug, is that correct?

Dr. GODDARD. We are barred by Congress from determining relative efficacy, but it is not quite as simple as saying more effective than nothing. Now, a drug that was only 10 percent effective against a serious condition—in 10 percent of the cases the patient benefited—for instance, if the drug were to be used against cancer, we would approve this drug, even though it had limited effectiveness. Now, 10 percent effectiveness on a new tranquilizer—what would your feeling be there, Dr. Ley?

Dr. LEY. There would be very little probability of that drug having really demonstrated effectiveness. "Beyond reasonable doubt," I believe is the phrase utilized in such decisions.

Mr. GOODRICH. That is, substantial evidence upon which it can fairly and conclusively be divided that the drug will have the effect claimed in the labeling.

Senator NELSON. Have you departed from the text of the law now?

Mr. GOODRICH. No, sir; I have not. My point was that in this area of relative effectiveness, although Congress said we were not to make that type decision in allowing the drug to go on the market or not, they also made the decision that where a drug claimed in its labeling that it was a superior product, there would have to be substantial evidence that it would actually perform in that way.

Senator NELSON. I realize this gets into a very difficult area. But supposing a New Drug Application issued on a drug to combat a serious disease, say pneumonia, is only half as effective as a dozen others on the market and is not misrepresented by the marketing firm. What do you do about that?

Dr. GODDARD. Dr. Ley?

Dr. LEY. This is a matter of balancing the benefit obtained from the drug with the risk of using it. If it has some unusual characteristic that makes it useful in a group of infections which other drugs may not be useful in, the decision is very clear. It depends also on the side effects observed with the drug, that is, if your benefits are less, if you have less risk of damage due to the drug, the balance may be in favor of approval of the application.

Senator NELSON. I am thinking of a case which may not occur very often where you have a drug to treat a serious condition. There is no problem of side effects, but there is a question of efficacy. It takes twice as long for this drug to have the proper effect as it does for another

drug, but it is still effective. How does the physician know? What do you do about it?

Dr. GODDARD. The only way for him to know, Senator, would be through the advertising and this would be strictly controlled by the claims that are permitted in the final printed label and our enforcement of the regulations on truthful advertising. So that is the only way he would know. The labeling has to say that the drug is effective against these organisms and that——

Senator NELSON. But there is no comparative proposition there?

Dr. GODDARD. No, sir.

There is no comparative proposition there. There are other sources of information available to the physician which he may use. A Medical Letter often provides that kind of information. The AMA publication, New Drugs, often provides data on relative effects.

Senator NELSON. If the clinical evidence reveals that a new drug is half as effective as other drugs on the market for treating the same disease, why doesn't the FDA require the advertising to state that it is half as effective?

Dr. GODDARD. We do in that instance.

Senator NELSON. You do?

Dr. GODDARD. Yes, we have.

Mr. GORDON. How do you notify the doctor of this relative efficacy you are talking about?

Dr. GODDARD. In this instance, it is by implication. I would like to give you an example. Say an ad for a drug which is only 50 percent effective against pneumococcus, is advertised in such a way that it is misleading. We would cause the sponsoring firm to send out to the medical profession a "Dear Doctor" letter which says in effect "The FDA has determined our ad to be misleading and we have failed to provide certain information about this drug; namely, that this drug is only effective in 50 percent of the instances of pneumococcal infection." The physician already knows that he has other agents that are of a higher level of effectiveness.

Mr. GORDON. Is that correct, that a physician really knows that there are other agents that are more effective?

Dr. GODDARD. Well, I can only go on averages, Mr. Gordon. I hope he knows. That is what the practice of medicine is about. He has had ample experience with these other drugs in the marketplace. He certainly, in the instance of the antibiotics, uses enough of them to have experience.

Mr. GORDON. Well, practically all our medical witnesses have testified that this knowledge is unavailable to the ordinary practicing physician.

Dr. GODDARD. In an organized, systematic fashion, yes. Now, I am very much interested that we do a better job of providing the practicing physician with good information on therapeutic agents that he is using. I asked the PMA a year ago to revive their interest in a drug compendium. They had at one time asked my predecessor, Mr. Larrick, to permit individual member firms to drop the publishing of the package insert and in return for this exemption, they would cause to be published a drug compendium. Mr. Larrick said he would agree with this, I am told, provided that there was a year's experience of publishing the drug compendium and distributing it to physicians before the package inserts were dropped.

I am told the package inserts, the printing and the packaging, thus required to insert costs the major PMA manufacturers about $6 million a year. I am perfectly willing to drop the package insert requirement at the moment a good drug compendium is distributed to the profession—the pharmacists, the physicians.

Senator NELSON. Drop what requirements? The insert?

Dr. GODDARD. The insert for all except intravenous and parenteral drugs.

Senator SCOTT. What would the compendium provide and how would you handle the distribution?

Dr. GODDARD. It would be distributed free of cost to every physician, pharmacy, and hospital in the United States. It would be assembled by a distinguished board of editors in the scientific community and, hopefully, paid for by the members of the pharmaceutical firms. Both the drug and allied products field and PMA have had these subjects discussed with them. There does not seem to be too much interest on their part in going this route, I am sorry to say. I had hoped they would exert leadership in this field.

Senator SCOTT. Now, with regard to what it would comprise.

Dr. GODDARD. On composition, the drugs sold in interstate commerce, listed by both generic and trade name; a brief description of the drug, its action, its recommended dosage, indications for usage, side effects, contraindications, and warnings, in brief. Now, this is not a compilation of the current package labeling as some people have misunderstood me to be recommending. This is a well done, in brief summary that could be useful to the practicing physician, just as PDR now is.

Senator SCOTT. It would seem to me that industry and the profession would be helped, would be glad to have such compendium. You said there did not seem to be much interest. What efforts have been made to enlist interest in this proposal?

Dr. GODDARD. Senator, let me comment if I may, first on your remark about the practicing physicians and others involved viewing this as being desirable.

For 10 years, the council on drugs of AMA have said this would be desirable. I know that for 4 years at least that the National Academy of Sciences Drug Research Board has recommended such a compendium.

Now, as to what has been done. There have been meetings held with the PMA leadership, both between FDA and PMA and the FDA and National Academy of Sciences and PMA. Specific recommendations have been made and no action has been taken.

Now, I am very dismayed by this, because I would like to see this done by the private sector of our economy. It would have to have FDA approval, because it would constitute labeling of sorts. We are perfectly willing to do this and to drop immediately the requirement that packaged circulars accompany every drug sold in the marketplace.

Now, I think that this is one of the most important things that could be done in terms of enhancing communications on therapeutic agents to those who need this kind of information.

Senator SCOTT. Have you made that statement before with regard to dropping immediately the package insert?

Dr. GODDARD. Yes, this has been clearly known to the Pharmaceutical Manufacturers Association and the Drug & Allied Manufacturers Guild.

Senator SCOTT. At this time, your agency can't 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 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 drugs are superior to anybody else's. I hear the statement made time and time 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, about the pre-1962 drugs, where effectiveness did not have to be proven.

Senator SCOTT. Is that not where the proverb applies that one man's Anacin is another man's Empirin?

Dr. GODDARD. I have not heard that proverb before.

Senator SCOTT. It is an old eastern proverb that I just made up.

Dr. GODDARD. There are two instances of lack of therapeutic equivalence know that have been cited in the literature. With one, tetracycline, that was sugar coated, involved all the producers of tetracycline. I do not think that size is any assurance of freedom from worry in this field. We are going to begin some clinical trials on those drugs that are available from more than one manufacturer on those 200 most frequently prescribed drugs. At some place down the line, I think we are going to have to make a hard nosed business decision in the Government. I am not opposed to doing that, either.

Senator SCOTT. I would applaud you for doing that.

Dr. GODDARD. If we find in group after group that there is therapeutic equivalency and we have gone down this road 30 times with 30 different drugs, I think I would be derelict in my duties if I did not cut off further clinical studies. Also, I would not want to expose unnecessarily the patients to the risks that can be involved.

So this kind of a question, we think, can be answered in about 18 months.

But make no mistake: I think the examples of lack of therapeutic equivalency are in the minority. The possibilities are actually that only in very few instances does therapeutic equivalence not exist. Among ourselves, physicians would argue as to whether or not it would be noticed in the intermittent therapy that is given in the private practice of medicine without continuous supervision. That is a valid point. That is why we are going ahead and carrying out these trials.

But as I say, I have not seen good data from any company, large or small, that says that their pre-1962 drug is more effective than anybody else's.

Senator NELSON. We have had testimony from a number of witnesses who have said that the burden ought to rest on those who assert that they are not therapeutically equivalent to come forward with the evidence. We had the Schering Co. president here last week. We read

the issue of the Medical Letter to him that demonstrated a cost differential of $2.59 a 100 tablets of prednisone to Schering's price of $17.90. He asserted that his firm's product is of higher quality. The proof is that doctors prescribe it. I said you have one-third of the market; why don't you contract for double blind clinical testing with an independent respected research lab? Then when you prove what you assert, you will have the whole market. The answer to that was it is not worth it.

Dr. GODDARD. On the other hand, I know one representative of a pharmaceutical firm, when this same issue came up in a meeting, who said, "I can assure you we are going to do that with our product and we will be able to say to the physician, ours are superior." I said that they were welcome to do it.

Senator NELSON. Have they done it?

Dr. GODDARD. Not yet. This meeting was within the past month. They have not had time to.

Senator NELSON. We are probably going to find out.

I will recess the hearing until 1:15.

(Whereupon, at 12 noon, the above hearing recessed, to reconvene at 1:15 p.m. of the same day.)

AFTERNOON SESSION

Senator NELSON. The hearing will resume.

Dr. Goddard, just at noon, the Pharmaceutical Manufacturers Association issued a news release taking issue with statements you made—maybe they take issue with you before you made a statement. I am not sure.

STATEMENT OF DR. JAMES L. GODDARD ET AL.—Resumed

Dr. GODDARD. I think they must have. It is a printed statement, Senator Nelson.

Senator NELSON. The statement says:

Commissioner Goddard commented in his statement before the Senate Subcommittee today that many NDA's—New Drug Applications—were "reviewed" by the FDA and "found not approvable." Unfortunately, Commissioner Goddard's statement does not adequately describe the present FDA procedure.

The following four points are important:

1. Commissioner Goddard referred to the "review" of NDA's. It would have been helpful if he had explained the preliminary review by FDA of a submission by a company to determine whether an application should officially be filed under FDA published regulations. The regulations of FDA expressly provide for this preliminary review and exchange of information between scientific personnel of FDA and industry. Under this present procedure, companies will submit—"not file"—NDA's for the purpose of clarifying questions which FDA scientific personnel may have so that the applicant company can expeditiously complete its application for filing.

Do you want to comment on that?

Dr. GODDARD. Senator, could I comment?

I think they have missed the point. The point here is that the statistics I have referred to were based on submissions that we had received. We were not carrying out a preliminary review. These statistics were derived from data compiled from formal, incomplete letters issued to the company, so I think they missed the point.

Senator NELSON. So his statement that these were preliminary is incorrect?

Dr. GODDARD. Their statement is incorrect.

Senator NELSON. Now, as to item 2:

2. Present FDA regulations expressly provide that after this preliminary review and upon completion of the application, it will then be accepted for filing by FDA and for formal consideration in accordance with the time schedule provided by statute. Requests by FDA for additional information from a company during this "review" process does not constitute a rejection by FDA of a New Drug Application.

Would you comment on that?

Dr. GODDARD. Yes. Again I do not understand their use of the word "rejection." It does constitute the filing of an "incomplete." We send an "incomplete" letter which spells out in detail where all the faults are with this particular NDA. It is not a rejection. It is an "incomplete" and the company receives written notice of the faults that I cited in this morning's testimony. So, again, it is——

Senator NELSON. So you did not assert that it is anything other than an incomplete in this particular case, is that right?

Dr. GODDARD. That is correct.

Senator NELSON (reading).

Commissioner Goddard stated before the Committee today that he planned to adopt a new procedure whereby each application submitted would be immediately "filed" within the technical meaning of the statute. We think his comment on this point would have given a "fairer balance" if he had noted that the Pharmaceutical Manufacturers Association in March 1963, and again in December 1966, expressly recommended to FDA in writing, on behalf of its member companies, the filing procedure which Commissioner Goddard now says he will adopt.

Dr. GODDARD. I do not think that is quite accurate, either, Senator. The PMA wanted us to start the clock running, the 180 days the Congress says we will have on these technical applications, on any kind of application. This is not what we contemplate. We said in our statement and this is how we intend to implement this. If we perceive immediately that an application is grossly inefficient, we are not going to waste our time, we are just going to box it up and send it back to them.

On the other hand, if after a preliminary review, the NDA seems to contain the required elements, we will notify the applicants and the clock will start running. So, again, this is what we said before.

I do not disagree that in general terms, they have suggested that the normal filing mechanism be adopted, but there was that nice little technicality in there that I wanted to bring to your attention.

Senator NELSON. At this point, we will formally give them credit for whatever they did get.

Dr. GODDARD. Thank you.

Senator NELSON (reading).

4. It would have been appropriate, accurate and scientifically supportable if Commissioner Goddard had said, in commenting upon the statistics of the review procedure, that there are often honest and justifiable differences of scientific opinion between FDA staff and industry scientific personnel.

Commissioner Goddard also made other observations on which PMA and member companies will undoubtedly have some pertinent comment when we have the opportunity of testifying before Senator Nelson's subcommittee.

Dr. GODDARD. I think I covered that. I am perfectly willing to subject our judgment to the review of the scientific community and I only hope they will be willing to do so as well.

Senator NELSON. Have you requested that they agree to submit these applications to review by the scientific community?

Dr. GODDARD. I did this morning in my testimony. I suggested that we could settle this difference of opinion about our subjective judgments by taking the last 10 or 20 IND's that we have deemed to be incomplete, have the PMA get from its member firms permission to open up this scientific data to acceptable review groups in the scientific community and, then, let the judgment be made by those groups. So in that fashion, I think we can get a pretty good fix on it.

Senator NELSON. That sounds fair.

You said there have been a few cases in which false data have been submitted to the agency. Was this data intentionally false?

Dr. GODDARD. Well, it is difficult to make a judgment of intent, Senator. There were only about five cases involving the submission of false data in a recent period of time. I cannot really ascribe intent in these instances. I have tried to point out, and I think it is significant, that with 25,000 investigators on our file, we have only had five such instances.

Senator NELSON. I think that is a good record.

Dr. GODDARD. I think it is a good record, too. I am not saying that there might not be others that exist, but I think there are very few.

Mr. GORDON. On page 5 of your statement, you talk about the quality of research in connection with the NDA's. In your opinion, does the poor quality of research in connection with the NDA's, apply also to other research conducted by the industry?

Dr. GODDARD. Are you talking about the IND?

Mr. GORDON. The IND's and the NDA's.

Dr. GODDARD. The IND's are the precursors of the NDA's and it is during the investigation and new drug exemption stage that these clinical studies are carried out. Of course, we think by initiating closer surveillance over the IND submissions and review of these at an earlier point in time, we can have a better understanding of the drug and perhaps will have a little better scientific data finally come into us. This, of course, is where we have in our meetings with the scientists in the industry been urging placement of greater emphasis on the need for better science. I submit that we are entering into an entirely different era of therapeutics—an era of more potent agents, as I mentioned before, agents intended for long term usage. We have to have rather exquisitely detailed knowledge of the effect of these drugs at the cellular level. We do not get that very often and I think it is just going to be absolutely mandatory that this kind of information be developed.

Mr. GORDON. Then would it be fair to say that a large number of drugs submitted to you are only minor modifications of old drugs developed in order to be able to secure patents?

Dr. GODDARD. I cannot, again, know why they are—whether they are submitted for us to——

Mr. GORDON. I did not ask why. I said is it correct?

Dr. GODDARD. You said in order to get patents.

Mr. GORDON. All right, let's forget that. They are just minor modifications rather than really interesting developments?

Dr. GODDARD. I said this morning that out of the 83 new drugs, 69 of them were not what would be described as new chemical entities,

significant new products. And, in general terms, I would have to agree with you, yes.

Mr. GORDON. What page of your statement were you on doctor?

Dr. GODDARD. Page 6, good manufacturing practice.

There are 20,000 firms registered with the FDA as engaged in the drug business, but 13,000 of these are in medicated feeds. Of the remaining 7,000 firms, some are in veterinary drugs, and some are repackers, leaving close to 2,000 companies who engage primarily in the manufacture of prescription or nonprescription drugs for human use.

Senator NELSON. When they register with the FDA do they describe the size of their operation, number of employees, things like that?

Dr. GODDARD. No, they just register the name of the corporation and the legal address.

Senator NELSON. That is all?

Dr. GODDARD. That is all of them, 900 of these, by actual count, Senator, 861 as of July 1, are principally manufacturers of prescription drugs. We are obliged by law to physically inspect each register firm no less than once every 2 years.

Senator NELSON. All 2,000?

Dr. GODDARD. Yes.

During inspection of the plants, we check the manufacturing and quality control procedures to see if the general regulations establishing Current Good Manufacturing Practices are being followed in actual production. For the most part, this is the case; however, as in any other manufacturing situation, there can be a tendency for those on the line and in quality control to deviate from approved guidelines. To do so is a violation of Current Good Manufacturing Practices. Our field investigations reveal numerous deviations from Current Good Manufacturing practices. These deviations are of varying degrees of importance and may be found in plants of every size and description.

Senator NELSON. In the first line of this section, you referred to 13,000 of these drug manufacturers engaged in manufacturing medicated foods for animals, livestock and so on?

Dr. GODDARD. Yes.

Senator NELSON. What kind of surveillance do you perform over them?

Dr. GODDARD. Very poor.

Let me clarify that by telling you the situation is this: Many of these medicated feed manufacturers are completely mobile now and they operate in trucks. We cannot carry out inspections of many of these establishments. With those that are fixed operators, so to speak, what you might call fixed base operators, we do inspect their establishment and try to determine that they are using the proper quantities of antibiotics in mixing a feed to be used specifically to prevent infection or to promote weight again in certain animals.

Senator NELSON. As you know—we did not, when I was on the farm, feed them anything but what they could find in the yard. There were no medicated feeds. What concern do you have about the problem of an excessive accumulation of these drugs in fatty tissue of the animals—sheep, beef, chicken, turkey—which are then consumed by the human being at the end of the food chain?

Dr. GODDARD. Senator, besides commenting on this, may I submit for the record a brief statement that I made at a meeting that was con-

cerned solely with this subject that took place here in Washington earlier this year. I spoke at a meeting that the National Academy of Sciences sponsored, and we were specifically talking of these problems. We are concerned about improper use of medicated feeds. For one thing, failure to stop the use of them in adequate time before slaughter to permit clearance from the tissue. Second, we were concerned about general recent findings which suggest that certain medications may persist in the animal tissue far longer than we had ever known heretofore. Some of these feeds are capable of sensitizing human beings to the drugs used so that subsequently the same drug could not be effectively used.

(The information referred to, subsequently received, follows:)

THE QUEST FOR DATA

(Welcoming Remarks by James L. Goddard, M.D., Commissioner of Food and Drugs)

INTRODUCTION

One year ago, you may remember, a report was delivered to me by the Advisory Committee on The Veterinary Medical and Non-Medical Uses of Antibiotics. Several members of that eminent Committee are, I am pleased to see, on the program for this Symposium. The Report was brief and to the point—and gave the Food and Drug Administration a great deal of valuable guidance on new directions we might explore in both research and regulation. I regard the holding of this Symposium as being the same kind of necessary activity in which we must engage in order to gather and evaluate all the research information we can, while moving forward—step-by-step—in our regulatory activity.

Eleven years ago, another Symposium on Medicated Feeds was held by the Food and Drug Administration. The issues raised at that meeting—and the subsequent developments in the use of drugs in animal feeds—have given all of us much to ponder. I think former Commissioner Larrick made a wise decision in organizing the veterinary advisory committee in 1965, for its Report last year was both timely, as far as the state of the art was concerned, and significant, as far as the state of the public health issue was concerned.

And, if I may, I would wish to emphasize that it is the health of the public which must be maintained and which must serve as the ultimate measure of our success, whether in research or regulation. I am sure, as I review your program and your list of speakers and participants, that all of us here today are quite aware of the heavy responsibility we must increasingly assume. I would like to point out, however, that this responsibility is two-fold: certainly we in the FDA see it this way and I would suspect that others in this audience do, also.

First, there is the responsibility for maintaining the health of the public, as I noted before. There is increased concern about the possibility of drug residues in edible meat, milk, eggs, poultry, and fish products. This concern has been expressed in a number of ways by veterinarians, by leaders in the drug and animal feed industries, by leaders in animal agriculture, as well as by Government officials. A great deal has been said, of course, about antibiotics. Back in 1963, the Expert Committee of the World Health Organization published in its report on antibiotics in food and feedstuffs this warning on the problem of sensitivity:

> "Individuals not previously sensitized might become so, or persons previously sensitized as a result, for example, of medical treatment with an antibiotic, might develop reactions of hypersensitivity."

The FDA's Advisory Committee was equally concerned in 1966 and asked that our agency, "give greater emphasis to its responsibilities for ascertaining and evaluating the long-term ecologic effects of the veterinary medical and nonmedical uses of antibiotics. "Criteria developed from such studies," the Committee said, "should be applied to the evaluation of new uses and the reevaluation of current uses and practices." It further recommended "continuous evaluation and surveillance of the safety and efficacy of these uses in terms of the public health."

The other aspect of the responsibility we all share at this time is to move forward in such a way that our supply of food—especially those foods that are protein-rich and vital to the people of the world—that this food supply continue to expand and not become entrapped by inflexible scientists, producers, or Government officials. We are achieving a higher meat yield from our herds today with our supply of feed, and this is due in large measure to the addition of antibiotics and other drugs to both the feed and the animals themselves. We have, then, found ways to produce healthier, heavier animals through new uses of drugs; we can draw additional benefits from a not-unlimited feed supply.

Now the question seems rather clear-cut; How can we maintain progress in the field of animal agriculture without jeopardizing the public health? I doubt if an *answer* will be that celar-cut. But I believe that a response, satisfactory to everyone involved, can be formulated and made effective.

You will note that I am speaking in terms of the future. This is no reflection on my part that our present situation is one full of danger. But it does reflect, to be sure, my feeling that we are conducting our business today more on hope and faith—and less on hard data. And we need much more hard data on veterinary drug usage—and the results of such usage—than we now have.

Last fall, Dr. M. R. Clarkson, who was then our Director of the Bureau of Veterinary Medicine, sought out what pertinent information was available from a number of other Government agencies. The yield, frankly, was small. Since then, Dr. C. D. Van Houweling, our present Bureau Director, has continued to gather data, not only from Government sources, but from non-government veterinarians, other related scientists, and from industry sources as well. A great deal of new information has come to us as a result of our policy statement of August 23, 1966, requiring all sponsors of veterinary antibiotics to come forward with residue data from treated animals.

In reviewing the work of the agency of the past half year—and, in particular, in reviewing the *kinds* of data we are receiving—it is clear to us that we are still only on the threshold of understanding the total problem. We are aware of the following actions the FDA had to initiate during the past year:

The recall of a number of products from the market, specifically mastitis products, as a result of new findings.

The denial of certification for new products because of a lack of acceptable information being submitted to us.

The revoking of certification of other products already on the market, because of uncertainty about the back-up data.

The denial of certification for oil-based injectable penicillin products, which required an unrealistic withholding time.

As you can see, one of our major problems at this time is to bring together and stabilize what we actually know and can count on as being scientifically assured. This is essential for both the protection of the public health and for maintaining orderly growth in this field of veterinary drug usage. To use a more familiar phrase, it is time for us to "get a better handle" on the entire situation. And, as the title of this Symposium indicates, we are not concerned only with antibiotics—we are concerned with drugs in general, as they are applied to veterinary use.

I urge everyone taking part in this three-day meeting to lend his best efforts here and to return to work later with a renewed sense of purpose and a deeper understanding of the significance of his future contributions. They will have a great bearing on the course of this valuable development in the expansion of the world's food supply. But let me recall once again that, during the past year, we have had to exercise a number of cautionary measures because of the lack of—or the conflict in—the data that our agency received.

We plan to publish shortly another Statement of Policy on antibiotics used in food-producing animals.

This statement will be based on studies we have carried out, as the Advisory Committee recommended, and on the kinds of industry information received since the last request for data, published in August 1966. This will outline the status of the oral, injectable, or other types of veterinary antibiotic preparations—except for topicals, ophthalmics, and those for which we have acceptable residue data and covered by a New Drug Application or antibiotic approval, with particular reference to prior sanctions. And, I must add, we are in the process of reviewing the data that supports those current approvals as well.

In order, however, to keep the industry moving ahead, to keep the information flowing in, and to protect the supply of food, this should lead to early publication of appropriate Food Additive Regulations; under those new regulations, new

data will be processed, and, we believe, progress in this whole area will be maintained. We expect many more products to be covered by Food Additive Regulations and/or placed in new-drug status. Shortly, we will be receiving the results of the NAS-NRC Efficacy Review Panels now working with veterinary drugs. As data from these different sources converge, we may all need to take a second look at labeling of these drugs, so that proper warnings, restrictions, and directions for use are well displayed.

In addition, we will continue to eliminate wherever possible those purely administrative delays in the introduction of new drugs for animal use, in the evaluation of Good Manufacturing Practices in premix establishments, and in other areas of our veterinary medicine activity. I personally am satisfied that our Bureau of Veterinary Medicine, with the generous help of the scientific community and with the cooperation and understanding of industry, is carrying well its share of responsibility.

However, that responsibility grows weightier as drug investigation expands in the veterinary field. We are meeting today in the wake of another Symposium cosponsored recently by Georgetown University School of Medicine and our agency. That Symposium was concerned with infectious multiple drug resistance. We are carefully reviewing the papers presented at that Symposium—which drew a number of international experts to this city—and we will attempt to fit the conclusions into the emerging patterns of new drug mechanisms, as we are now beginning to see them.

I doubt that I need go into the details of the R-factor—or Resistance Transfer Factor—with this distinguished audience. But I would want to emphasize here that the Food and Drug Administration is approaching these new investigational areas with the utmost seriousness. Ultimately, we will have to come to sensible conclusions to carry out our regulatory mission in the interest of the public health. Those conclusions must have as their base the best research and the best deductions that are available.

That is why I am grateful to be among you this morning, to convey to you the welcome of the Food and Drug Administration, and to assure you that your presence at this Symposium is extremely significant. We are bound together in these opening phrases of new scientific frontiers. And we are bound together in a commitment to the protection of the Nation's health. As colleagues—in science or in industry, in Government or in the private sector—we can cross those frontiers and fulfill that high commitment.

President Seitz, Dean Poppensiek, ladies and gentlemen, it has been a privilege to be a part of this morning's program. I look forward to reviewing your deliberations here.

Thank you.

Senator NELSON. Are there allergic reactions?

Dr. GODDARD. This is what I am referring to. Also, it could create a situation where the drug might not be effective against the organisms that are involved when an individual needs it to ward off an infection. So there are a number of scientific concerns that are being examined carefully today by those who work with veterinary feeds. These are veterinary medical specialists; the National Academy of Sciences, USDA, FDA, and Public Health Services are working cooperatively in this area.

Senator NELSON. What concerns me is that if we proceed, in the same fashion here as we have with pesticides, the consequence, which I think we will recognize within a year or two will be that we will have dangerously polluted the whole atmosphere with DDT, that we are killing the bald eagle, the fish, accumulating DDT in the fatty tissue of deer and other creatures. We have no idea what the consequence is to the human consumers of the DDT. We can only guess. But who is really carefully monitoring or examining the consequences of the feeding of medicated foods to find out what residues are there, what their effect is, and what ought to be done about it?

Dr. GODDARD. Well, our Bureau of Veterinary Medicine and the U.S. Department of Agriculture both are working in this area, looking at

residues. We are intensifying our activity with respect to residues, medications, and meats. Our program for this year calls for, I believe, 4,000 samples to be taken and analyzed for drug residues. We have met with the U.S. Department of Agriculture—Assistant Secretary George Mehren, myself, and staff members—twice within the past 30 days to look at how we as two agencies involved in this area can tackle the problems and not duplicate efforts and unknowingly go down separate paths working on the same problem. So the scientists brought together by the National Academy of Sciences are working together. There are efforts being funded by NRC in this area as well.

Senator NELSON. How many samples are there?

Dr. GODDARD. I think we are taking 4,000 this year in our veterinary medical program to check for drug residues—4,000 samples of meat.

Senator NELSON. From all over the country?

Dr. GODDARD. Yes.

Senator NELSON. Then is somebody else doing some checking in addition?

Dr. GODDARD. I understand the USDA also is doing considerable checking in this area. That is why our staffs are now meeting to parcel out the particular problem.

Senator NELSON. Has this ever been done before?

Dr. GODDARD. We have never done it.

Senator NELSON. Has anybody in the Government ever done it?

Dr. GODDARD. The USDA is responsible, of course, for meat surveillance. That means poultry as well.

Senator NELSON. I mean, has anybody been doing a continuous scientific study of the residue of various drugs in the tissue of animals?

Dr. GODDARD. I cannot answer that accurately, Senator. I would rather refrain. I know they have done some testing, but I do not know on how broad a scale it has been done.

Senator NELSON. I do not want to reflect on the Department of Agriculture, which leans very strongly to what the farmer wants. It was a long time before any of us could get them to slow up on DDT, before they would recognize that it had any damaging effect. One of the greatest supporters of pesticides is the Department of Agriculture. I wonder what kind of a careful study they are doing. I know it was brought to Secretary Freeman's attention that of all the jobs he has, he should be interested in it and push forward on it. I don't know who is doing what.

Dr. GODDARD. You recognize in the pesticide field, Senator, there are three different agencies that have responsibility. First, the USDA must make a determination that the pesticide proposed for use on a given crop has economic significance. Then the Public Health Service must make a determination that the manner in which the pesticide is to be applied is safe for the operator who is going to be making application. Then the Food and Drug Administration must make a determination whether or not a residue will occur and if so, what tolerance will be allowed. How much residue is to be allowed? Is this harmful to human beings in terms of our food supplies?

None of these are easy questions. The Department of Agriculture probably has the easiest one to answer; that is, the economic significance. The long term effects of pesticide residues have not been adequately documented, and that is our job.

Senator NELSON. I think the system has been a tragic and colossal failure. The scientists attacked Rachael Carson because she had not accumulated scientific evidence, which to the scientist means if the patient dies the hypothesis was correct. Well, it turned out that her whole thesis was correct, but we are late now in dealing with the problem of DDT in many States. The community is saying, for heavens sake, let's not destroy the insects, fish, animals, and birds, but it is awfully late in the game. That is what concerns me.

Dr. GODDARD. I think Rachael Carson actually did a very fine service in the very forceful manner in which she brought before the public and the Congress some of the abuses that are going on, just as Ralph Nader and others did.

Senator NELSON. Go ahead.

Dr. GODDARD. I would like to submit for the committee's information, Senator Nelson, this copy of our Current Good Manufacturing Practices regulations.

Senator NELSON. Is that a report to be printed in the record?

Dr. GODDARD. If it is your desire, sir.

Senator NELSON. We will print it in the record.

(The information referred to follows:)

PART 133—DRUGS; CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING, OR HOLDING

DEFINITIONS

Sec.
133.1 Definitions.

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133.7 Master formula and batch-production records.
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MEDICATED FEEDS; MANUFACTURING PRACTICE

133.100 Current good manufacturing practice.
133.101 Buildings.
133.102 Equipment.
133.103 Personnel.
133.104 Components.
133.105 Formula and production records.
133.106 Production and control procedures.
133.107 Packaging and labeling.
133.108 Laboratory controls.
133.109 Distribution records.
133.110 Complaint files.

AUTHORITY: §§ 133.1 to 133.110 issued under secs. 501, 701; 52 Stat. 1050 as amended 76 Stat. 780, 781; 1055; 21 U.S.C.A. 351, 371.

DEFINITIONS

§ 133.1 Definitions.

(a) As used in this Part 133, "act" means the Federal Food, Drug, and Cosmetic Act, sections 201–902, 52 Stat. 1052 (21 U.S.C. 321–392), with all amendments thereto.

(b) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in the regulations in this Part 133.

(c) As used in this Part 133, the term "medicated feed" means any "complete feed," "feed additive supplement," or "feed additive concentrate," as defined in

§ 121.200 of this chapter, which feed contains one or more drugs as defined in section 201(g) of the act. The term "medicated feed" does not include any undiluted drug or "premix," as defined in § 121.200 of this chapter, intended for manufacturing use in the production of a medicated feed, since these are subject to §§ 133.3–133.14, inclusive.

FINISHED PHARMACEUTICALS; MANUFACTURING PRACTICE

§ 133.2 Current good manufacturing practice.

The criteria in §§ 133.3–133.13, inclusive, shall apply in detersining whether the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of a drug conform to or are operated or administered in conformity with current good manufacturing practice to assure that a drug meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this Part 133 permit the use of precision automatic mechanical or electronic equipment in the production of drugs when adequate inspection and checking procedures are used to assure proper performance.

§ 133.3 Buildings.

Buildings in which drugs are manufactured, processed, packaged, labeled, or held shall be maintained in a clean and orderly manner and shall be of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The buildings shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which it is employed, to minimize any risk of mixups between different drugs, their components, packaging, or labeling, and to control the possibility of cross-contamination of one drug by another drug that is manufactured, stored, or handled on the same premises:

(1) The receipt, sampling, or storage of components.

(2) Any manufacturing and processing operations performed on the drug.

(3) Any packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finished products.

(5) Control and production-laboratory operations.

(b) Provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, filtering, dust, humidity, temperature, and bacteriological controls, as for example, to prevent contamination of products by extraneous adulterants (including the prevention of cross-contamination of one product by dust or particles of ingredients arising from the manufacture, storage, or handling of another drug); to prevent the dissemination of micro-organisms from one area to another; to facilitate the sterilization of special work areas, such as those used for production of parenteral preparations; to provide suitable housing for any animals; and to avoid other conditions unfavorable to the safety and integrity of the product.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

§ 133.4 Equipment.

Equipment used for the manufacture, processing, packaging, labeling, holding, or control of drugs shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location in relation to surroundings to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with drugs are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug or its components.

(b) Be so constructed that any substances required for the operation of the equipment, such as lubricants or coolants, may be employed without hazard of becoming additive to drug products.

(c) Be constructed to facilitate adjustment, cleaning, and maintenance as necessary to assure the reliability of control procedures, to assure uniformity of production, and to assure the exclusion from drugs of contaminants, including those from previous and current manufacturing operations.

(d) Be of suitable size and accuracy for use in any intended measuring, mixing, or weighing operations.

§ 133.5 Personnel.

The key personnel involved in the manufacture and control of the drug shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the drug has the safety, identity, strength, quality, and purity that it purports to possess.

§ 133.6 Components.

Components used in the manufacture and processing of drugs, regardless of whether they are intended to appear in the finished product shall be identified, stored, examined, tested, inventoried, handled, and otherwise controlled in a manner to assure that they conform to appropriate standards of identity, strength, quality, and purity, and are free of contaminants at time of use, and are so stored and handled as to assure that dust or particles resulting from such storage or handling does not contaminate other substances or preparations on the premises, and to provide that appropriate records are maintained of their origin, receipt, examination, testing, disposition, and use in drug manufacture or processing.

§ 133.7 Master-formula and batch-production records.

(a) For each drug product, master-formula records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent and responsible individual. The record shall include:

(1) The name of the product, a description of its dosage form, and a specimen or copy of the label and each other portion of the labeling contained in a retail package of the drug.

(2) The weight or measure of each ingredient per dosage unit or per unit of weight or measure of the finished drug, and a statement of the total weight or measure of any dosage unit.

(3) A complete batch formula for each batch size to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristic; an accurate statement of the weight or measure of each ingredient, regardless of whether it appears in the finished product, except that reasonable variations may be permitted in the amount of components necessary in the preparation in dosage form, provided that the variations are stated in the master formula; an appropriate statement concerning any calculated excess of an ingredient; appropriate statements of theoretical weight or measure at various stages of processing; and a statement of the theoretical yield.

(4) A description of the containers, closures, packaging, and finishing materials.

(5) Manufacturing and control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) A separate batch-production and control record shall be prepared for each batch of drug produced and shall be retained for at least 2 years after distribution has been completed. The batch-production and control record shall include:

(1) An accurate reproduction of the appropriate master-formula record, checked and endorsed by a competent responsible individual.

(2) Records of each step in the manufacturing, processing, packaging, labeling, and controlling of the batch, including dates, specific identification of each batch of components used, weights or measures of components and products in course of processing, in-process and laboratory-control results, and the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation.

(3) A batch number that permits determination of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of drugs from the batch.

§ 133.8 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the drugs produced have the identity, strength, quality, and purity they purport to possess.

(a) Each critical step in the process, such as the selection, weighing and measuring of components; the addition of active ingredients during the process; weighing and measuring during various stages of the processing; and the determination of the finished yield shall be performed by a competent, responsi-

ble individual and checked by a second competent, responsible individual, or if such steps in the processing are controlled by precision automatic mechanical or electronic equipment their proper performance is adequately checked by one or more competent, responsible individuals.

(b) All containers and equipment used in producing a batch of drugs shall be clearly labeled at all times to identify fully and accurately their contents, the stage of processing, and the batch, and shall be stored and handled in a manner adequate to prevent mixups with other drugs.

(c) Equipment, utensils, and containers shall be thoroughly cleaned and previous identification removed between batches and in continuous batch operations at suitable intervals, to prevent contamination and mixups.

(d) Appropriate procedures control the hazard of contamination with microorganisms in the production of parenteral drugs, ophthalmic solutions, and any other drugs purporting to be sterile, and appropriate procedures to control the hazard of cross-contamination of nonpenicillin products by penicillin in those establishments that manufacture, store, or handle penicillin products and nonpenicillin products.

(e) To assure the uniformity and integrity of products, there shall be adequate in-process controls, such as checking the weights and disintegration time of tablets, checking fill of liquids, and checking the adequacy of mixing, the homogeneity of suspensions, and the clarity of solutions.

(f) Competent and responsible personnel shall check actual against theoretical yield of a batch of drug, and in the event of any significant unexplained discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of drugs that may have been involved in a mixup with it.

§ 133.9 Products containers.

Suitable specifications, test methods, cleaning procedures, and when indicated, sterilization procedures shall be used to assure that containers, closures, and other component parts of drug packages are suitable for their intended use, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug, and furnish adequate protection against its deterioration or contamination.

§ 133.10 Packaging and labeling.

Packaging and labeling operations shall be adequately controlled to assure that only those drugs that have met the specifications established in the master-formula records shall be distributed; to prevent mixups between drugs during the packaging and labeling operations; to assure that correct labeling is employed for the drug; and to identify finished products with lot or control numbers that permit determination of the history of the manufacture and control of the batch of drug. Packaging and labeling operations shall:

(a) Be performed with adequate physical segregation of such operations from operations on any other drugs to avoid mixups.

(b) Provide that each type of labeling used shall be stored in a manner that avoids mixups between labelings and shall be carefully checked for identity and conformity to the labeling specified in the batch-production records.

(c) Provide adequate control of the quantities of labeling issued for use with the drug. (Competent, responsible personnel shall reconcile any discrepancy between the quantity of drug finished and the quantity of labeling issued. In the event of any significant unexplained discrepancy, key personnel shall prevent distribution of the batch in question and other associated batches of drugs that may have been involved in a mixup.)

(d) Provide for an inspection of the facilities to be used prior to labeling a drug to assure that all the previously used labeling and other drugs have been removed.

(e) Provide for adequate examination or laboratory testing of adequately representative samples of finished products after packaging and labeling to safeguard against any error in the finishing operations, and to prevent distribution of any batch until all specified tests have been met.

§ 133.11 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that components, drug preparations in the course of processing, and finished products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications for each component used in drug production and a description of the test procedures used to check them, including provision for testing adequately representative samples. Such records shall also provide for appropriate retesting of materials subject to deterioration.

(b) The establishment of appropriate specifications, when needed, for drug preparations in the course of processing, and a description of the test procedures to check them, including provision for testing adequately representative samples.

(c) The establishment of appropriate finished-product specifications and a description of laboratory test procedures to check them, including provision for testing adequately representative samples.

(d) Adequate provision for checking the identity and strength for all active ingredients of drugs, for assuring the sterility of articles purporting to be sterile, and the freedom from pyrogens of articles that should be tested for freedom from pyrogens.

(e) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedures used.

(f) A reserve sample of at least twice the quantity of drug required to conduct all the tests performed on the batch of drug shall be retained at least 2 years after distribution has been completed.

(g) Provision for complete records of all data concerning laboratory tests performed, including the dates and endorsements of individuals making the tests, and provision for specifically relating the tests to each batch of drug to which they apply. Such records shall be retained for at least 2 years after distribution has been completed.

(h) Firms that manufacture nonpenicillin products, including certifiable antibiotic products, on the same premises or use the same equipment as that used for manufacturing penicillin products, or that operate under any circumstances that may reasonably be regarded as conducive to contamination of other drugs by penicillin, shall test such nonpenicillin products to determine whether any have become cross-contaminated by pencillin. Such products shall not be marketed if intended for use by man and the product is contaminated with an amount of pencillin equivalent to 0.05 unit or more of pencillin G per maximum single dose recommended in the labeling of a drug intended for parenteral administration, or an amount of penicillin equivalent to 0.5 unit or more of penicillin G per maximum single dose recommended in the labeling of a drug intended for oral use.

§ 133.12 Distribution records.

Complete records shall be maintained of the distribution of each batch of drug in a manner that will facilitate its recall if necessary. Such records shall be retained for at least 2 years after distribution has been completed, and shall include the name and address of the consignee, the date and quantity shipped, and the lot or control numbers identifying the batch of drug.

§ 133.13 Stability.

Adequate provision shall be made for testing the stability of components, drug preparations in the course of processing, when needed, and finished drugs. Such stability tests shall:

(a) Make adequate provision for determining the reliability and specificity of stability test methods employed.

(b) Make adequate provision to determine the stability of products in the containers in which they are marketed to assure, among other things, that the container is suitable, in that it is not reactive, additive, or adsorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug.

(c) Provide for stability studies of any solution prepared as directed in the drug labeling at time of dispensing.

(d) Provide for suitable expiration dates to appear in the labeling of the drug when needed to assure that the drug meets appropriate standards of identity, strength, quality, and purity at time of use.

§ 133.14 Complaint files.

Records shall be maintained of all written or verbal complaints for each product. Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action taken. The record shall indicate the evaluation and action.

MEDICATED FEEDS; MANUFACTURING PRACTICE

§ 133.100 Current good manufacturing practice.

The criteria in §§ 133.101–133.110, inclusive, shall apply in determining whether the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or holding of a medicated feed conform to or are operated or administered in conformity with current good manufacturing practice to assure that a medicated feed meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this Part 133 permit the use of precision, automatic, mechanical, or electronic equipment in the production of a medicated feed when adequate inspection and checking procedures are used to assure proper performance.

§ 133.101 Buildings.

Buildings in which medicated feeds are manufactured, processed, packaged, labeled, or held shall be maintained in a reasonably clean and orderly manner and shall be of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The buildings shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which they are employed, to minimize any risk of mixups between different medicated feeds, their components, packaging, or labeling:

(1) The receipt, control, and storage of components.

(2) Any manufacturing and processing operations performed on the medicated feed.

(3) Any packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finishing products.

(b) Provide adequate lighting and other physical facilities necessary to prevent unsafe contamination of raw materials and finished products before, during, and after production.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

Work areas and equipment used for the production of medicated feeds or for the storage of the components of medicated feeds shall not be used for the production, mixing, or storage of finished or unfinished insecticides, fungicides, or rodenticides or their components.

§ 133.102 Equipment.

Equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding, or control of medicated feeds or their components shall be maintained in a reasonably clean and orderly manner and shall be of suitable design, size, construction, and location in relation to surroundings to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with medicated feeds are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the medicated feed or its components.

(b) Be so constructed that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the medicated feed.

(c) Be constructed to facilitate adjustment, cleaning, and maintenance, and to assure uniformity of production and reliability of control procedures and to assure the exclusion from medicated feeds of unsafe contamination, including cross-contamination from manufacturing operations.

(d) Be suitably grounded electrically to prevent lack of uniform mixing due to electrically charged particles.

(e) Be of suitable size and accuracy for use in any intended measuring mixing, or weighing operations.

§ 133.103 Personnel.

The key employees and/or consultants responsible for the formulation, manufacture, and control of the medicated feed shall have a background of education or experience or a combination thereof that is adequate to assure proper composition and labeling of the medicated feeds.

§ 133.104 Components.

(a) Drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of medicated feeds, shall be received, stored, handled, and otherwise controlled in a manner to maintain the integrity and identification of such articles. Appropriate receipt and inventory records shall be maintained for 1 year and such records shall show the origin of any drug components, the batches in which they were used, and the results of any testing of them by or on behalf of the medicated-feed manufacturer.

(b) Nondrug components shall be stored and otherwise handled in a manner to avoid unsafe contamination, including cross-contamination from manufacturing operations.

(c) Statements relating to the identification and the quantitative composition appearing on the labels of undiluted drugs or other drug components received by the medicated-feed manufacturer from other suppliers may be relied upon by the medicated-feed manufacturer as acceptable evidence of the identity and composition of the drug or drug components in lieu of actual testing of each such drug or drug component if such reliance is made in good faith.

§ 133.105 Formula and production records.

(a) For each medicated feed, a master formula record or card shall be prepared, checked, and maintained by a responsible key employee and retained for at least 1 year after production of the last batch. The formula record or card shall include at least the following:

(1) The name of the medicated feed, together with any other information necessary for the correct identification of the feed.

(2) The weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the medicated feed.

(3) A copy, description, or notation adequately identifying the label, labeling, or placard necessary to be used on or with the complete medicated feed.

(4) Manufacturing instructions for each medicated feed produced on a batch or continuous operation basis, including mixing steps, mixing times, and batch formulas that have been determined to yield an adequately mixed medicated feed; and in the case of medicated feeds produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment that have beeen determined to yield an adequately mixed medicated feed of the specified formula.

(5) Appropriate control directions, including the manner and frequency with which any necessary samples of the medicated feed are to be taken for specified laboratory tests, the criteria for using laboratory test results to change formulations or manufacturing procedures, and the procedures to be observed to avoid unsafe contamination of the medicated feed with other medicated feeds or drug components.

(b) A production record shall be prepared for each batch or run of medicated feed produced, and shall be retained for at least 1 year. The production record shall include:

(1) Product identification, date of production, and endorsement by a responsible individual.

(2) A record of the quantity of drug components used.

(3) A record of the quantity of medicated feed produced.

(c) In the case of a customer-formula feed made to the specifications of a customer, the formula and production records required by this section may consist of copies of customers' purchase orders and sellers' invoices bearing the information required by this section.

§ 133.106 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the medicated feeds produced are of proper composition and labeling:

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of drugs or components during the process; the control of mixing times; the adjustment of the equipment involved in continuous production processes; and the determination of the finished yield, shall be performed in a manner that has been determined by appropriate methods, including laboratory testing of the medicated feed, to be adequate to assure the integrity of the final product. If such steps in the processing are

controlled by precision, automatic, mechanical, or electronic equipment, provision shall be made to adequately check its performance.

(b) All containers to be used for undiluted drugs, drug components, intermediate mixtures, and finished feeds shall be received, adequately identified and properly stored and handled in a manner adequate to prevent mixups or contamination.

(c) Equipment, including dust-control and other equipment, such as that used for holding and returning recovered or flush-out materials back into production, shall be maintained and operated in such a manner as to prevent unsafe contamination of the medicated feed.

(d) The steps used to prevent unsafe contamination of medicated feed include one or more of the following, or other equally effective procedures:

(1) Cleaning of those parts of storage, mixing, conveying, and any other equipment coming in contact with the drug component of the medicated feed for the purpose of cleaning out of the equipment any drug, drug component, or medicated feed prior to the use of the same equipment for the production of a different medicated feed.

(2) The cleaning of the equipment as required in subparagraph (1) of this paragraph, may be achieved by flushing all feed-contacting surfaces of such equipment used in the production of a medicated feed with a quantity of an appropriate drug-free feedstuff that has been found sufficient to remove any significant quantity of a drug component or an intermediate mix or complete medicated feed prior to the production of a different medicated feed. The yield from any such flushing operation may be incorporated in appropriate amounts in the subsequent production of a medicated feed intended to contain the same drug component (or components) to produce a complete medicated feed conforming to its composition and labeling specifications.

(e) If there is sequential production of batches of a medicated feed containing the same drug component (or components) at the same or lower levels, there shall be sufficient safeguards to avoid any buildup above the specified levels of the drug components in any of the batches of the complete feed.

(f) A sampling and assay schedule on the finished medicated feed, or a schedule at least as reliable, for checking on the composition of the finished article shall be applied as follows:

(1) In the case of a medicated feed that requires an approved new-drug application or antibiotic form 10 for its manufacture and marketing, the schedule of assays established in such application shall be used.

(2) In the case of a medicated feed that does not require an approved new-drug application or antibiotic form 10 for its marketing, three appropriately drawn samples from each 400 tons of such medicated feeds produced shall be taken at appropriately spaced intervals over the production period, and, in any event, not less than three such samples of each particular medicated feed during any 1 year shall be collected and analyzed. For the purposes of this subparagraph, the term "each particular medicated feed" shall be construed to include all feeds containing the same drug component (or the same mixture of components) at different levels. The collection and analysis of samples shall be from the medicated feed containing the highest level of the drug component (or mixture of components).

(3) A medicated feed covered by subparagraph (2) of this paragraph shall be exempt from the prescribed sampling and analytical schedule under the following conditions:

(i) The manufacturing practices used in the production of the medicated feed were consistent with the regulations of this part; and

(ii) The manufacturer of the medicated feed has produced at least 3 batches of such feed conforming to composition and labeling specifications during the 1-year period immediately preceding the date of manufacture of the feed and during that period has not been notified by the Food and Drug Administration or any State regulatory official that his manufacturing practices were in conflict with section 501(a)(2)(B) of the act or the regulations of this part and has not distributed a medicated feed during that period which has been proceeded against under the act because of failure of such feed to comply with its composition or labeling requirements or which has been analyzed by any State official and found to be deficient: and

(iii) The medicated feed contains only, as the drug component (or components), a low-level growth-promotion antibiotic (or antibiotics) as provided by and in accordance with the regulations in Part 121 of this chapter; it was

manufactured from a feed additive premix, feed additive concentrate, or feed additive supplement that, at the time of receipt by the medicated-feed manufacturer, bore a label, or was accompanied by labeling, containing a quantitative composition statement of its antibiotic content together with directions for its use in the manufacturing of a legal medicated feed; and the medicated-feed manufacturer, in good faith, relied upon and followed the feed additive premix, concentrate, or supplement label or labeling information and directions for use in the manufacturing of the medicated feed; or

(iv) The medicated feed contains only, as the drug component (or components), a drug (or drugs) as provided by and in accordance with the regulations in Part 121 of this chapter; it was manufactured from a feed additive concentrate or feed additive supplement that, at the time of receipt by the medicated-feed manufacturer, bore a label, or was accompanied by labeling, containing the quantitative composition of its drug content together with directions for its use in the manufacturing of a legal medicated feed; and the medicated-feed manufacturer, in good faith, relied upon and followed the feed additive concentrate or supplement label or labeling information and directions for use in the manufacturing of the medicated feed; or

(v) The medicated feed contains only drug components as provided by and in accordance with the regulations in Part 121 of this chapter and was manufactured from a feed additive supplement, a low level growth-promotion antibiotic premix, a low level growth-promotion antibiotic concentrate, a feed additive concentrate, or a combination of any two of these used in accordance with the conditions set forth in subdivisions (ii), (iii), and (iv) of this subparagraph.

(g) Production and control procedures shall include provision for discontinuing distribution of any medicated feed found by the assay procedures, or any other controls performed, to fail to conform to appropriate specifications. Distribution of subsequent production shall not begin until it has been determined that proper control procedures have been established.

§ 133.107 Packaging and labeling.

Packaging and labeling operations shall be adequately performed and controlled to assure that only those medicated feeds made in compliance with established formula records and manufacturing and control directions shall be distributed; to prevent mixups between the medicated feeds during the packaging and labeling operations; and to assure that correct labeling is employed for the medicated feed. In the case of medicated feeds distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery. Such labeling may consist of an invoice or placard identifying the medicated feed and bearing adequate information for the safe and effective use of the medicated feed. Labels and labeling shall be received, handled, and stored in a manner that avoids labeling mixups. Previously used containers shall be adequately cleaned and labeled before reuse to avoid adulteration or misbranding.

§ 133.108 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that the drug components and the finished medicated feeds conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug used in the manufacture of medicated feeds; this may consist of the manufacturer's or supplier's statement of specifications.

(b) The establishment of finished-product specifications for medicated feeds and a description of any necessary laboratory test procedures to check them, including methods of assay for the active drug ingredient.

(c) A determination that the drug components remain uniformly dispersed and stable in the medicated feed under ordinary conditions of shipment, storage, and use; this may consist of a supplier's or consultant's determination made on a feed of substantially the same formula.

(d) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used; the official Methods of Analysis of the Association of Official Agricultural Chemists, methods described in an official compendium, and any method, submitted as a part of a food additive petition or new-drug application, which has been accepted by the Food and Drug Administration shall be regarded as meeting this provision.

(e) Provision for the maintenance of the results of any assays, including dates and endorsement of analysts. Such records, together with records of analyses reported by any State feed control official shall be retained in the possession of the manufacturer or in the possession of a consulting laboratory operating in his behalf. Such records shall be maintained for a period of at least 1 year after distribution of the medicated feed has been completed.

§ 133.109 Distribution records.

Complete records shall be maintained for each shipment of medicated feeds in a manner that will facilitate the recall, diversion, or destruction of the medicated feed, if necessary. Such records shall be retained for at least 6 months after the date of the shipment, and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the medicated feed shipped. If the medicated feed is held under control of the manufacturer for further shipment at establishments other than where produced, records as outlined in this section shall be maintained at these establishments.

§ 133.110 Complaint files.

The medicated-feed manufacturer shall evaluate by responsible key personnel each complaint received by him on a feed that is manufactured or distributed by him and, where indicated, make such further investigations or take such appropriate action as appears to be warranted in the circumstances. A record of complaints and the action taken by the feed manufacturer shall be maintained for a period of 2 years. If the medicated feed is the subject of an approved new-drug application held by the feed manufacturer, he shall make such reports as are required by § 130.13 of this chapter.

Dr. GODDARD. We are at this time reevaluating the current good manufacturing practices regulations for prescription drugs. Frankly, we are going to have to make them more definitive, much as the drug industry requested in regard to prescription drug advertising regulations. We had expected that the present regulations would assure adequate quality control by all manufacturers, large and small. But the increasing recalls indicate that we must provide more detailed specifications to be followed and precautions to be observed to cut down the risk of failure of drug products to perform properly when they are administered to the patient.

Senator NELSON. How many firms had drug recalls last year?

Dr. GODDARD. 584 in fiscal 1967.

Senator NELSON. How many of those were products marketed by members of the Pharmaceutical Manufacturers Association?

Dr. GODDARD. 131 were members of the PMA and 471 were non-PMA members.

Let me make certain these statistics are right. Let me go back over those.

There were 584 drug recalls for all reasons. One hundred thirteen of these involved PMA members.

Mr. GORDON. We are talking about firms having recalls.

Dr. GODDARD. There were 46 PMA firms that were responsible for the 113 recalls. One hundred eighteen firms were responsible for the 471 recalls of drug products manufactured by non-PMA members.

Senator NELSON. So 32 percent of PMA's members had recalls last year?

Dr. GODDARD. Now, in order that there will not be any argument about the numbers at a later date, Senator, may I submit a table for the record, because we did exclude from our published recall list in preparing for this hearing 38 investigator determinations, six veterinary vitamin preparation recalls, 20 veterinary drug recalls, two diagnostic agents, and one medicated feed recall. So the numbers would

not jibe if someone were to add up our weekly recall lines and check it against this testimony.

(The information referred to follows:)

DRUG RECALLS, FISCAL YEAR 1967

Reason	Total	PMA number	Non-PMA member
Label mixup	29	12	17
Subpotent	120	26	94
Ex. potent	8	2	6
X. con. pen	1	1	0
X. con. other	3	1	2
Substandard	41	4	37
Rx—OTC	2	0	2
No NDA	5	0	5
IND term	5	0	5
Disintegration	45	3	42
Adulteration	180	33	147
Misbranded	19	6	13
Decomposition	8	5	3
Nonsterile	15	1	14
Cert. revoked	42	1	41
Other	61	18	43
Total	[1] [2] 584	[3] 113	[4] 471

[1] Excluding 38 investigator terminations, 6 vet. vitamins, 20 vet. drugs, 2 diagnostic agents, and 1 med. feed.
[2] 584 recalls by 164 firms.
[3] 113 recalls by 46 firms.
[4] 471 recalls by 118 firms.

RECALLS, FISCAL YEAR 1967—DRUGS

Reason	Rx	Non-Rx	Anti-biotics	Bulk drugs	New drugs	Invest new drugs	Vita-Human	Total
Label mixup	25	4	0	0	0	0	0	29
Subpotent	75	3	30	0	0	0	12	120
Ex. potent	8	0	0	0	0	0	0	8
X-Con.-Pen	0	0	1	0	0	0	0	1
X-Con.-Other	1	1	1	0	0	0	0	3
Substandard	29	2	1	0	0	0	9	41
Rx—OTC	2	0	0	0	0	0	0	2
No NDA	0	0	0	0	5	0	0	5
IND term	0	0	0	0	0	5	0	5
Investor. term	0	0	0	0	0	38	0	38
Disintegration	25	19	0	0	0	0	1	45
Adulteration	112	14	3	31	0	0	20	180
Misbranded	10	3	5	0	0	0	1	19
Decomposition	3	4	0	0	0	0	1	8
Nonsterile	4	6	5	0	0	0	0	15
Certificate revoked	0	0	42	0	0	0	0	42
Other	41	9	6	0	0	0	5	61
Total	335	65	94	31	5	43	49	[1] 622

[1] Excluding 6 vet. vitamins, 20 vet. drugs, 2 diagnostic agents, and 1 med. feed.

Mr. GORDON. As I understand it, 46 firms of the PMA's 140 had recalls?

Dr. GODDARD. That is correct.

Mr. GORDON. That means 32.5 percent, is that right?

Dr. GODDARD. Yes, sir.

Mr. GORDON. Of the 760 non-PMA members, 118 firms had recalls, is that correct?

Dr. GODDARD. That is correct.

Mr. GORDON. That is 15.5 percent of non-PMA firms. In other words, PMA members had twice as many recalls as non-PMA members?

Dr. GODDARD. Correct. As far as number of firms go. Now, they manufacture 19 times the units of drugs as the small companies, so that has to be taken into account, too.

Senator NELSON. I am going to put in the record, a chart showing some major recalls in fiscal 1966–67. I am not inserting it to embarrass the PMA firms, but since the PMA is continuously insisting that other firms do not do well, the record ought to be balanced. I have a list here of nine drugs on which there were recalls. One of them involved 570,-374,450 tablets; serious recall; injuries sustained. Only 17.9 percent of that quantity was recovered. They were tablets and they were adulterated. There is another recall listed here involving 17,000,500 tables of Mycostatin. I would like to ask a question about this drug. It is an antibiotic, is it not?

Dr. GODDARD. That is correct.

Senator NELSON. Since you do batch testing, this was not a very serious recall I suppose. It was subpotent.

Dr. GODDARD. I think that is serious, Senator.

Senator NELSON. It is listed here as moderate hazard.

Dr. GODDARD. Any time a subpotent antibiotic gets out, I think that is serious. I am not talking about hazard. I am talking about it is a serious breach of good manufacturing practive.

Senator NELSON. How would a subpotent antibiotic get by your batch testing?

Dr. GODDARD. I can submit for the record the history on this one.

Do not forget, with some of these recalls you have to keep in mind that the drug has a shelf life. Some of the recalls occurred because the drug is obviously becoming subpotent. It was not necessarily subpotent at the time of its manufacture. So this may have simply been an earlier decline in the potency of the drug.

Senator NELSON. This will be printed in the record.

(The documents referred to follow:)

MAJOR RECALLS, FISCAL 1966–67

Company	Drug	Quantity	Hazard	Depth	Percent recovered	Reason
Ayerst Laboratories (American Home Products).	Progesterone (Lingusords)	15,045,092 tablets	Moderate	Doctor	30.0	Cross contamination pencillin.
Squibb	Nystatin (Mycostatin)	18,500,000 tablet	do	Branch warehouse.	10.0	Subpotent.
Abbott	Sterile water solutions	3,500,000 bottles	Serious	Doctor	10.0	Nonsterile.
Roche	Chlordiazepoxide (Librax)	570,374,450 tablets	Serious (injury)	do	17.9	Adulterated.
Pfizer	Meclizine HC–1 (Bonine)	6,905,408 tablets	Moderate (injury)	Retail	40.0	Not given.
Ciba	Aminoglutethimide (Elipten) NDA	41,600,000 tablets	Serious (injury)	Doctor	20.0	Do.
Pfizer	Physician's samples	40,000,000 tablets	Serious	do	(1)	Label mixup.
Richardson-Merrell	Bacitracin (Bacimycin)	656,700 ½-oz. tubes; 810/100 gm. jars; 10,450 ⅛ tubes.	do	Wholesale	(1)	Subpotent.
Burroughs-Wellcome	Polymixin B sulfate (Aerosporin)	1,258,533 10 cc	Moderate	Retail	4.0	Do.

[1] Not given

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING THE HISTORY OF THE DRUG RECALL ON MYCOSTATIN (RECALL NO. 49)

The antibiotic (Nystatin) potency of most lots of this drug dropped below label strength before the end of the one year expiration date, thus causing a reduction in the antifungal properties of the preparation. No adverse reactions have been reported.

Approximately 1,300,000 cartons containing 15 tablets each were originally manufactured under 26 lot numbers and packaged under 48 package control numbers. A total of 45,876 cartons were frozen at the Brooklyn manufacturing plant. Remaining cartons were distributed domestically and also exported to many countries.

During July of 1965, stability studies by the manufacturer, E. R. Squibb & Sons, found that several lots fell below label strength.

On August 23, 1965, Squibb notified by letter FDA's Division of Antibiotic and Insulin Control that seven lots packaged under 18 controls had fallen below labeled strength. In November and December, 1965, they notified our New York District office by phone of other lots being recalled.

After conferring with the Division of Antibiotic and Insulin Control, the firm had voluntarily sent recall telegrams to their 17 distribution branches. (These telegrams were sent July 20, August 20, September 2, November 11, and December 10, 1965.) In addition to this branch level recall, the firm informally instructed its salesmen to remove recalled lots from retail and wholesale shelves.

FDA monitored the firm's branch level recall and also tabulated returns from salesmen. During September 1965, certification privileges were suspended for this product until labeling and formulation changes were made.

The firm voluntarily destroyed the following recalled merchandise on two occasions by grinding in a Somat waste disposal unit:

75,238 Strips (5 tablets each) frozen plant stock destroyed: November 23, 1965.

45,876 cartons (15 tablets each) frozen plant stock destroyed: November 23, 1965.

13,320 cartons (15 tablets each) branch returns destroyed: November 23, 1965.

15,481 cartons (15 tablets each) salesman returns destroyed: November 23, 1965 and March 9, 1966.

Mr. GORDON. Can we conclude, Dr. Goddard, that when PMA members have a recall, the consequences are considerably more serious because of the firm's size, than when one of the smaller, non-PMA firms has a recall?

Dr. GODDARD. I would have to qualify that by saying all other things being equal. In other words, if we are dealing with a serious hazard, the more units of a drug that are out, the more magnified the effect. So the answer would be yes with that qualification.

Senator NELSON. Go ahead, Doctor.

Dr. GODDARD. Our district offices, in cooperation with our Bureau of Education and Voluntary Compliance, have held 22 regional seminars and workshops involving 912 firms during the past year on this very subject. Five national conferences have also been held on GMP. We hope that voluntary compliance will prevail and that all companies will greatly improve their manufacturing processes.

The FDA's inspection and sampling programs are a necessary safeguard between each company's quality control system and the patient's use of the drug. Members of the drug industry and the Food and Drug Administration recognize that there is much to be accomplished in this area of quality control. My own first inkling of the magnitude of the problem came from the rising recall lists.

I determined that we had two basic problems which needed immediate attention. First, I was not satisfied that all drugs on the market were of the highest quality.

Second, I was not satisfied that the FDA was properly tooled up to monitor the drug supply so that the public had the assurance it wants and deserves—that all drugs in the marketplace will perform as intended.

To answer my first dissatisfaction, we have brought to the attention of the drug industry—through the seminars and workshops I mentioned, as well as through personal contacts between our people and industry quality control managers—our serious concern about adherence to Current Good Manufacturing Practices.

To answer my second dissatisfaction, we have established a National Center for Drug Analysis in St. Louis to act as the public's control laboratory. Using automated equipment, the newest assay techniques, and a constantly evolving technology, this National Center will help our agency keep abreast of industry's output and assure the consumer that drugs in the marketplace are closer to perfection than before. Let me repeat, Senator Nelson, that this National Center is an endpoint, it is after the fact. The samples are collected from commercial channels providing us with a consumer-level reading of the drug supply—but leaving us with the disadvantage of having to go back through the entire drug distribution system, if we find anything seriously wrong with one of them.

We believe probably as many as 300,000 samples a year will be required in order to have good statistical sampling, but this has to be worked out in detail at the present time.

We have begun modestly at the National Center, checking out our equipment and giving our chemists and pharmacists the experience which the later expanded efforts will necessitate. Our goal is to examine many thousands of samples a year. We are making good progress, but it is too early to draw any conclusions from the relatively few samples that have been tested. We are still in the "shakedown" period.

Mr. GORDON. Although you say it is too early to draw any conclusions so far from the National Center, can you give us any indication of what the results have shown to date?

Dr. GODDARD. Dr. Banes, do you wish to comment?

Dr. BANES. There are two programs now in progress, one on anticoagulants and the other one in mild tranquilizers. There are 870 samples that have been collected in each of these two categories, but this is not enough to give significant results. On the basis of what we have already seen, the ratio of samples outside of the required limits runs about half a percent in the minor tranquilizers and about 2 percent in the anticoagulants. The anticoagulants are considered a much more significant class of drugs and the 2 percent is something to cause us concern.

Dr. GODDARD. Again, may I caution that these are preliminary results and one cannot draw conclusions from them. The additional samples are programed for both of these categories in the very near future—in fact, in a matter of weeks, and we could perhaps, before your hearings have ended, give you a readout on these first two categories.

Senator NELSON. We would like to have that at a later date when it becomes available.

I have something I would like to clarify for the record. When

Dr. Durward Hall testified some weeks back, we had a little colloquy about the 4,600 drugs that FDA tested. I quote from his testimony:

I agree with you and with Dr. Goddard perfectly, when we hear that all drugs are the same but it is a myth—and that Dr. Goddard himself has exploded the myth. He says he would like to say that they are all the same potency, that they are all of the same value, that they will all have the same effect on the human, which is what we are interested in, and that will have the same quality, but that actually it is not true.

Now, actually, you know, and I know that recently, his studies—

referring to Dr. Goddard's studies—

on potency have been found to be off and I think that he and his office have admitted this.

Senator NELSON. No, I am sorry. They concede out of 4,600 samples only five errors; is that not correct?

And that is a small margin of error.

Dr. HALL. Mr. Chairman, I would have to disagree with that source of information. I don't know where you got it because I spent all day Friday with Dr. Goddard and in his laboratory, and with his chief scientists in his laboratory where these analyses are performed. Dr. Summerson, and they are very free to admit that the initial analysis—and they have no funds for further detailed analysis—was very sketchy and they wished that the statement had not been made. They made the statement.

Senator NELSON. They made the statement, as I understand it on Friday, conceding five mistakes, and we checked with their office.

Do you want to make an observation about this so we will have the record straight? The PMA, I believe, has criticized the study to me personally in my office and in news releases. I think it would be helpful to have the record correct.

Dr. GODDARD. If I may, sir, I have a brief statement I would like to submit for the record on this.

Senator NELSON. It will be printed in full in the record.

(The document referred to follows:)

MARKET AND MANUFACTURERS SURVEY: POTENT DRUGS—1966

This program projected the analysis of approximately 5,000 samples of drugs in 20 categories to be completed by May 6, 1966, based on available analytical resources.

The program was limited to composition analysis of products containing one of the following listed drugs as the single or principal active ingredient:

1. Digitalis and cardiac glycosides
2. Corticosteroids
3. Anabolic steroids
4. Sex steroids
5. Other Hormones
6. Anticoagulants
7. Antihypertensives
8. Ergot Preparations
9. Hypoglycemics
10. Menadione and derivatives
11. Antihistamines
12. Antiarrhythmic-cardiac Drugs
13. Diuretics
14. Nitrites
15. Anticonvulsants
16. Central Nervous System Depressants
17. Central Nervous System Stimulants
18. Antimalarials
19. Chemotherapeutics
20. Antithyroid Drugs

The stated objective of the sampling program was to obtain at least one sample of each dosage form in the listed categories from each primary manufacturer. Repackers and distributors were specifically excluded. Provision was made, at the Districts' discretion, to collect more than one sample from manufacturers having a substantial production of a given drug or where there was a questionable compliance background.

Official USP or NF analytical procedures were specified for some drugs and reference made to NDA procedures for others. In absence of specific instructions, the Districts were instructed to examine official drugs by methods in official

compendia and non-official drugs by procedures from the NDA. The assignment directed that regulatory action be instituted as usual where violations were encountered.

Samples were classified at headquarters as being outside potency limits if the results were beyond: Official compendia limits, NDA specifications, and (for other drugs) 90–110% of label declaration.

A total of 245 manufacturers were represented in the 4,573 samples examined. The Districts originally estimated 261 primary manufacturers of drugs in the 20 categories.

A total of 371 samples, or 8.1%, were classified as outside the potency limits defined above.

The detailed findings were made public, after the general findings were announced, on repeated requests from the drug industry.

As expected, a number of the manufacturers (38 to date) requested additional information concerning code and batch numbers, methods of analysis, and quantitative findings. On receipt of this information, some of the manufacturers examined portions of the same code or batch. In one instance, the manufacturer told us FDA findings were confirmed. In 16 instances the manufacturer reported different results within the acceptable potency range. In 6 samples involving 5 firms after review of the original data, FDA concluded that the original findings were in error. In three samples involving two firms the NDA potency limits were incorrectly tabulated. In the remaining 3 samples the examining laboratory had not followed the prescribed methodology. In such cases, a letter acknowledging the error was sent to the firm. These were:

Hygroton Tablets—Geigy Pharmaceuticals, Ardsley, New York
Furadantin Sodium Sterile-Norwich Pharmacal Company, Eaton Laboratories Division, Norwich, New York
Thyroid Tablets—Parke, Davis & Company, Detroit, Michigan
Methotrexate—Lederle Laboratories, Pearl River, New York
Aristomin Capsules—
Dartal Tablets—G. D. Searle & Company, Chicago, Illinois

The gravimetric method used on the sample of Suspension Tydrocortone TBA, manufactured by Merck, Sharp and Dome, West Point, Pennsylvania, was not sufficiently accurate to warrant the conclusion that the product did not meet potency limits. In other instances, it has not been concluded that the original findings were incorrect.

The following compliance actions resulted from this survey:

6 seizures
15 citations
41 product recalls
11 products discontinued
2 prosecutions filed
2 injunctions granted
4 voluntary destructions

Dr. GODDARD. In summary, this program was carried out between March 24, 1966, and the end of May 1966, when some 4,600 samples were drawn from manufacturers' available stocks. The repackagers and distributors were not included in this survey.

Senator NELSON. Just manufacturers' stock, not products already on the retail market and——

Dr. GODDARD. Those are the instructions that were issued. To my knowledge, that is the procedure that was followed.

Now, we wanted to get at least one sample of each dosage form in 20 listed categories from each of the primary manufacturers. Now, these 20 categories include drugs that commonly used such as digitalis and cardiac glycosides, corticosteroids, diuretics, nitrites, and so forth. The districts were given discretion to collect more than one sample from manufacturers, where they had a substantial production of a given drug or where there was a questionable compliance background.

Now, the procedures that were to be followed were the USP, NF, or NDA procedures and in the absence of a USP or NF standard the

tolerances allowed were a range of 90 to 110 percent of the stated label potency.

Now, this was not presented as being a statistically significant survey. That has been talked about a great deal, and I think the facts still speak for themselves. There were 245 manufacturers represented in these 4,573 samples examined. Three hundred and seventy-one of those samples, or 8.1 percent, were classified as being outside the potency limits defined as I have mentioned.

We did make available the detailed findings, both to the public and to the industry, after repeated requests from the drug industry. Thirty-eight of the manufacturers to date have requested additional information concerning the code and batch number, method of analysis, and quantitative finding. Now, upon receipt of this information, some of these manufacturers examined portions of the same code or batch and in one instance, the manufacturer said "Yes, you were right, we confirmed your findings."

In 16 instances, the manufacturer reported different results within the acceptable potency range.

In six samples involving five firms, after the review of the original data, we did concede that we had made an error.

Now, in three of these six samples involving two firms, the NDA potency limits were incorrectly tabulated. In the other three samples, the examining laboratory had not followed the prescribed methodology and the letter acknowledging the effort were sent to five firms: Geigy, Norwich, Parke-Davis, Lederle, and Searle.

Now, the other original findings, I still say, are correct. We stand behind those as long as it is understood that this is not a representative sample of the market place. The compliance action——

Senator NELSON. It was a random sample, so to speak?

Dr. GODDARD. No, it was not random. The compliance actions resulting from this survey were six seizures, 15 citations, 41 product recalls, 11 products discontinued, two prosecutions filed, two injunctions granted, and four voluntary destructions.

Now, I do not know what else we can say about this survey.

Mr. GORDON. I do not think you have to say anything else.

Senator NELSON. I am happy to have that in the record.

Dr. GODDARD. Later, the reports from the National Center, combined with those from our 17 district laboratories, will give a good picture of manufacturing and quality control of drugs throughout the Nation.

One indicator we now have is our weekly recall list, a list of those products recalled from the market, either voluntarily by the manufacturer or distributor or at the request of the FDA, during each 7-day period.

Drug recalls have risen over the past year. During fiscal 1966, out of 538 recalls of all foods, drugs, cosmetics, devices, and hazardous substances, there were 446 drug recalls. Out of 900 total recalls in fiscal 1967, there were 651 drug recalls, an increase of 45 percent for drug recalls. Some of the factors to consider in evaluating this rise in recalls are the following:

An increased ability—through better programing—of our agency to sample the drug supply and turn up defective products.

An increase in hospital, clinic, physician, and patient reporting leading to product investigation by either the manufacturer or our agency.

An increased sense of responsibility by drug makers that quality assurance is essential to continued industry growth, and corresponding efforts on their part to catch their own defective products.

The introduction of new methodology and new technology to accomplish more sample tests in less time than before, thus increasing the identification of products warranting action.

When all of these things are considered, we find that the record of drug recalls in recent months shows that the drug industry—large companies as well as small—has much to do before we can conclude that the drug supply is what the Nation deserves. We hope to see the time when it is rare indeed that we must ask a company to remove a drug from the market.

Your staff already has a print-out showing drug recalls by company during this past year.

One of the questions you have raised with me and my staff, Senator Nelson, is the therapeutic equivalency of identical drugs. All of our efforts in St. Louis and in production control are aimed at making every drug available today a drug which the doctor, the pharmacist, and the patient may trust to achieve the desired results. As a preface, I must stress, Senator Nelson, that drugs are intended to affect physiological functioning of the body. Thus, the values of the effect of a drug must be weighed against the dangers of the disease or condition being attacked. No drug can ever be guaranteed to be completely safe. You do not have "safe drugs" on the one hand and "unsafe drugs" on the other. When we talk about drug safety, we are talking about relative safety.

The Secretary of Health, Education, and Welfare has appointed a task force which is studying the problems of including prescription drugs in the medicare program. This study, among other things will of necessity cover in depth the areas of relative drug safety and of relative therapeutic equivalency.

Here, as you know, Senator Nelson, certain guidelines are available for our use. The U.S.P. and the N.F. have for many years set standards for laboratory examination in the expectation that every drug conforming to these standards will produce the required results in patients. The manufacturing and testing procedures contained in NDA's and the test procedures in antibiotic and insulin regulations also constitute such standards.

In large measure, we believe that these standards serve their intended purposes. This appears to be particularly true for most antibiotics and insulin; as you are aware, the FDA certifies each batch of antibiotics and insulin to be marketed to see that each meets the appropriate standards, but, as noted before, are not necessarily full guarantees.

However, the science of drug production and formulation is becoming increasingly complex. The establishment of standards adequate to meet our increasingly complicated needs is a continuing process in which the private organizations maintaining the U.S.P. and the N.F., and the Government working with them, are constantly striving to keep ahead.

I think it is important, Senator Nelson, to keep this question of therapeutic equivalency in perspective. There are some who would

have you believe that no reliance can be placed on any drug unless it has been produced by a firm that is widely known. There are others who would have you believe that you can buy any drug in the marketplace and expect it to be therapeutically equivalent to others sold under the same name. I must reiterate that we do not have controlled clinical studies to decide the issue in all cases. We are preparing to have the necessary studies made on about 50 widely employed drugs.

Mr. GORDON. You say in all these cases you have controlled clinical studies showing the lack of therapeutic equivalency?

Dr. GODDARD. It is my understanding that controlled clinical studies have been carried out in a number of instances demonstrating lack of therapeutic equivalency.

Mr. GORDON. How many such cases are there altogether?

Dr. GODDARD. Well, we were talking about this in preparation for the hearings. The best figure we could come up with was approximately two dozen such instances have occurred where lack of therapeutic equivalency has been demonstrated.

Mr. GORDON. Do you know what they are? Can you name the 12 of them?

Dr. GODDARD. Dr. Banes, perhaps, who has been involved in this field—you see, even one of these is significant and we then have to try to ferret out the reason. Some of these are the sugar-coated tetracycline, chloromycetin, and diphenylhydantoin.

Mr. GORDON. So far you have named antibiotics.

Dr. GODDARD. Diphenylhydantoin. Prednisone is one.

Senator NELSON. One what?

Dr. GODDARD. That there has been demonstrated lack of therapeutic equivalence.

Senator NELSON. When was that case?

Dr. BANES. There have been reports in the literature, isolated reports from physicians, stating that one brand of prednisone would maintain a patient satisfactorily, but when the brand is switched, the new medicaments will not maintain that patient.

On the other hand, going back to the first product, the patient responded satisfactorily. We have recently received a letter from a physician from the Mayo Clinic to the same purport.

These situations, of course, require investigation and we have looked into the possible differences in these medications. It turns out that chemically they appear to be the same, but that pharmacologically on testing in animals, there are some differences apparent.

Senator NELSON. It might be valuable, then, if you would be willing to look at the Medical Letter showing the results of their tests on 22 prednisone products. They found no clinical evidence to indicate a lack of equivalency among these drugs. They go on to say, "We therefore recommend that at least to the impecunious patients, you ought to prescribe generically."

Would you look at the Medical Letter and see whether or not any one of these drugs you are mentioning is included in the Medical Letter? It would be interesting to find that out.

Dr. GODDARD. I would be happy to do so.

I might also add that in the potency survey we did there were two prednisone products that were below potency.

So there may be no reason for there being substance to the complaints of these individual physicians.

Senator NELSON. I suppose that in order to be scientific about it, you have to check some other batches to find out whether this is a shelf problem or accident.

Dr. GODDARD. Surely. Exactly; yes, sir.

Dr. BANES. These products are used, of course, in huge volume and these instances that I have cited are isolated instances. Nevertheless, we do wish to investigate them to see if there is any substance to these complaints.

Mr. GORDON. Do you know from the FDA's own experience that, even in these limited cases, there was a lack of clinical equivalence?

Dr. GODDARD. Do you mean our own direct experience? No; for example, the Defense Supply Administration has asked us upon occasion to check a particular drug they have purchased for potency and all other aspects that can be measured in the laboratory—particle size, dissolution rate, all the other characteristics. This we have done. They have told us there are problems with therapeutic equivalency, that their physicians have complained. And in at least one instance that I can recall, we checked it and chemically it was identical. But it subsequently developed on that one that too much of the crystalline form was present, not enough of the amorphous form, so there was a rationale for the physician's complaint.

Mr. GORDON. Did it meet USP standards?

Dr. GODDARD. At that time.

Mr. GORDON. How about at the present time?

Dr. GODDARD. USP standards are in the process of being changed.

Mr. GORDON. So if it meets USP standards, today's USP standards, it might have been violative?

Dr. GODDARD. I do not want to leave the committee with the impression that I am convinced that simple adherence to USP standards alone or NF standards will guarantee therapeutic equivalency. This is a complicated business. I think it is our job, however, to make certain that if manufacturers adhere to those standards, there is a very slight probability that there will not be therapeutic equivalency. That is going to require some clinical testing and that is what we are engaged in.

Senator NELSON. Would it be fair to extend your remark further to say that there is very little clinical evidence to show that if USP standards are met, drugs are not clinically equivalent either?

Dr. GODDARD. That is correct. They are only isolated instances.

Senator NELSON. And the FDA intends presently to begin selecting frequently used drugs and to test them to settle this issue?

Dr. GODDARD. Yes, sir.

Senator NELSON. I think that this testing program will be a great contribution to the public, the medical profession, and even the manufacturers if we can settle the question of equivalency.

Dr. GODDARD. Even at this time I would challenge the claim that you always have to buy a brand-named product in order to be sure that a drug is good. Poor manufacture and control will produce a bad brand-named drug just as surely as it will produce a bad generic-named drug. Manufacturers of brand-named drugs have yet to show that their products are, in fact, produced in all cases to meet subtle refinements over and above basic standards of therapeutic excellence that in any significant way affects the health and well-being of our people. I hope

you will not misunderstand me; many brand-named drugs are good products just as many generic drugs are.

The scientific community has long recognized that in some cases laboratory tests applied outside the body may not give an accurate index of the clinical response that will follow administration of a drug to man. It was for this reason that liver extracts used in treating pernicious anemia had to be tested on patients suffering from the disease to determine their true effectiveness. Representative batches were so tested by a special board recognized by the USP. We now know that pernicious anemia can be treated adequately with vitamin B_{12}, we know how to produce vitamin B_{12} and how to test it for potency in the chemical-bacteriological laboratory; and I know of no one who doubts that the USP potency test for vitamin B_{12} gives a true measure of its therapeutic effectiveness in treating pernicious anemia.

Senator NELSON. You mean there has been enough clinical experience so that that would seem to be the indication?

Dr. GODDARD. That is what I am told.

Thus, we have moved in the past 30 years in this particular area from a situation in which representative batches of a drug for treating pernicious anemia had to be tested on sick people to insure therapeutic equivalency, to one in which an active principle of the original drug is available in highly purified form and is reliably tested for therapeutic equivalency outside the human body.

In the years since the 1930's, we have found a few other products who clinical effect was not accurately measured by the in vitro tests then being applied. No doubt there will be such examples from time to time in the future. But this does not mean that the tests now employed to check the effectiveness of the drug supply are generally bad, nor that you always have to buy a brand-named drug to get the therapeutic effect desired.

At the present time, our feeling is that in only a limited number of drug categories will two drug products with the same active ingredients not produce clinically equivalent results.

Senator NELSON. This is a rather blunt refutation of the brand-name claims, is it not?

Dr. GODDARD. I have to qualify it by saying it is our feeling, now. As I say, I have challenged brand-name representatives, manufacturers of brand-named drugs, to produce their evidence. I have not received that evidence. One or more have admitted that they have no more evidence than anybody else.

The exact number is now under intensive examination by the Government, but for most drug preparations, the identical dosage forms seem, for practical purposes, to perform the same.

In those relatively few instances in which a drug product complies with current specifications but nevertheless fails to deliver the desired therapeutic effects, the deficiency is a proper subject for concern, and a proper justification for considering changes in the specifications. Failure of drug products to yield predictable results represents a potential hazard to thousands of patients, and accordingly cannot be dismissed as unimportant.

It is our purpose to discover the reasons for drug failures, or drug malfunctions, and to eliminate them. We have much to learn in this

field. It will require a great deal of research in the laboratory and in the clinic. Through our own activities, those of the Public Health Service, hopefully those of the Veterans' Administration, with whom discussions are also being held, and Secretary Gardner's task force on prescription drugs, we are now embarked on such investigations.

TRUTHFUL INFORMATION

After the research, after the product comes off the production line, the sponsor must sell it. Most promotion of prescription drugs is directed to the prescriber, not the patient. Honest, fair promotion must be fully realized whether it is through circulars, detail men, magazine ads, TV or whatever medium is employed. The recent history of the regulation of prescription drug advertising is set forth in one of our newest FDA publications—"Compendium of Medical Advertising"—which I offer to the committee at this time.

Senator NELSON. Thank you.

Dr. GODDARD. I would also like to present for the committee's information a copy of our proposed advertising regulations, which reflect a number of items published in the "Compendium." We have extended to September 1 the period for comment on the proposed regulations; after that date, we will review all comments and objections, and then issue the best regulation possible. We solicit a constructive response from the pharmaceutical industry.

The promotion of a drug to physicians, Senator Nelson, is based upon the approved claims that may be made for the product. If a claim or an indication for use does not appear in the final printed labeling—the package insert—then it cannot appear in any of the promotion for the drug. The package insert, then, is a guide for prescription drug advertising and promotion. The insert represents the clinical data supporting the drug, it reflects the ability of the sponsor to produce it according to exacting specifications, and it is the authentic guide to the prescribing physician, short of a complete review of all the NDA files—an impossible task for the busy practicing physician to perform, even if the files were available to him.

Senator NELSON. We will print the proposed advertising regulations. What is the previous bulletin?

Dr. GODDARD. It is called "Compendium of Medical Advertising."

Senator NELSON. What does that mean? Is it a collection your agency has made of the different types of advertising?

Dr. GODDARD. The contents—I might read a portion of it to give you an idea of the coverage:

The "Pharmaceutical Manufacturers Association Principles"; excerpts from the Federal Food, Drug and Cosmetic Act; general regulations on drug advertising; questions on prescription drug advertising; answers on prescription drug advertising; memorandum of understanding between PMA, FDA, and industry——

Senator NELSON. Who published this?

Dr. GODDARD. We did.

Senator NELSON. I will make that available in the committee files, but it will not be printed in the record.

Dr. GODDARD. It is available through GPO.

Senator NELSON. But the listing of your advertising regulations, will be printed in the record.

(The document referred to follows:)

[Reprinted from Federal Register of May 23, 1967; 32 F.R. 7533]

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

Prescription drug advertising and labeling regulations

[21 CFR Part 1]

NOTICE OF PROPOSED RULE MAKING

On the basis of experience with and in response to requests from the pharmaceutical manufacturing industry for clarification of the regulations concerning prescription drug advertisements (§ 1.105) and the regulations establishing exemptions from the requirement that prescription drug labeling bear adequate directions for use (§ 1.106 (b) and (c)), the Commissioner of Food and Drugs proposes the amendments set forth below.

A. Under the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 502(n), 701(e), 52 Stat. 1050, as amended 76 Stat. 791; 1055 as amended 70 Stat. 919; 21 U.S.C. 352(n), 371(e)) and delegated by him to the Commissioner (21 CFR 2.120), it is proposed that § 1.105 be amended by revising paragraph (e) and (l) and by revoking paragraphs (f), (g), (h), and (i). The revised paragraphs would read as follows:

§ 1.105 Prescription-drug advertisements.

* * * * * * *

(e) True statement of information in brief summary relating to side effects, contraindications, and effectiveness:

(1) *When required.* (i) Any advertisement for a prescription drug shall present a true statement of information in brief summary relating to side effects, contraindications (when used in this section, side effects and contraindications include side effects, hazards, warnings, precautions, and contraindications), and effectiveness, if the advertisement recommends or suggests any indication for use in words or by written, printed, or graphic matter, or suggests a dosage for use of the drug (other than quantitative ingredient information), or contains any claim for safety or effectiveness.

(ii) A so-called "reminder advertisement" may be employed if it contains only the name of a drug (which necessitates declaring the established name ,if any, naming a dosage form, and furnishing its quantitative ingredient information) and information relating to quantity, price, and the name and address of the manufacturer, packer, or distributor. To qualify for exemption from the requirements of subdivision (i) of this subparagraph, the advertisement shall not recommend or suggest by printing or graphics any indication for use, drug dosage, or claim for safety, effectiveness, or other quality of the drug.

(iii) An advertisement that incorporates the name of a drug, dosage form name, and quantitative ingredient information, with similar information for other drugs in a composite price list, but does not recommend or suggest any indication for use or dosage for use of the drug, is not required to include information relating to side effects, contraindications, and effectiveness.

(iv) An advertisement for a drug sold in bulk packages, in accordance with the practice of the trade, solely to be processed, manufactured, labeled, or repacked in substantial quantities, is not required to include a statement of information relating to side effects, contraindications, and effectiveness if it does not contain claims for the therapeutic safety or effectiveness of the drug.

(v) An advertisement for a drug sold for use as a prescription chemical or other component for use by registered pharmacists in compounding prescriptions, and which otherwise complies with the conditions for the labeling exemption contained in § 1.106(k), is not required to include a statement of information relating to side effects, contraindications, and effectiveness if it does not contain claims for the therapeutic safety or effectiveness of the drug.

(2) *Scope of information to be included in brief summary.* (i) The advertisement as a whole and each representation and suggestion in the advertisement shall be consistent with the requirement that it present a true statement of in-

formation in brief summary relating to side effects, contraindications, and effectiveness whether or not it relies on a distinct part of the advertisement to present information relating to side effects and contraindications.

(ii) The information relating to effectiveness may be limited to the effectiveness and limitations of the effectiveness of the drug in the conditions for which it is recommended or suggested in the advertisement.

(iii) The information relating to side effects and contraindications shall disclose all of the side effects and contraindications pertinent to the uses of the drug dosage form(s) recommended or suggested in the advertisement, all other uses for which the advertised dosage form is commony prescribed, and all other uses for which such dosage form(s) is recommended or suggested in any labeling or advertising disseminated by or on behalf of the manufacturer, packer, or distributor of the drug.

(3) *Substance of information to be included in brief summary.* (i)(*a*) An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962, or any approved supplement thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement. The advertisement shall present information from labeling approved or permitted in a new-drug application concerning all side effects and contraindications mentioned in such labeling; each side effect and contraindication idea in the labeling shall be contained in the advertisement.

(*b*) If a prescription drug was covered by a new-drug application or a supplement thereto that became effective prior to October 10, 1962, an advertisement may recommend or suggest:

(*1*) Uses contained in the labeling accepted in such new-drug application and any effective or approved supplement thereto.

(*2*) Additional uses contained in labeling in commercial use on October 9, 1962, to the extent that such uses did not cause the drug to be an unapproved "new drug" as "new drug" was defined in section 201(p) of the act as then in force, and to the extent that such uses would be permitted were the drug subject to subdivision (iii) of this subparagraph.

(*3*) Additional uses contained in labeling in current commercial use to the extent that such uses do not cause the drug to be an unapproved "new drug" as defined in section 201(p) of the act as amended. The advertisement shall present information from such labeling concerning all side effects and contraindications mentioned in such labeling.

(ii) An advertisement for a prescription drug subject to certification under section 507 of the act shall not recommend or suggest any use that is not in the labeling covered by the certification or covered by the applicable certification regulations or regulations providing for exemption from certification. The advertisement shall present information from such labeling covered by the certification, or the applicable certification regulations, or regulations provided for exemption from certification, concerning all side effects and contraindications mentioned in such labeling and such regulations.

(iii) In the case of an advertisement for a prescription drug other than a drug the labeling of which causes it to be an unapproved "new drug" and other than drugs covered by subdivisions (i) and (ii) of this subparagraph, an advertisement may recommend and suggest the drug only for those uses contained in the labeling thereof:

(*a*) For which the drug is generally recognized as safe and effective among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs; or

(*b*) For which there exists substantial evidence of safety and effectiveness, consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of the drug involved, on the basis of which it can fairly and responsibly be concluded by such experts that the drug is safe and effective for such uses; or

(*c*) For which there exists substantial clinical experience, adequately documented in medical literature or by other data (to be supplied to the Food and Drug Administration, if requested), on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses; or

(*d*) For which safety is supported under any of the preceding clauses in (*a*), (*b*), and (*c*) of this subdivision and effectiveness is supported under any other of such clauses.

The advertisement shall present information concerning all of the side effects and contraindications that are pertinent to the uses of the drug recommended or suggested in the advertisement, all other uses for which the dosage from advertised is commonly prescribed, and all other uses for which such dosage form is recommended or suggested in all labeling and/or advertising disseminated by or on the behalf of the advertiser. The information relating to effectiveness shall include specific indications for use of the drug for purposes claimed in the advertisement; for example, when an advertisement contains a broad claim that a drug is an antibacterial agent, the advertisement shall name the types of infections and micro-organisms for which the drug is effective clinically, consistent with the information required or permitted in the drug package labeling.

(4) *"True statement" of information.* An advertisement does not satisfy the requirement that it present a "true statement" of information in brief summary relating to side effects, contraindications, and effectiveness if:

(i) It contains any untrue statement; or

(ii) It fails to present adequately a fair balance between claims for safety or effectiveness of the drug and information relating to the limitations of safety or effectiveness pertinent to the uses of the drug; or

(iii) It fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the advertisement or under such conditions of use as are customary or usual; or

(iv) It is misleading in any other particular.

(5) *False, lacking in fair balance, or otherwise misleading advertisement.* An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, among other reasons, if it:

(i) Contains a representation or suggestion, not approved or permitted for use in the drug package labeling, that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence, whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

(ii) Contains a drug comparison claiming advantages for a drug without simultaneously disclosing any pertinent disadvantages (including, for example, disclosure of the fact that the advertised drug has the other disadvantages of a category of drugs and additional disadvantages).

(iii) Contains favorable information or opinions about a drug previously regarded as valid but which have been rendered obsolete by contrary and more recent information, or fails to contain significant recent literature references that are less favorable to a drug than older references used.

(iv) Contains information from published articles that report no side effects with a drug but fails to contain significant information from the literature or other sources that report side effects, or otherwise selects information from any source in a way that makes a drug appear to be safer than it is.

(v) Contains information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does.

(vi) Contains literature references or representations that may exaggerate the effectiveness of a drug by failure to disclose the extent to which claimed results may be due to placebo effect or concomitant therapy.

(vii) Contains data or conclusions from studies of a drug in animals or in vitro in a way that suggests they represent clinical studies, or in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated.

(viii) Contains information from published or unpublished reports or opinions erroneously represented or suggested to be authentic or authoritative.

(ix) Contains information or an opinion from a recognized authority or based on a study favorable to a drug, but fails to reveal that such information or opinion is contrary to or inconsistent with information or opinions from other recognized authorities or other reliable studies.

(x) Uses a statement by a recognized authority that is apparently favorable about a drug, but fails to use unfavorable data or statements from the same authority.

(xi) Contains information or conclusions from a study that lacks significance because it was uncontrolled or for other reasons.

(xii) Uses a quote or paraphrase out of context to convey a false or misleading idea.

(xiii) Uses literature quotations or references that purport to support an advertising claim but in fact do not support the claim or have relevance to the claim.

(xiv) Uses literature, quotations, or references to recommend or suggest conditions of drug use that are not approved or permitted in the drug package labeling or for which there is insufficient evidence to establish safety and effectiveness.

(xv) Offers a combination of drugs for the treatment of patients suffering from a condition amenable to treatment by any of the components rather than for patients who require concomitant therapy as provided by the fixed combination drug, unless approved or permitted drug package labeling recommends the drug for such use.

(xvi) Uses a study on a small number of patients or on normal subjects without disclosing the limitations of the study by calling attention to the small number of patients or the fact that the subjects were normal.

(xvii) Uses "statistics" on numbers of patients, or counts of favorable results or side effects, derived by pooling data from various insignificant or dissimilar studies in a way that suggests that such "statistics" are valid or are derived from large or significant studies supporting favorable conclusions.

(xviii) Uses the concept of "statistical significance" to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results.

(xix) Uses statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

(xx) Uses inversely or otherwise erroneously a statistical finding of "no significant difference" to claim clinical equivalence or to deny or conceal the potential existence of a real clinical difference.

(xxi) Uses tables or graphs to distort or misrepresent the relationships, trends, differences, or changes among the variables or products studied, or uses graphs that are not appropriately titled; for example, fails to label abscissa and ordinate so that the graph is not readily interpretable without reference to the text.

(xxii) Uses reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles or statistical theory, methodology, applied practice, and inference, or that are derived from clinical studies, the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretations, or evaluations.

(xxiii) Uses statements or representations that a drug differs from or does not contain a named drug or category of drugs, or that it has a greater potency per unit of weight, in a way that suggests erroneously or without substantial evidence that the advertised drug is safer or more effective than such other drug or drugs.

(xxiv) Contains claims concerning the mechanism or site of drug action that are not supported by substantial evidence.

(xxv) Uses those parts or the whole of studies or reports of studies that include dosages in excess of those authorized in approved package labeling if the drug advertised is subject to section 505 or 507 of the act, or in the case of other drugs, if the dosages employed were in excess of those recommended in the labeling and generally recognized as safe.

(xxvi) Uses misleading headline, subheadline, or pictorial or other written, printed, or graphic matter.

(xxvii) Fails to present the pertinent limitations of the effectiveness of the drug in immediate conjunction with and as prominently as any claim for effectiveness, whether or not such limitations are disclosed in another part of the advertisement.

(xxviii) Fails to present with equal prominence the limitations of safety of the drug; for example, specific side effects or contraindications pertinent to any claim for safety in immediate conjunction with each such claim for safety even though such limitations are disclosed in another part of the advertisement.

(xxix) Fails to present information concerning side effects and contraindications in as much depth and detail (not exceeding that required in the drug

package) as claims for effectiveness or safety of the drug, taking into account the length of the advertisement and the nature of its message. This means that there may be two permissive levels of summarization:

(*a*) If the claims for effectiveness or safety are presented briefly without dosage information and the advertisement as a whole appears on three pages or less, the side effects and contraindications may be presented concisely provided that each such idea expressed in the approved or permitted drug package labeling is presented in a "Brief Summary"; or

(*b*) If the claims for effectiveness or safety are presented in detail or in discussion form, or dosage information is presented, or parts of the advertisement appear on more than three pages of a periodical of page size larger than 50 square inches, or more than four pages of a periodical of 50 square inches or smaller page size, the side effect and contraindication information shall be presented as a "Brief Discussion Summary" comparable in depth and detail with the information required in the drug package labeling under § 1.106(b)(3).

(xxx) Fails to provide sufficient emphasis for the information relating to side effects and contraindications contained in a distinct part of an advertisement by reason of repetition or other emphasis in that part of the advertisement of claims for effectiveness or safety of the drug.

(xxxi) Fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis.

(xxxii) Fails to present on a page facing another page (or on another full page) of an advertisement on more than one page, information relating to side effects and contraindications when such information is in a distinct part of the advertisement.

(xxxiii) Fails to provide adequate emphasis by the use of borders, headlines, or other copy that extends across the gutter for the fact that two facing pages are part of the same advertisement, when one page contains information relating to side effects and contraindications.

(xxxiv) Fails to include on each spread of an advertisement of more than one page a prominent reference to the presence and location of the information relating to side effects and contraindications when presented as a distinct part of an advertisement.

(f) Revoked.

(g) Revoked.

(h) Revoked.

(i) Revoked.

* * * * * * *

(l)(1) Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communications systems.

(2) Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter concerning a drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor, including reference publications (for example, the Physicians' Desk Reference) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug, are regarded as labeling not subject to section 502(n) of the act, but subject to the labeling requirements of § 1.104 and § 1.106 (b) or (c).

B. Under the authority vested in the Secretary by the act (secs. 502(f)(1), (n), 701(a), 52 Stat. 1051, as amended 76 Stat. 791; 1055; 21 U.S.C. 352(f)(1), (n), 371(a)) and delegated as cited above, it is proposed that:

1. Section 1.105 *Prescription-drug advertisements* be amended by adding to the end of paragraph (d)(2) a new sentence reading "The requirement that an advertisement name at least one dosage form and furnish the related quantitative ingredient information for a drug does not apply to advertisements promoting the sale of a drug in bulk for use in the manufacture of another drug or for use as a component in prescription compounding.".

2. Section 1.106 *Drugs and devices; directions for use* be amended:

a. By adding a heading to paragraph (b) (3) and by revising subdivisions (i) and (ii) thereunder, as follows:

(3) Adequate information for use in drug package:

(i) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use including indications, effects, dosages, routes, methods, and frequency and duration of administration, and all side effects, hazards, warnings, precautions and contraindications under which practitioners licensed by law to administer the drug can use the drug safely and for all purposes for which it is intended, including all purposes for which it is advertised or represented; and

(ii) If the article is subject to section 505 or 507 of the act, the labeling incorporating such information is the labeling approved or permitted under the provisions of section 505 or 507, respectively.

b. By revising paragraph (b) (4) to read as follows:

(4) Promotional labeling options and requirements.

(i) *When required.* All matter determined under § 1.105(1) to the labeling as defined in section 201(m) of the act shall conform to one of the following options unless it is subject to the requirements of subparagraph (3) of this paragraph or optionally conforms to such requirements:

(*a*) "*Full Disclosure.*" (*1*) All labeling disseminated by or on behalf of the manufacturer, packer, or distributor of the drug purporting to present adequate information for its use, or intended for employment as a reference to drug-use information, incorporates as an integral part of such labeling adequate "full disclosure" information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and all side effects, hazards, warnings, precautions, and contraindications under which practitioners licensed by law to administer the drug can use the drug safely and for all purposes for which it is intended, including all purposes for which it is advertised or represented; and

(*2*) If the article is subject to section 505 or 507 of the act, the labeling incorporating such information is substantially the same as the labeling approved or permitted under the provisions of section 505 or 507, respectively.

(*b*) "*Full Warning Disclosure.*" Unless such labeling is subject to or optionally conforms to the requirements of subparagraph (3) of this paragraph or (*a*) of this subdivision, if the labeling:

(*1*) Recommends or suggests a drug dosage; or

(*2*) Presents information for drug use relating to one or more selected indications, but not all indications; or

(*3*) In the case of brochures, booklets, mailing pieces, and related presentations is of more than three pages,

the labeling shall present with respect to each indication for use of the drug suggested in such labeling, substantially the same information for its use, including effects, dosages, routes, methods, and frequency and duration of administration as the corresponding information in the approved or permitted drug package labeling, and shall incorporate as an integral part of such labeling a "Full Warning Disclosure"; i.e., substantially the same information concerning all side effects, hazards, warnings, precautions, and contraindications as that in the approved or permitted drug package labeling.

(*c*) "*Brief Summary.*" Unless such labeling is subject to, or optionally conforms to the requirements of subparagraph (3) of this paragraph or (*a*) or (*b*) of this subdivision, the labeling shall present a true statement of information in brief summary relating to side effects, contraindications (when used in this section, side effects and contraindications include side effects, hazards, warnings, precautions, and contraindications), and effectiveness of the drug, if the labeling recommends or suggests any indication for use in words or by written, printed, or graphic matter, or contains any claim for safety or effectiveness.

(*d*) *Reminder labeling.* If the labeling is not subject to the requirements of subparagraph (3) of this paragraph or (*a*), (*b*), or (*c*) of this subdivision, so-called reminder labeling may be employed. Such labeling may contain the name of a drug (which necessitates declaring the established name, if any, naming a dosage form, and furnishing its quantitative ingredient information) and information relating to quantity, price, and the name of the manufacturer, packer, or distributor, but shall contain no other information or representation in words or by means of graphic matter.

(*e*) *Price list or catalog.* Labeling that incorporates the name of a drug, dosage form name, and quanitative ingredient information with similar information for other drugs in a composite price list or catalog, but does not recommend or suggest any indication for use, or dosage for use of the drug, or contain any information regarding frequency or duration of administration or any claim for safety, effectiveness, or other quality of the drug, is not required to include information relating to side effects and contraindications.

(*f*) *Motion picture films, film strips, sound recordings, and related audio or visual promotional labeling.* (*1*) Motion picture films, film strips, sound recordings, and related audio or visual presentations by or on behalf of the manufacturer, packer, or distributor of a drug that promote the use of a drug distributed by such a person, irrespective of whether the drug is named specifically or is in a category of drugs named, shall present, unless it conforms to the requirements of subparagraph (3) of this paragraph or (*a*), (*b*), or (*c*) of this sub-division, as an integral part of such audio or visual presentation information relating to the major side effects and contraindications of such drug. The audio or visual presentation shall close with a statement to the effect that the drug has side effects and contraindications in addition to those mentioned in the presentation and that "full disclosure" information to supplement the audio or audio-visual presentation will be presented to the audience in printed form. If the drug is subject to section 505 or 507 of the act, the information relating to the major side effects and contraindications of the drug is information that is approved or permitted by written notification from the Food and Drug Administration for such use in motion picture films, film strips, sound recordings, and related audio or visual promotional labeling under the provisions of section 505 or 507, respectively: *Provided, however,* That the requirement that information relating to the major side effects and contraindications of a drug be presented as an integral part of audio or visual promotional labeling will be met in the case of such labeling produced prior to the effective date of this requirement if such information is added to the end of the audio or visual presentation, and if information relating to any major side effects and contraindications acquired after production of the audio or visual promotional labeling is added to the end of the audio or visual presentation.

(*2*) Audio and audio visual aids that are generally promotional, in the sense that they relate to a class of drugs one member of which is marketed by the firm sponsoring the preparation or the presentation of the film or recording, become product labeling when used in a promotional setting (such as when used by detail men), when associated with product promotional pieces, or when other means are used to associate the general message with a particular product in the class.

c. By adding to the proposed revision of paragraph (b)(4) above new subdivisions (ii), (iii), (iv), and (v) that would be similar with respect to labeling as proposed § 1.105(e) (2), (3), (4), and (5) above would be for advertising.

d. By inserting the following subdivisions after § 1.106(b) (4)(v) as contemplated in proposal "c" above.

(—) Fails to incorporate as an integral part of any labeling, required information relating to side effects and contraindications; for example, the required information shall be incorporated in the audio or visual elements of films or sound recordings, bound as an integral part of a reprint, printed on the reverse side of a letter, etc.; provided, however, that in the case of an exhibit, this requirement will be met if a "Brief Summary" of side effects and contraindications is presented on at least one panel of the exhibit, other panels bear a prominent reference to the presence and location of the "Brief Summary" on the exhibit, and drug package or other "Full Disclosure" labeling is made available to viewers at the exhibit.

(—) Fails to present in the case of motion picture films, film strips, sound recordings, and related audio or visual promotional labeling, required information relating to side effects and contraindications so that it will be seen or heard with a prominence reasonably comparable to the information relating to effectiveness of the drug, taking into account all implementing factors such as space, timing, and audio-visual or any other techniques apt to achieve emphasis.

(—) Disseminates reprints of literature reports, reports of symposia, or other reports that include claims of effectiveness or safety or recommend or suggest conditions of use of the drug not approved or permitted in the drug package labeling unless such representations are excluded prior to dissemination.

e. By revising paragraph (b) (5) to read as follows:

(5) All labeling, except labels and cartons, bearing any information for use of the drug, or information relating to side effects, contraindications, safety, or effectiveness of the drug also bears the date when the labeling was placed into use and the same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed.

f. By revising paragraph (c) (3), (4), and (5) to be similar in effect to paragraph (b) (3), (4), and (5) as proposed above.

Any interested person may, within 60 days from the date of publication of this Notice in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, written comments, preferably in quintuplicate, on this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: May 17, 1967.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

Senator NELSON. Does the law require a package insert?

Dr. GODDARD. The regulations and the law both require that a package insert be available. However, the Secretary of Health, Education, and Welfare may exempt the company or the industry from this requirement.

Senator NELSON. But the regulations now require it, and as I understood your testimony this morning, it costs the industry about $6 million a year?

Dr. GODDARD. I am told that this was their estimate when they were discussing with my predecessor the possibility and their desire to publish a compendium in lieu of the package insert. It would simplify their entire packaging problem; individual cartons would not be required.

Now, I think that is fine. More important, however, is the desire to get accurate, reliable information to all physicians, and this is not occurring today. I think it is extremely important. I am mystified as to why the industry will not pick up the ball and exert some leadership in this field and say, yes, we do want good information to get to the practicing physician; we do want them to know about the drugs that are available to them to be used, and we therefore on our own initiative, have caused this compendium to be published. I was hopeful that by now, we could say we are well down the road, but I still have not gotten any response from the industry on this issue.

Senator NELSON. As you know, the idea of a compendium has been widely supported by medical educators and practicing physicians. When the PMA appears before the committee, we will explore this in some detail to find out their viewpoint and to determine whether or not the industry is prepared to support it.

Dr. GODDARD. I think we really have a unique opportunity. The National Academy of Sciences' National Research Council review of the 2,000 drugs still in the marketplace that were marketed between 1938 and 1962 will provide a basis for updating the claims of efficacy of all of these drugs. This means, in effect, that we will have a sound basis for a good compendium as far as the therapeutic claims are concerned. It would seem to me with relatively little additional work, we could cause a truly important book on therapy to come into existence. It should be something that is done, hopefully, with private venture capital, and would not require us to come before Congress and say we

need additional authority to impose a tax upon the industry. Such a tax might accompany the registration, for example, and say for every drug in the marketplace and for x number of units of that drug, so many dollars per annum might be charged for a revolving fund in order for the Government to cause a compendium to come into being.

Sir, I would like to avoid that. I would like to see us operate as men of science, with good reason behind this, a demonstrated need, a desire on the part of everyone to have this occur on a voluntary basis. Those who decry Government regulations, it seems to me, should be in the leadership of avoiding them by their own voluntary efforts, and I would hope this would occur.

Senator NELSON. Thank you.

Dr. GODDARD. To say that our agency has had some difficulty with claims made by many companies in drug advertising is to understate our experience of the past year or so. Basically, the issue has been the inclination of a number of companies to go beyond the approved claims in the inserts and to evade the requirements for a brief, honest statement of the bad and the good to be expected from a drug. In a way, this has been a remarkable situation because at times FDA has not been as rigid on the language in package inserts as it might have been. But even with some small latitude, a number of companies sought even more. At this time, I would like to deposit with this committee copies of eight so-called "Dear Doctor" letters concerning 14 heavily promoted prescription drugs. These letters were sent to the medical community during the past 7 months. You will note that these letters seek to correct misinformation contained in advertising and labeling. In each instance they were written and mailed at our insistence.

Would you like to have for the record, Senator Nelson, the "Dear Doctor" letters that have been sent out?

Senator NELSON. Yes.

Dr. GODDARD. Thank you.

(The documents referred to follow):

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.

SUMMARY

(NOTE.—This revised "Brief Summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert which remains unchanged.)

THE USE OF CHOLOXIN® (SODIUM DEXTROTHYROXINE) DOES NOT REPLACE OR DIMINISH THE DESIRABILITY OF DIETARY MANAGEMENT OF HYPERCHOLESTEROLEMIA. THE INFLUENCE OF LOWERED SERUM CHOLESTEROL ON MORBIDITY AND MORTALITY OF ATHEROSCLEROTIC DISEASE CANNOT BE ASSESSED UNTIL LONG-TERM CLINICAL TRIALS HAVE BEEN COMPLETED.

INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. Strict attention should be paid to the indications and contraindications. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS: 1) Known organic heart disease, INCLUDING ANGINA PECTORIS; HISTORY OF MYOCARDINAL INFARCTION; CARDIAC ARRHYTHMIA OR TACHYCARDIA, EITHER ACTIVE OR IN PATIENTS WITH DEMONSTRATED PROPENSITY FOR ARRHYTHMIAS; rheumatic heart disease; HISTORY OF CONGESTIVE HEART FAILURE; AND DECOMPENSATED OR BORDERLINE COMPENSATED CARDIAC STATUS. 2) Hypertensive states (OTHER THAN MILD, LABILE SYSTOLIC HYPERTENSION). 3) Advanced liver or kidney disease. 4) Pregnacy. 5) Nursing mothers. 6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; WHEN EITHER OR BOTH ARE PRESENT, THE ADVANTAGES OF SODIUM DEXTROTHYROXINE THERAPY MUST BE WEIGHED AGAINST THE POSSIBILITY OF DELETERIOUS RESULTS.

WARNINGS: Because the effects of anticoagulants may be potentiated, REDUCE DOSAGE OF ANTICOAGLANTS BY ONE-THIRD ON INITIATION OF THERAPY and readjust as necessary ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. Concentration of Factors VII, VIII, IX, and platelet activity SHOULD ALSO BE MONITORED, since these factors may be decreased. CONSIDER WITHDRAWAL OF CHOLOXIN (SODIUM DEXTROTHYROXINE) 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients WITH CARDIAC DISEASE is required, and the drug should be withdrawn or dosage reduced if AGGRAVATION OF ANGINA, INCREASED MYOCARDIAL ISCHEMIA, CARDIAL FAILURE, OR CLINICALLY SIGNIFICANT ARRHYTHMIA develops. HYPOTHYROID PATIENTS ARE MORE SENSITIVE THAN EUTHYROID PATIENTS, ESPECIALLY IF TREATED CONCOMITANTLY WITH OTHER THYROID PREPARATIONS; SPECIAL CONSIDERATION TO THE DOSAGE OF THE LATTER MUST BE GIVEN.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias OR CORONARY INSUFFICIENCY. DRUG WITHDRAWAL OR CAREFUL OBSERVATION OF PATIENTS RECEIVING SUCH INJECTIONS IS RECOMMENDED, ESPECIALLY BEFORE ELECTIVE SURGERY.

In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and SUBSEQUENT REAJUSTMENT IF DEXTROTHYROXINE IS LATER WITHDRAWN.

USE IN WOMEN OF CHILDBEARING AGE: In women exercising birth control procedures, the drug should only be administered AFTER WEIGHING POSSIBLE RISK TO THE FETUS AGAINST POSSIBLE BENEFITS TO THE MOTHER. TERATOGENIC STUDIES IN TWO ANIMAL SPECIES HAVE BEEN NEGATIVE.

PRECAUTIONS: UNUSUALLY HIGH PBI VALUES ARE COMMON IN TREATED PATIENTS AND ARE NOT EVIDENCE OF HYPERMETABOLISM. IN CHILDREN, USE ONLY WHEN A SIGNIFICANT CHOLESTEROL LOW-

ERING EFFECT IS OBSERVED. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to metabolism, AND THUS MORE COMMON IN THE HYPOTHYROID PATIENT, ESPECIALLY THE HYPOTHYROID CARDIAC. Cardiac changes have rarely been precipitated in non-cardiac patients. Angina pectoris (0.2% incidence), arrhythmia (0.5%), MYOCARDIAL ISCHEMIA (<0.1%), CARDIOMEGALY (<0.1%), FATAL AND NON-FATAL myocardial infarctions (<0.2%). Insomnia, nervousness, palpitations, tremors, WEIGHT LOSS, LID LAG, SWEATING, FLUSHING, HYPERTHERMIA, HAIR LOSS, CHANGES IN BOWEL HABITS, DIURESIS, AND MENSTRUAL IRREGULARITIES MAY ALSO BE RELATED TO THE MILD METABOLIC ACTION. A FEW PATIENTS DEVELOPED ITCHING AND SKIN RASHES, APPARENTLY FROM IODISM.

DYSPEPSIA, NAUSEA AND VOMITING, AND CHANGES IN APPETITE OCCURRED IN LESS THAN 1%. HEADACHE, CHANGES IN LIBIDO, HOARSENESS, TINNITUS, DIZZINESS, PERIPHERAL EDEMA, MALAISE, TIREDNESS, VISUAL DISTURBANCES, PSYCHIC CHANGES, PARESTHESIA, MUSCLE PAIN, AND BIZARRE COMPLAINTS WERE REPORTED IN LESS THAN 1% OF TREATED PATIENTS. GALLSTONES WERE NEWLY DISCOVERED IN 13 PATIENTS, AND CHOLESTATIC JAUNDICE IN ONE, ALTHOUGH RELATIONSHIP TO DRUG THERAPY WAS NOT ESTABLISHED. IN A TOTAL OF 19 PATIENTS, PRE-EXISTING PERIPHERAL VASCULAR DISEASE, EXOPHTHALMOS, RETINOPATHY, AND DISTURBED SENSORIUM CONTINUED TO WORSEN, CEREBROVASCULAR ACCIDENTS, THROMBOPHLEBITIS, AND G.I. HEMORRHAGES EACH OCCURRED IN LESS THAN 1% OF PATIENTS, BUT THERE APPEARS TO BE NO RELATIONSHIP TO DEXTROTHYROXINE THERAPY.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

PHARMACOLOGY: MOST EVIDENCE INDICATES THE MECHANISM OF ACTION IS TO STIMULATE THE LIVER TO INCREASE CATABOLISM OF CHOLESTEROL; SYNTHESIS OF CHOLESTEROL IS NOT INHIBITED, AND ABNORMAL METABOLIC END PRODUCTS DO NOT ACCUMULATE IN THE BLOOD.

DOSAGE RECOMMENDATIONS: Dosage should start at 1.0 or 2.0 mg. daily to be increased monthly in 1.0 or 2.0 mg. increments to a maximum of 6.0 to 8.0 mg. daily if necessary for control of serumcholesterol in the adult. In hypothyroid patients, the more conservative dosage schedule should be observed. Pediatric dosage is 0.05 mg./kg. daily, increased monthly in 0.05 mg./kg. increments to 0.1 mg./kg. or 4.0 mg. daily if necessary for control.

SUPPLIED: 2.0 mg. and 4.0 mg. scored tablets in prescription bottles of 30.

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 nearly 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 Summary," 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 Department.*

BRIEF SUMMARY OF WARNING INFORMATION FOR QUESTRAN® (CHOLESTYRAMINE)

(NOTE.—This revised "Brief Summary," for use in medical journal advertising, contains additional information, in capital letters, taken from the official package insert.)

Indication.—Questran relieves pruritus associated with partial biliary obstruction.

Contraindication.—Patients with complete biliary obstruction.

WARNING.—ALWAYS ADMIX QUESTRAN WITH WATER OR OTHER FLUIDS BEFORE INGESTING. TO PREVENT DEFICIENCIES OF VITAMINS A, D AND K, SUPPLEMENT THE DIET, AND SEE PRECAUTIONS BELOW.

USAGE IN PREGNANCY.—THE SAFE USE OF QUESTRAN BY PREGNANT AND LACTATING WOMEN HAS NOT BEEN ESTABLISHED.

PRECAUTIONS.—WITH PROLONGED QUESTRAN ADMINISTRATION, GIVE VITAMINS A AND D DAILY. INCREASED BLEEDING TENDENCIES MAY DEVELOP. PROMPT RESPONSE TO PARENTERAL VITAMIN K_1 MAY BE ANTICIPATED. ADMINISTER CHLOROTHIAZIDE, PHENYLBUTAZONE OR WARFARIN ONE HOUR BEFORE QUESTRAN. AS A PRECAUTIONARY MEASURE, ADMINISTER ALL OTHER DRUGS 30 MINUTES TO 1 HOUR BEFORE QUESTRAN. A THEORETICAL POSSIBILITY EXISTS THAT PROLONGED USE MAY LEAD TO DEVELOPMENT OF HYPERCHOLOMERIC ACIDOSIS. THERE IS NO ESTABLISHED RATIONALE FOR USE OF QUESTRAN IN THE RELIEF OF PRURITUS ASSOCIATED WITH OTHER DISEASE PROCESSES.

ADVERSE REACTIONS

Gastrointestinal and Dermatological.—Constipation, diarrhea, nausea, gastrointestinal distress, and vomiting have been reported by about 20% of patients using cholestryamine. Reported less frequently were ABDOMINAL PAIN AND DISTENTION, rash, irritation of the skin, tongue and perianal area.

Bleeding.—In 1% of patients, increased bleeding tendencies occurred due to hypoprothrombinemia.

Steatorrhea.—Steatorrhea occurred but rarely, and then on doses in excess of 24 grams per day.

Cholesterol.—In patients with pruritus associated with partial biliary obstruction, serum cholesterol levels usually decrease during Questran therapy. (Clinical experience has not established the therapeutic use of Questran to reduce serum cholesterol.)

Biliary Calcification.—Two possible instances have been observed, but a casual relationship has not been established.

GEIGY PHARMACEUTICALS,
DIVISION OF GEIGY CHEMICAL CORP.,
Ardsley, N.Y.

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 reported 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 in Hygroton in a previous study.

In addition, the tablet-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.

BRIEF SUMMARY

HYGROTON®—BRAND OF CHLORTHALIDONE

(NOTE.—This revised "Brief Summary," for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

Indications: Hypertension and many types of edema involving retention of salt and water.

Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.

Warning.—With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED. DISCONTINUE ENTERIC-COATED POTASSIUM SUPPLEMENTS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Precautions.—ANTIHYPERTENSIVE THERAPY WITH HYGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS OR OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates,

narcotics or alcohol may potentiate hypotension. BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL DAMAGE, PERIODIC DETERMINATION OF THE BUN IS INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated. HEPATIC COMA MAY BE PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, HYGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids. ACTH, or digitalis. Salt restriction is not recommended.

Adverse reactions.—Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, hyperuricemia, headache, muscle cramps, orthostatic hypotension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, ACUTE GOUT, AND PANCREATITIS WHEN epigastric pain or UNEXPLAINED G.I. symtoms DEVELOP after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

Average dosage.—One tablet (100 mg.) with breakfast daily or every other day.

Availability.—White, single-scored tablets of 100 mg. in bottles of 100 and 1000.

BRIEF SUMMARY

REGROTON®—CHLORTHALIDONE, 50 MG.; RESERPINE U.S.P., 0.25 MG.

(NOTE.—This revised "Brief Summary," for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

Indications.—Hypertension.

Contraindications.—History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.

Warning.—With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED.

DISCONTINUED COATED POTASSIUM-CONTAINING FORMULATIONS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use cautiously during pregnancy since adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs.

Precautions.—ANTIHYPERTENSIVE THERAPY WITH REGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS, OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half.

BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL DAMAGE, PERIODIC KIDNEY FUNCTION TESTS ARE INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated. HEPATIC COMA MAY BE PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, REGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. BILIARY COLIC MAY BE PRECIPITATED (IN PATIENTS WITH GALLSTONES) AND BRONCHIAL ASTHMA MAY OCCUR IN SUSCEPTIBLE PATIENTS.

Adverse reactions.—The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and ACUTE GOUT. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hy-

perglycemia, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, THROMBOCYTOPENIA, AGRANULOCYTOSIS, nasal stuffiness, increased gastric secretions, nightmare, purpria, urticaria, ecchymosis, weakness, uvetis, optic atrophy and glaucoma, and PRURITUS. ERUPTIONS AND/OR FLUSHING OF THE SKIN, A REVERSIBLE PARALYSIS AGITANS-LIKE SYNDROME, INCREASED SUSCEPTIBILITY TO COLDS, DYSPNEA, weight gain, decreased libido, DRYNESS OF THE MOUTH, deafness, ANOREXIA, AND PANCREATITIS WHEN EPIGASTRIC PAIN OR UNEXPLAINED G.I. SYMPTOMS DEVELOP AFTER PROLONGED ADMINISTRATION. Jaundice, xanthopsia, PARESTHESIA, PHOTOSENSITIZATION and necrotizing angiitis ARE POSSIBLE.

Average dosage.—One tablet daily with breakfast.

Availability.—Pink, single-scored tablets in bottles of 100 and 1000.

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 deserpidine). 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 is 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.

BRIEF SUMMARY

ENDURON AND ENDURONYL

(NOTE.—This revised "brief summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert which remains unchanged.)

Indications.—Enduron is used to control edema and mild to MODERATE hypertension; also used with other drugs for hypertension. Enduronyl is used in mild to moderately severe hypertension; WHEN USED WITH ENDURONYL, MORE POTENT AGENTS CAN BE GIVEN AT REDUCED DOSAGE TO MINIMIZE UNDESIRABLE SIDE EFFECTS.

Contraindications.—Neither Enduron nor Enduronyl should be used in severe renal disease (except nephrosis) or shutdown; in severe hepatic disease or impending hepatic coma; in patients sensitive to thiazides. HEPATIC COMA HAS BEEN REPORTED AS A RESULT OF HYPOKALEMIA IN PATIENTS RECEIVING THIAZIDES. Enduronyl is contraindicated in patients with severe mental depression and SUICIDAL TENDENCIES, active peptic ulcer, or ulcerative colitis.

Warnings.—Consider possible sensitivity reactions in patients with a history of allergy or asthma. If added potassium intake is indicated, dietary supplementation is recommended. Enteric-coated potassium tablets should be reserved for cautious use only when adequate dietary supplementation is not practical because these tablets may induce serious or fatal small bowel lesions CONSISTING OF STENOSIS WITH OR WITHOUT ULCERATION. THESE SMALL BOWEL LESIONS HAVE CAUSED OBSTRUCTION, HEMORRHAGE AND PERFORATION FREQUENTLY REQUIRING SURGERY. MEDICATION SHOULD BE DISCONTINUED IMMEDIATELY IF ABDOMINAL PAIN, DISTENSION, NAUSEA, VOMITING OR GASTROINTESTINAL BLEEDING OCCURS.

Precautions.—Use thiazides with caution in severe renal dysfunction, impaired hepatic function, or progressive liver disease. In surgical patients, thiazides may REDUCE the response to vasopressors and INCREASE the response to tubocurarine. Use thiazides with caution in pregnancy (bone marrow depression, thrombocytopenia, or altered carbohydrate metabolism HAVE BEEN REPORTED in certain newborn infants). Blood dyscrasias INCLUDING THROMBOCYTOPENIA WITH PURPURA, AGRANULOCYTOSIS AND APLASTIC ANEMIA; elevations of BUN, serum uric acid, or blood sugar HAVE ALSO BEEN REPORTED. SYMPTOMATIC GOUT MAY BE INDUCED. ANTIHYPERTENSIVE RESPONSE MAY BE ENHANCED FOLLOWING SYMPATHECTOMY. Use Enduronyl with caution in patients with a history of peptic ulcer, as rauwolfias may increase gastric secretion. Discontinue at the first sign of mental depression. Rauwolfia alkaloids may increase hypotensive effects of surgery or anesthesia, and SHOULD BE discontinued two weeks prior. THEY ALSO LOWER THE CONVULSIVE THRESHOLD AND SHORTEN SEIZURE LATENCY. IN EPILEPSY DOSAGE ADJUSTMENT OF ANTICONVULSANT MEDICATION MAY BE NECESSARY. Alcohol, barbiturates, or narcotics may potentiate action of deserpidine.

Adverse reactions.—During intensive or prolonged therapy, GUARD AGAINST HYPOCHLOREMIC ALKALOSIS AND HYPOKALEMIA (especially the latter if patient is on digitalis). ALL PATIENTS SHOULD BE OBSERVED FOR SIGNS OF HYPONATREMIA ("LOW-SALT" SYNDROME). REPORTED

THIAZIDE REACTIONS INCLUDE: ANOREXIA, NAUSEA, VOMITING, DIARRHEA, headache, skin rash, dizziness, paresthesia, weakness, photosensitivity, jaundice, and pancreatitis. Reported rauwolfia reactions include: nasal stuffiness, nausea, weight gain, diarrhea, aggravation of peptic ulcer, epistaxis, skin eruption, AND REDUCTION OF LIBIDO AND POTENCY EXCESSIVE DROWSINESS, FATIGUE, WEAKNESS, AND NIGHTMARES MAY SIGNAL EARLY SIGNS OF MENTAL DEPRESSION.

WALLACE PHARMACEUTICALS,
DIVISION OF CARTER-WALLACE, INC.,
Cranbury, N.J.

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.

ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LA ROCHE, INC.,
Nutley, N.J.

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.

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR LIBRIUM®
(CHLORDIAZEPOXIDE HCL)

(NOTE.—This revised "brief summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package circular which remains unchanged.)

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications.—Patients with known hypersensitivity to the drug.

Warnings.—Caution patients about possible combined effects with alcohol and other CNS depressants. AS WITH ALL CNS-ACTING DRUGS, CAUTION PATIENTS against hazardous occupations requiring complete mental alertness (*E.G.*, OPERATING MACHINERY, DRIVING). THOUGH PHYSICAL AND PSYCHOLOGICAL DEPENDENCE HAVE RARELY BEEN REPORTED ON RECOMMENDED DOSES, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions.—In the elderly and debilitated, and in children over SIX, limit to smallest effective dosage (INITIALLY 10 MG OR LESS PER DAY) TO PRECLUDE ATAXIA OR OVERSEDATION, increasing gradually as needed and tolated. NOT RECOMMENDED IN CHILDREN UNDER SIX. THOUGH GENERALLY NOT RECOMMENDED, IF COMBINATION THERAPY WITH OTHER PSYCHOTROPICS SEEMS INDICATED, CAREFULLY CONSIDER INDIVIDUAL PHARMACOLOGIC EFFECTS, PARTICULARLY IN USE OF POTENTIATING DRUGS SUCH AS MAO INHIBITORS AND PHENOTRIAZINES. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*E.G.*, EXCITEMENT, STIMULATION AND ACUTE RAGE) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies MAY BE PRESENT AND PROTECTIVE MEASURES NECESSARY. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse reactions.—Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. IN A FEW INSTANCES syncope HAS BEEN REPORTED. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reductions; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction HAVE BEEN REPORTED occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

Usual daily dosage.—Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (SEE PRECAUTIONS.)

Supplied.—Capsules, 5 mg, 10 mg and 25 mg—bottles of 50.

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 CORP.

Senator NELSON. Senator Javits did leave a question with the staff that he wanted me to ask.

He asks what is the feasibility of the Public Health Service establishing a formulary on a national or a regional basis that would be available for doctors to rely upon. I do not want to assume that he means a voluntary formulary, but that is probably what he does mean. Do you have any comment to make?

Dr. GODDARD. I am still a commissioned officer in the Public Health Service, but I would hate to assume the Surgeon General's prerogative in trying to answer that question.

Senator NELSON. Do you think it would be feasible for anybody to do it?

Dr. GODDARD. I do not see why it would not be, depending on how it is to be implemented. This would be the controlling factor, in my determination. There are many formularies in existence today. Hospitals quite commonly have formularies. It simply says to the doctor, when you operate in these confines, these are the drugs that are available; unless you have some good reason that your patient needs something special and beyond our formulary, you will prescribe those listed.

Now, if the Senator were referring to the medicare activities that are currently under review, again this would be more appropriate for the Department of Health, Education and Welfare to respond to. But as a physician, I could see where an appropriate formulary could be developed.

Senator NELSON. Thank you.

Dr. GODDARD. There seems to have been some improvement in pharmaceutical advertising during the past year, but this impression is based upon my own close observation and may well be colored by my hope for improvement.

But, Senator Nelson, we are speaking not only about the advertising and promotion of drugs approved since the passage of the Kefauver-Harris amendments in 1962. We are also responsible for watching the promotion of drugs that came into the marketplace between 1938 and 1962, about 3,000 drugs whose claims are now under scrutiny by 27 scientific panels at the National Academy of Sciences. When these scientific groups have studied the drugs they will state the therapeutic uses for which they believe the respective products may properly be offered. This widespread cooperative effort on the part of many of the Nation's medical leaders will furnish benchmarks for judging the promotion of those products that have not had to clear the efficacy review established by the 1962 amendments.

In order to further an honest promotional effort, our agency has supported the idea of an up to date, complete, free compendium of drug data for every health professional. This is because we anticipate the need of the medical community—doctors, pharmacists, nurses, medical schools, and hospital and clinical staffs—for a basic source of accurate prescribing information for all drugs in the marketplace. We have taken part in symposia on the matter.

Mr. GORDON. How many civil and criminal cases have been brought against drug firms in the last couple of years for false and misleading advertising?

Mr. GOODRICH. Seven or eight. I would have to get the exact figure for you.

Mr. GORDON. Are these criminal?

Mr. GOODRICH. Some criminal and some seizures.

Mr. GORDON. What has been the disposition of these?

Mr. GOODRICH. The seizures? I believe there were three of them. All four of them were settled by consent decree. One of them may not have been finally settled—in any event, we have worked up a consent decree with them and it will be the fourth.

One of the criminal cases was settled on a plea of nolo contendere, and the other three or four are pending on motions to dismiss in that kind of a setting.

Dr. GODDARD. We will provide this information, as you will recall, in response to Senator Javits' question as well.[1]

Mr. GORDON. Which publication has been most prominent in the carrying of false or misleading medical advertising?

Dr. GODDARD. We have not made any study of publications. One would have to really carry on a comprehensive analysis of this. I cannot answer that question intelligently, because we have not carried out such a study.

Now, of course, you realize that most of these advertisements that we were striking at were carried by many publications. You know, the editors' plight is really a difficult one, because it takes our staff 3 to 4 man-days as a minimum, and usually around 10 man-days, to analyze an ad completely and to provide me with a report.

Mr. GORDON. In reading the complaints of the Justice Department, I notice that one name stands out among others. That is the Journal of the American Medical Association.

Dr. GODDARD. Well, I am told they have the largest paid advertising receipts of any journal published, so that does not really surprise me. But I would not limit it to the JAMA. It is not solely their problem. It is a tough problem for the editor to contend with.

We have worked very closely with the Drug Research Board of the National Academy of Sciences, which has also vigorously supported this concept. We have urged the leading trade associations of the drug industry to underwrite the costs of the compendium in the interests of better medical therapy and with the possibility of a more rational approach to the package insert by both industry and Government.

Senator Nelson, FDA is making every effort to make sure that the claims for a drug and the guidance for its proper usage, will be in the hands of all those who prescribe or compound or otherwise are responsible for drug therapy. Thus far, neither industry nor organized medicine has come forward to undertake such a compendium. We have had to make a start in this direction on our own.

This cartridge of microfilm, Senator Nelson, is our beginning effort in the production of a drug labeling compendium for our own agency's use. We are putting into this film record updated package inserts, to make sure that only approved inserts are accompanying the drug products coming off the production line.

[1] See pp. 751, 752.

We are starting with post-1962 drugs. We will be shortly feeding into the system the pre-1962's, as they are corrected to meet the recommendations of the scientific panels of the NAS.

The 1962 amendments authorized FDA to establish simple, useful names for drugs. You have heard testimony pointing out the difficulty the busy physician faces in the area of drug nomenclature—trade names are simple, short, and easily remembered while generic names are often neither pronounceable nor meaningful. Obviously, it is much easier for the doctor to prescribe by brand name.

The United States Adopted Name Council, a nongovernmental group, has studied the problems in this area. Working with the drug industry and in consultation with FDA, the council has made a significant start. Last fall, we proposed regulations to adopt 27 names recommended by the council as established names.

Senator NELSON. Do you have a list of them?

Dr. GODDARD. Yes, I shall be happy to provide that.

Senator NELSON. I would like to have the record contain that information.

(The document referred to follows:)

§ 138.1 Definitions and interpretations.

(a) As used in this Part 138. "act" means the Federal Food, Drug, and Cosmetic Act, sections 201–902, 52 Stat. 1040 (21 U.S.C. 321–392), with all amendments thereto.

(b) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this Part 138.

(c) The term "official name" means, with respect to a drug or ingredient thereof, the name designated in this Part 138 under section 508 of the act as the official name.

§ 138.2 Drugs; official names.

The following are designated official names under section 508 of the act and are "established" names within the meaning of section 502(e) of the act:

Chemical name or description	Official name
Alkaloid ($C_{46}H_{54}N_4O_{10}$) from *Vinca rosea*, Linn	Vincristine.
9-Aminoacridine, salt with 4-hexylresorcinol	Acrisorcin.
6-(D-2-Amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]-heptane-2-carboxylic acid.	Ampicillin.
2-Aminopurine-6-thiol, hemihydrate	Thioguanine.
Bis (dimethylthiocarbamoyl) disulfide	Thiram.
2-*sec*-Butyl-2-methyl-1,3-propanediol dicarbamate; or 2-methyl-2-*sec*-butyl-1,3-propanediol dicarbamate.	Mebutamate.
1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid	Indomethacin.
7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Oxazepam.
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Diazepam.
6-Chloro-3,4-dihydro-2-methyl-3-([(2,2,2-trifluoroethyl) thio]-methyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	Polythiazide.
6-Chloro-3,4-dihydro-3-(5-norbornen-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	Cyclothiazide.
l-2-(*p*-Chloro-*α*-[2-(dimethylamino)-ethoxy]-benzyl)pyridine	Rotoxamine.
Dihydrohydroxycodeinone-*l*-3-(3,4-Dihydroxyphenyl)-2-methylalanine	Oxycodone.
	Methyldopa.
1-(2,3-Dihydroxypropyl-3,5-diiodo-4(1*H*)-pyridone	Iopydol.
3,5-Diiodo-4(1*H*)-pyridone-1-(*p*,*α*-Dimethylbenzyl) camphorate 1:1 salt with 2,2′-iminodiethanol.	Iopydone.
	Tocamphyl.
α,*α*-Dimethylphenethylamine	Phentermine.
5-Ethyl-3-methyl-5-phenylhydantoin	Mephenytoin.
N-Ethyl-2-phenyl-*N*-(4-pyridylmethyl)-hydracrylamide	Tropicamide.
2-Ethylthioisonicotinamide	Ethionamide.
17*β*-Hydroxy-2-(hydroxymethylene)-17*α*-methyl-5*α*-androstan-3-one	Oxymetholone.
6-Hydroxy-*β*,2,7-trimethyl-5-benzofuranacrylic acid, *δ*-lactone	Trioxsalen.
D-3-Mercaptovaline	Penicillamine.
3-Methoxy-19-nor-17*α*-pregna-1,3,5(10)-trien-20-yn-17-ol	Mestranol.
2-Methyl-2-propyltrimethylene butylcarbamate carbamate; or 2-(hydroxymethyl)-2-methylpentylbutylcarbamate carbamate.	Tybamate.
2,4,7-Triamino-6 phenylpteridine	Triamterene.
5-[(3,5-Xylyloxy)methyl]-2-oxazolidinone	Metaxalone.

Dr. GODDARD. Although this beginning is modest, greater emphasis will be placed on this program in coming years, and additional names, many of which have already been selected by the council, will be adopted by regulation. Along these lines, Senator Nelson, I would make a few more remarks about the continuing education of physicians in this country. Data such as will be available within FDA on the microfilm are needed throughout the medical community; I have already commented upon our support for compendia containing such information. Medical advertising has been cited before this committee as one of the forms of continuing education of the doctor. I would agree with this appraisal, for—whether good or bad—industry spends some $3,000 per year per doctor on promotion. I have described to you our attempts to assure better medical advertising. We will continue to strengthen our monitoring of such advertising.

It has been suggested that further educational activities could take the form of FDA announcements of newly approved drugs to the medical community. This suggestion deserves consideration, but mailings of this volume are extremely costly and would be impossible without larger appropriations.

We are currently working with Duke University, the Universities of Wisconsin and Pittsburgh, and others to get specialized drug information to doctors and students in surrounding areas. We will continue to broaden these programs and strengthen them.

There is one subject, Senator Nelson, which has not been discussed recently, and one which might well benefit from a comprehensive review by a committee of the Congress. Today, as we all know, there is a tremendous shortage of scientific personnel. Research activities all over the country are hampered because of this shortage. Yet, under the policy FDA has followed since 1938, clinical data submitted to FDA by one firm cannot be utilized by a second firm wishing to market the same compound. It would reduce much duplicative research to place such data in the public domain, available on a specific request, making it usable by all once it is employed to support a new drug approval. This is essentially the procedure presently followed under the food additive and pesticide chemicals provisions of the Federal Drug and Cosmetics Act. We recognize that such a change raises the questions about the circumstances under which data purchased with private money shall be placed in the public domain. But we also realize that the scientific-medical community may have a valid need to know the detailed scientific basis for approval of a new drug that may be used by millions of people. This is, indeed, a basic policy question that deserves the most careful attention of all concerned, including the Congress.

Mr. GORDON. Dr. Goddard, I am a little bothered about these statistics on drug recalls. Do you have before you the sheet which we compiled?

Dr. GODDARD. Yes.

Mr. GORDON. You will notice that the Pfizer Co. sent out 40 million physician samples which were subsequently recalled.

Dr. GODDARD. Yes.

Mr. GORDON. The hazard is stated as serious, and the samples were received by practicing physicians. Is this not probably the most dangerous type of recall? Because it is in a doctor's drawer he merely

opens the drawer and gives it to a patient. Could you make any comments about that?

Dr. GODDARD. Well, the only comment I could make is that we wanted to have a bill passed by the Congress that would prohibit the mailing of unsolicited samples to physicians. This is one complaint I still commonly get from practicing physicians: Why are the drug companies permitted to send unsolicited samples? Why cannot they be only made available upon request?

Now, in terms of danger and risk, we thought this was a serious hazard and did ask that company to recall it from the physicians.

Mr. GORDON. What percentage was recovered?

Dr. GODDARD. I would have to ask Mr. Barnard.

We do not have figures as to percentage recovered on label mixup. This involved at least two products.

Mr. GORDON. When I see these small percentages of recovery I wonder what happens to the rest. For example, 570 million tablets of Librax were recalled. This involves a serious hazard and actually caused injury. Yet only 17.9 percent were actually recovered. What happened to the rest of it?

Dr. GODDARD. It has been used.

Mr. GORDON. It has been used?

Dr. GODDARD. Or it is discarded by the pharmacy or the physician involved if he stocks it, upon receipt of the notice. In other words, some pharmacies may have a minimal quantity on hand, or some physicians. I used to dispense drugs when I was in practice in a little farm town. I would get a notice like this and it was just easier to dump the doggone stuff away. It was never that expensive. I do not mean Librax, of course.

Mr. GORDON. This drug is quite expensive, is it not?

Dr. GODDARD. Well, I practiced in the days before we had expensive products.

I do not think anybody could account for the difference in these figures. Let us ask Mr. Barnard.

Was 570 million tablets the total produced up to that point in time, or that was available in the marketplace?

Mr. BARNARD. Those figures reflect the total of the batches that were recalled. In other words, that is the total of the number of dosage units of the particular bath or batches involved in the recall.

Dr. GODDARD. Some of those batches may have been made and gone into the distribution system and actually been used by patients before the recall was effective—before the deficiency was known. So, in fact, I would say when you get up to 50 percent of the drug recall, you have a pretty effective recall.

Other specific reforms have been suggested to this committee. Continuous inspection has been mentioned, as has the extension of batch certification to all drugs. We are not proposing either of these alternatives now. However, if the studies on therapeutic equivalency currently underway in the Department do show a few more cases in which supposedly similar products on the market give divergent therapeutic effects, we may need to consider measures for dealing with that situation. One possible solution—and I merely mention it here without taking a position on it—would be to require all makes of a drug on the market to be therapeutically equal, in addition to the present require-

ments of safety and effectiveness. This could be accomplished by authorizing FDA, where there may be a lack of therapeutic equivalency, to establish by regulation, requirements to insure production of drugs of uniform effectiveness; a firm would then be required to follow the procedures in the regulation when manufacturing the drug unless it had presented adequate evidence that an alternative procedure would produce a comparable product and had FDA's approval for use of the alternate method.

In conclusion, Senator Nelson, we must recognize that many difficulties still exist in the drug area; however, we do not believe these problems are insurmountable. We will continue to foster meaningful cooperation among the industry, the scientific community, and the Federal Government to the optimum extent. We will also continue to emphasize the need for education, not only for the medical profession but for the general population as well. When necessary, we will impose the full force of our regulatory authority to achieve our objectives.

The approval process for drugs, the review of drug efficacy, the regulation of manufacturing quality controls, and the regulation of prescription drug advertising will be improved and strengthened. Our endeavors in these areas, we believe, will be of significant value in assuring the public of a drug supply of impeccable quality and purity.

I can also assure you, Senator Nelson, that every effort will be made to solve the complex and varied questions this committee has broached. We must maintain perfection—and no less—as our goal in this vital, life-sustaining field of science.

I will be happy to answer any additional questions you may have.

Senator NELSON. I must leave shortly but first I want to say that the committee appreciates very much your coming here today to present your testimony. It is most helpful to the record that we are accumulating here. As you know, we hope that at some subsequent date you will be available to come back to explore some other aspects of the drug field with us.

Dr. GODDARD. Be glad to make myself available at your request.

Senator NELSON. As a member of the Department of Health, Education, and Welfare task force on prescription drugs, are you familiar with Joseph Barrows' proposal? Joseph Barrows is the president of the Drug & Allied Products Guild, a trade association which represents small manufacturers of generics. He proposed that the Government utilize academic facilities for the preparation of, "complete master formulas," providing detailed instructions and procedures for making and testing all official drugs. Do you have any comment you would like to make on that?

Dr. GODDARD The university community will have an opportunity, I believe, to comment, make their suggestions as we improve our good manufacturing practices. I do not know any high degree of expertise, and this is a reflection of my own ignorance, frankly, that exists in the university community with respect to the technical aspects of the production of drugs. I just do not know of this existing. There is some expertise of this type in the food area, oddly enough. We have it at the MIT Institute of Food Technology. There is nothing comparable for the training of drug industry personnel, and this is a need that has been recognized both by us and members of the drug industry.

I would be somewhat reluctant to turn that job over to the uni-

versity community. I think it is something that the drug industry itself and the FDA could work out with some consultations from the university community.

Senator NELSON. Well, as you proceed to clinically test the most frequently used drugs, will you be doing some contracting?

Dr. GODDARD. Oh, yes. I may have misunderstood the chairman's question, but I thought you were talking about the technical aspects of manufacture. If you are talking about the determination of therapeutic equivalency we will be working with the Public Health Service, hopefully the Veterans' Administration. We have opened discussions with them. We have a contract with the Georgetown University facility, defining certain drug classes that they are going to examine. Hopefully other parts of the university community will become involved.

Senator NELSON. I talked to Mr. Barrows just very briefly at one of the hearings. My interpretation of our brief conversation was that he was hoping that some of the distinguished universities could take over some of the testing job that needs to be done. Let me ask you this. Do you intend, in the clinical testing of these drugs, to follow a procedure in which you might contract with teaching hospitals to do double blind clinical testing?

Dr. GODDARD. We will be involved with contracts with teaching hospitals. As I indicated, we are negotiating with Veterans' Administration now. Many of these are teaching hospitals, research centers. We will also be working with the Public Health Service and also hopefully other parts of the academic world.

Senator NELSON. How many drugs are you selecting for such testing?

Dr. GODDARD. Probably no more than 50 classes, in other words, 50 different products where the drugs are made by more than one manufacturer, and the number of drugs then will be a function of how many are available in the class. For example, with rauwolfia, there 42 different products in the market in place of straight rauwolfia. Obviously, I think it would be unwise to test all 42 of these. So, we will select some and test them and try to identify critical benchmarks to be tested with respect to the others, either in a laboratory or in animal testing.

Senator NELSON. So, you will be doing both chemical testing in the lab and, with a certain number of the drugs that you select, clinical testing as well?

Dr. GODDARD. Yes.

Senator NELSON. Then, if you can establish some kind of benchmarks, you may require that the other companies meet those benchmarks?

Dr. GODDARD. Or we may just simply carry out the test on the other products in that particular class and check those benchmarks in animals, let us say, as an example. If we find those acceptable, then we can publish the results and say, look, doctor, as far as drugs in this category are concerned, at this time of testing there were no differences.

Now, it could be made as part of the quality control procedure in the GMP's to require that certain animal tests, if these benchmarks are established, be carried out by the manufacturer. That is possible. So, we still have a way to go on this.

Senator NELSON. You select the 50 categories? You mean——

Dr. GODDARD. Fifty different products for which the drug is available from more than one manufacturer. I am not saying we will necessarily do all 50 of those. With some of them it does not make sense to do the tests because nobody can prove that they are even effective.

Senator NELSON. When you say 50 categories, do you mean 50 categories of diseases?

Dr. GODDARD. No. I mean 50 drugs in the top 200 in terms of most prescriptions written. There are 50 different drugs at least on this list for which more than one company manufactures the product.

Senator NELSON. It might cover just 10 or 15 diseases, is that correct?

Dr. GODDARD. It is hard to tell how many diseases. We have not analyzed it that way, Senator.

Senator NELSON. How long do you estimate will it take you to carry out the first phase of clinical testing on 50 drugs?

Dr. GODDARD. I think we can have the job done in 18 months if we get cracking.

Senator NELSON. Well doctor, I think this will be one of the most dramatic contributions to the solution of this dispute about the matter of physicians and hospitals being able to trust the drug that they prescribe.

Dr. GODDARD. I would agree, Senator. If they cannot trust them, then we are not doing our job.

Senator NELSON. If this can be done we will have resolved a major problem in the drug field and the FDA will be entitled to great credit for it.

The committee counsel wanted to ask two or three more questions. I have to catch a plane for Denver, and must leave now.

Dr. GODDARD. Thank you very much. Appreciate it.

Mr. GORDON. Dr. Goddard, about how many different private product names for prescription drugs are there today? Have you any idea?

Dr. GODDARD. I have no idea. There are 22,000 drugs in the marketplace, I am told, in this country. This is not quite as bad as Germany where there are 58,000.

Mr. GORDON. Do you think many physicians know all those names?

Dr. GODDARD. I would doubt if any physician knows all those names.

Mr. GORDON. The ingredients in each and manufacturer of each?

Dr. GODDARD. I would be amazed if anybody did.

Mr. GORDON. Some segments of the drug industry have stated that brand name products may differ significantly from generic name products in at least two dozen ways. They also say that these differences may seriously affect the patient's response to the drug and that the physician is the only person who can determine which product is best for the patient. I believe I am describing their position accurately.

Now, for several months we have been trying to pin down these alleged differences between brand names and generic names. One witness brought in a large number of package inserts—I believe it was Dr. Garb—and showed that no mention of such differences appears on the package insert. In my mind this raises a series of questions.

Does the law not require that any important ingredients in a medication be adequately described in the package and insert?

Dr. GODDARD. Yes.

Mr. GORDON. If there is in fact, a difference in formulation of one brand of drug as compared to another, is not the manufacturer required to announce that difference?

Dr. GODDARD. No.

Mr. GORDON. I am thinking of important differences.

Dr. GODDARD. Well, now——

Mr. GORDON. Binders, flavoring agents, additives, particle size, solubility, or any of the factors that make a difference in the therapeutic effect or the efficacy of a drug.

Dr. GODDARD. Mr. Barnard, do you want to try to answer this?

Mr. BARNARD. The answer is, "No, insofar as flavors, incipients and things of this sort are concerned. Differences in active ingredients, differences in proportion of active ingredients, yes."

Dr. GODDARD. Let me point out, though, that this is a very complex issue again.

Mr. GORDON. How about solubility, practicle size?

Dr. GODDARD. Any time a manufacturer changes, let us say, the incipients in his formula, if it is an NDA drug, he may be required by us to do clinical testing to demonstrate that this product is now the same and is indeed clinically effective and safe. And in fact, we have required firms to do this in changes in the antibiotic field, as I recall. I know one manufacturer of an oral contraceptive that would like to change the size of its pill by increasing the amount of excipient but will not, does not want to, because it would require additional clinical testing. So, I hesitate to give you an unqualified categorical answer.

Mr. GORDON. Well, what kind of answer can you give, then?

Dr. GODDARD. Under certain circumstances, yes, and under others, no. And I would like to submit a statement for the record, to clarify that inconsequential answer.

Mr. GORDON. Will you, please?

(The information referred to, subsequently received, follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING REQUIREMENTS DUE TO CHANGE IN FORMULATION OF PROCESSING

In the case of a new drug covered by an effective New Drug Application, any significant change in manufacturing process or formulation would require the submission to FDA of a supplement to the existing NDA. So-called minor changes, such as a change in flavoring material, would require notification to FDA but the change could be made without awaiting FDA approval of an NDA supplement.

Insofar as "announcing" any changes, the firm is not required by law to notify the medical profession or anyone else, either through label changes or package inserts, of changes other than changes in quantity or nature of active ingredients. In other words, tetracycline syrup 100 milligrams is tetracycline syrup 100 milligrams regardless of whether it is chocolate, strawberry, or vanilla. There is, however, an exception in the case of injectables where all ingredients are generally required to be declared whether active or not. Thus, in the case of an injectable, a change in even a minor ingredient would have to be communicated in the drug's labeling. However, changes in manufacturing practices which might unwittingly alter absorption or other significant characteristics are not required to be communicated to the user, be he lay or professional.

Mr. GORDON. Can a manufacturer or his detail men legally make advertising claims for the alleged superiority of his product over similar products if such statements do not appear in the package insert and are not approved by the FDA?

Dr. GODDARD. No, they cannot. They can make claims only if they are approved by us; if such claims are demonstrable scientifically and appear in the final printed labeling.

Mr. GORDON. A previous witness, Dr. Fitelson, who did the laboratory testing for the Medical Letter, testified that there was more than an 800 percent difference in price between two brands of prednisone both made by large companies. Deltra, made by Merck, Sharp & Dohme, sold for $2.20 per 100 tablets, while Meticorten made by Schering sold for $17.90 per 100 tablets. Both, of course, are prednisone. Do you know any reason why the Merck, Sharp & Dohme product may be inferior or less reliable?

Dr. GODDARD. No.

Mr. GORDON. Do you know of any reason why the Schering product should be better?

Dr. GODDARD. No.

Mr. GORDON. Apparently doctors are prescribing the Schering product even though they could save their patients large sums of money by prescribing the Merck or the Upjohn brand. Could you tell us why a doctor would prescribe something that costs more than eight times as much when he could just as easily prescribe an equally effective and pure product made by a reliable firm at one-eighth the price?

Dr. GODDARD. This is pure supposition on my part and I hesitate to engage in it, but having practiced medicine, I can tell you that we rarely get the price information on drugs. I got it because I was purchasing them and dispensing them direct. And so price was of concern to me as a practicing physician. But when you are writing prescriptions for the patient you are often not aware of what the pharmacy markup is, what the pharmacist pays for the drug. This information is not generally put in the hands of the physician and he prescribes on the basis of his belief in what drug will do the job.

Mr. GORDON. Do you think that the physician prescribes Meticorten because of the pressure of advertising and the promotional activities of the drug companies?

Dr. GODDARD. Well, let me answer that in somewhat different words. I would say the advertising engaged in on all products obviously has some impact or the firm would not spend the money they do on advertising and drug promotion. I am not saying that is wrong. I am simply observing that this is, in my belief, how these products gain a place. First of all, some of them come into the marketplace ahead of others, then aggressive promotion does establish them in the physician's mind. As Senator Javits pointed out, some of the names are unpronounceable and so a physician writes Meticorten or brand name. It is much easier. That name gets hammered at them in advertising and promotion of all kinds. It is not unexpected, then, that they write for that product. I would be surprised if they did not.

Mr. GORDON. So actually, you have given us two reasons why they prescribe a drug which is eight times more expensive even though it is not any better than another: One, they do not know the prices; two, promotion and advertising.

Dr. GODDARD. These are assumptions on my part. There may be other reasons that I am not aware of.

Mr. GORDON. Now, the compendium, of course, that you were discussing with Senator Nelson would include prices, too?

Dr. GODDARD. It could include prices, yes.

Mr. GORDON. Now, along the same line, we have been told by some witnesses that there are drugs on the market which are subjected to a greater degree of the governmental surveillance than most drugs.

This concerns batch testing of insulin and antibiotics. Can you explain to us what the inspection or testing consists of with regard to these drugs? At what point are they tested?

Dr. GODDARD. On insulin and antibiotics?

Mr. GORDON. Antibiotics.

Dr. GODDARD. On both these products the manufacturer receives approval from us after inspection of his facility, detailed discussion of the protocol that will be followed in the manufacture of the drug, and examination of samples that are submitted. Now, the manufacturer submits his own samples and sends them to the Food and Drug Administration laboratories where they are checked. We then carry out an analysis. We charge the manufacturer a fee for this service. This fee is carried through a revolving fund and I think the cost of it is something like $3 million a year total, or less than a mill per dose of the drug involved.

Mr. GORDON. So in effect, then, there are some drugs on the market, the batch tested drugs, in which the physician can have a higher degree of confidence because of Government supervision and inspection, is that correct?

Dr. GODDARD. Yes, from this point of view of the existing system, yes.

Mr. GORDON. Could you give us an estimate of the percentage of prescriptions which are written for these drugs?

Dr. GODDARD. I would like to provide that for the record, if I might.

Mr. GORDON. About how much would it cost to extend this to all drugs?

Dr. GODDARD. If I may, I would like to submit that in a fairly detailed fashion for the record, and give you the assumptions used in computing the estimated cost. The estimate that we have for batch certification of all drugs, as I recall, was around $90 million per year.

Mr. GORDON. Per year?

Dr. GODDARD. Yes.

(The information referred to, subsequently received, follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING TOTAL NUMBER OF PRESCRIPTIONS WRITTEN FOR ANTIBIOTICS AND INSULIN

The FDA keeps no detailed records reflecting numbers of prescriptions filled for certain drugs. We do have access to information of this nature supplied in an independent report by the R. A. Goslin Company, Dedham, Massachusetts, the "National Prescription Audit."

The National Prescription Audit is compiled by this company through 24 audits a year of each of 210 representative pharmacies throughout the country. These pharmacies have been selected because of a better than average prescription volume and because their prescriptions represent a wide cross-section of different prescribers. From the study of these pharmacies an estimate of the total is projected.

For the year 1966, the following figures have been given for antibiotics and insulin:

	Total number writen in category	Total of all drug prescriptions written
Antibiotics	127,603,000	12 percent.
Insulin	832,000	Less than 0.05 percent.

These figures represent both new prescriptions and refilled prescriptions.

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING COST OF BATCH CERTIFICATION OF ALL DRUGS

Assumptions:

(a) The number of batches of drugs started in a day in a medium and large plants does not vary greatly with the size of the plant. The size of the batch will vary greatly with the size of the plant. Starting as many as 10 batches in one day would be unusual. The figure, 5 batches, started in one day is more probable. For small plants (less than 20 employees), the figure one batch started per day may be used.

(b) 1500 manufacturers of Rx drugs.

(c) Batch certification cost $90.

(d) Working days per annum—250.

Estimates	Number of firms	Batches per day	Batches
Large (12 percent, over 100 employees)	180	8	1,440
Medium (19 percent, 20 to 99 employees)	285	5	1,425
Small (69 percent, 1 to 19 employees)	1,035	1	1,035
Total			3,900

On the basis of 250 working days per annum, the number of batches started in a year is 975,000.

Cost of batch certification at $90 ea. equals $88,000,000.

Mr. GORDON. Have there ever been occasions when detail men have made claims to doctors which the FDA has subsequently found out were false and misleading? If so, could you furnish us with a list of some representative examples?

Dr. GODDARD. I do not know of any examples of that kind. First of all, we have no way of monitoring what the detail man tells the physician. I think the physician does that himself and that is why we think the drug advertising controls that we exert are important. Further, that is why I think a good compendium is important, it sort of puts a fence around what can be said about a drug. And a proper kind of fence, too. I do not think we should unduly restrict firms but rather proper scientific restrictions should be imposed.

Now, we cannot monitor what detail men say. I know of one instance—a physician brought to our attention a telegram that was being—had been sent to him and his conferees in that area urging the doctors to prescribe on that day a given product which was entering the marketplace. The company did not even know when we checked with them that their salesman in that area had done this.

I think the companies are anxious to have their 6 minutes of a doctor's time used well, without getting involved in things that are questionable, and excessive claims are questionable. They tell me this, and I have no reason to doubt it. But, we have no way of knowing how often this occurs and no other examples of it having occurred.

Mr. GORDON. Well, since you cannot monitor what the detail man says, a large part of the advertising cannot be supervised by the FDA, is that not correct?

Dr. GODDARD. That is true, except in the sense that I mentioned before: the journal advertising, the printed advertising that goes out in the form of labeling, direct mail pieces, and other forms that are produced, do place certain constraints around the detail man. And the compendium would put another constraint around him as well.

Now, beyond that I see no practical way of carrying this any further, nor do I necessarily think it has to be done in any other fashion.

Mr. GORDON. Dr. Goddard, I have no further questions, but Senator Hatfield would like to have some of his questions answered for the record. I shall submit them to you.

Dr. GODDARD. Be happy to do so.

Mr. GORDON. Fine. I think that will be all.

Dr. GODDARD. Thank you.

Mr. GORDON. Thank you very much.

(The information referred to, subsequently received, follows:)

RESPONSE BY FDA TO SENATOR HATFIELD'S QUESTIONS

1. Dr. Goddard, we have heard a great deal about generic and therapeutic equivalency. I notice when you appeared before a subcommittee of the House Interstate and Foreign Commerce Committee some months ago that you agreed that comparing generic and brand name drugs was like comparing a Model-T Ford to a Cadillac. Is this still your view?

Dr. Goddard never stated agreement to this comparison. Prior to a question from Congressman Nelson, the Congressman himself made the above mentioned comparison. Dr. Goddard noted his agreement with the Congressman's question, which followed the earlier comparison statement.

So that there will be no misunderstanding, the text of this exchange, found on pp. 230–31, "Agency Hearings" before the Committee on Interstate and Foreign Commerce, House of Representatives, March 1, 1967, is as follows:

> Mr. NELSON. It has come to my attention that, for example, to compare drugs by generic name would be like comparing a model T to a Cadillac and that the effectiveness of drugs with similar generic names may not be exactly the same.
>
> Then when you get into the prescription of a drug, is it true or is it not true that there may be a variation as to the effectiveness of drugs of the same generic name ignoring the trade or brand name?
>
> Dr. GODDARD. Yes; this is unfortunately true. I say unfortunately, because it means we are not performing our functions as well as we have to. We view our goal as being one where the physician can prescribe any drug that is in the marketplace on any basis he wishes, using brand names or generic names, and be assured that those drugs are all effective and they are all safe. Now, this is not the case today; there is this variation. The Defense Supply Agency in its procurement program for drugs has clearly demonstrated differences between different manufactures' drug brands and we have also seen some of this.
>
> So we do have a considerable task to undertake and this is one of the reasons, of course that we are trying to set up the National Drug Testing Center. Of course, other methods as well must be used, but it is clear that the differences do exist with as many drugs as we have in the marketplace.

2. Legislation is pending in the Senate which would limit the present ability of a doctor to prescribe drugs to beneficiaries under the Social Security Act. As a physician, do you believe such limitations are proper? Should they be accomplished by Government fiat?

We have reviewed the legislation referred to and support in principal the objectives of paying drug costs under medicare. However, the subject is filled with tremendous complexities, and is presently being reviewed in depth by the Secretary of HEW's Task Force on Prescription Drugs of which I am a member. I have seen many hospital formularies which are adequate and accepted by the physicians practicing within the limits of that formulary system. We shall have to defer consideration of such measures until the entire subject has been adequately studied and a report submitted by the Task Force.

3. If two drugs meet U.S.P. or N.F. standards, are they therapeutically equivalent?

See pages 1325–6 of the transcript; page 9 of Dr. Goddard's prepared Statement.

4. In June, Senator Sparkman of this Committee introduced into the record of this hearing some material which cast serious doubt on the validity of the so-called "drug potency study" conducted by the Food and Drug Administration in 1966.

> a. Were the analyses of drugs conducted in your central laboratory or in the field? Are you equipped with technical personnel and facilities in your field offices to conduct intricate tests of this type?

The analysis was carried out in both the district labs and Washington headquarters lab. All these labs are equipped and staffed to handle very sophisticated scientific analyses.

b. You have stated during the past few months that you have some doubts or question about the sampling technique used in this survey, or the way in which the study was conducted. Would you please explain.

You would not want to project the results of this test to the nation's entire drug supply?

Yet on at least one occasion you did say that the study showed that "one out of every 14 products in our nation's drug supply was violative on the basis of potency alone." I gather you would not make that statement today based on the 1966 test.

See the prepared statement submitted for the record "Market and Manufacturers Survey-Potent Drugs—1966" and Dr. Goddard's summary of same, pages 1321 and following of the transcript.

c. It has been stated that some companies have complained about the results of the tests and that on re-testing you have found errors. How many times has this occurred? Have you notified the companies? Have you corrected the results of the study and republished the new figures?

See prepared statement submitted for the record, "Market and Manufacturers Survey-Potent Drugs—1966," and Dr. Goddard's summary of the statement, pages 1321 and following of the transcript.

d. I understand that the samples used in the survey have been destroyed by FDA. Isn't this unusual, particularly when serious questions were being raised by the industry re the results?

The samples were retained or destroyed in accord with standard procedures used by FDA. Samples on which no legal actions are recommended are routinely destroyed usually 30 days after analysis.

e. I am told that the companies keep identical samples and that the tests could be reconstructed. Would FDA be willing to work with company scientists in this effort? Would you permit an independent laboratory to do the testing?

Some companies collect duplicate samples at the time of FDA's collection. Some companies retain a portion of one batch as "reserve" samples. There are variations within batches of drugs and variations can be caused by conditions under which samples are stored and handled after leaving the manufacturer. We do not believe the tests can be reconstructed in those instances where the FDA sample was disposed of. We have discussed the analyses of the survey samples with company scientists on several occasions. We do not believe there are any benefits to be obtained through an independent laboratory analysis.

f. It seems to me you would want the tests validated, or the results set aside, if the survey is questionable or was improperly conducted, as you have stated (inferred).

As it is now, the study is continually being referred to as proof that there is no difference in drugs regardless of the identification of the manufacturer or their source. This, in my opinion, should not be permitted to continue. Dr. Goddard states on page 1322 of the transcript: "Now, the other original findings I still say, are correct. We stand behind those as long as it is understood that this is not a representative sample of the marketplace."

(Whereupon, at 3:10 p.m., the hearing was concluded.)

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