opinion. It was believed that their proposed additional paragraphs would weaken the labeling's public-spirited appeal to physicians to reserve the use of these drugs to the serious need for which they are so uniquely valuable. For that reason, the Bureau of Medicine did not accept the Bristol addition.

Data from the National Drug Trade Index (1966) indicates that, in spite of the relatively restrictive labeling of the semisynthetic penicillins, these drugs were being widely prescribed for respiratory diseases, etc. Furthermore, the position of the Bureau has been based on the belief that liberalizing, instead of further restricting, the indications, would be followed by even more open promotion and use of these drugs as routine agents in general office practice for the treatment of common upper and lower respiratory tract infections. This would lead to a much more widespread use than has been the case in the past and could, therefore, contribute to the probability of a more rapid development of strains of staphylococci resistant to these agents. More recently, the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci. (Methicillin is another semisynthetic penicillin.)

Because of these facts and concerns, and because of the permissiveness of the labeling for several of these (semisynthetic penicillin) products, e.g., oxacillin and cloxacillin, it is the intent of the Bureau of Medicine to bring the labeling for all the semisynthetic penicillins, and other antibiotics where appropriate, into consistency with its Medical Advisory Board's recommendations, and the approved dicloxacillin labeling.

Senator NELSON. May I interrupt just a moment? If the FDA considers it important that these semisynthetics not be used in circumstances where another penicillin G or another drug is effective for the purpose of avoiding development of penicillin-resistant strains to this drug, why not make much tougher labeling than you have? Obviously, it would appear from your statement that it isn't working, it isn't persuading doctors to avoid voluntarily using it when penicillin G or other penicillin will do the job, and it is in the public interest. Why shouldn't the labeling be a whole lot tougher, and simply tell the doctor, positively, "You should not use it under these circumstances"?

Dr. MINCHEW. The extent of the restrictions which had been in the semisynthetic penicillins prior to dicloxacillin was principally just a switch statement advising the physician that he should consider switching if the organism is in fact sensitive to the other penicillins. We feel that the dicloxacillin labeling we have implemented is much tighter, and is a basic labeling which would enable us to much more rigidly restrict the promotion or more widespread promotion of the drug. We do feel the dicloxacillin represents a significant tightening.

Senator NELSON. A significant what?

Dr. MINCHEW. Tightening.

Senator NELSON. But I take it you consider it important that they not be widely used to avoid the development of a resistant strain of any kind.

Dr. MINCHEW. Yes, sir.

Senator NELSON. And that this has been, and still is, a serious problem in the hospitals around the country. If that is the case, why not much more strictly limit its use with much stronger language?

Dr. MINCHEW. Our feeling is that the dicloxacillin labeling in essence restricts it to its appropriate place and that with the dicloxacillin labeling we have placed the drug in its proper place for use, and that the labeling is strict enough to enable us to limit promotion and act if promotion is outside of these very restricted indications.

Senator NELSON. What do you do in the event that the doctors

don't pay much attention to this and do the same thing that they did with chloramphenicol?

Dr. MINCHEW. Of course, what the doctor does is something that we don't have any direct authority over.

Senator NELSON. No, but you do have control over the labeling. You had control over labeling, but the advertising and promotion of chloramphenicol didn't work.

Dr. MINCHEW. Our feeling is that if the physician uses these products in keeping with the labeling of dicloxacillin he will be using it appropriately. If he is not using it in keeping with the labeling, he perhaps would not observe tighter label restrictions.

Senator NELSON. But you did decide, after the chloramphenicol hearings and the publicity on them, that you had to do something much more dramatic; so you wrote your "Dear Doctor" letters. As I understand it you wrote to the medical journals of the country and advised them, and to hospitals, and so forth, that, if this is important, then why not toughen up the labeling and put a special box in there? Just tell the doctors that one of the problems around the country has been the development of resistant strains, and so forth, of various kinds. It has created a tremendous problem, of which you are aware. These semisynthetics should be limited solely to this purpose or we are going to have exactly the same problem again, and box it in, in double black lines, and send them all a letter.

Dr. MINCHEW. We feel that the dicloxacillin labeling is tight enough in regard to being certain that the physicians have been notified of this. I think further testimony, which I will give, will show you what action has been taken in regard to seeing that all physicians have gotten a letter.

Senator NELSON. Then when it is all over with, if it ends up that the doctors haven't noticed or haven't paid any attention or the companies have continued somehow or other to blur the point by their promotional activities, and find, as we did in chloramphenicol, that it is being widely used in circumstances where it is not desirable to use it, because there is another drug that is as effective, what do you intend to do then?

Dr. MINCHEW. That, of course, we would have to respond to at the time. In this instance, as you will subsequently see, we have already responded in our relationship with the manufacturer when he promoted it outside of the labeling.

Senator NELSON. The test will be, you recite—I don't know what they did in Switzerland, France, and Denmark, but your sentence is that "More recently the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci."

Supposing that develops in this country?

Dr. MINCHEW. I would like for Dr. McCleery to offer a comment here.

Dr. MCCLEERY. Mr. Chairman, in some, I believe real, sense what you are asking today, what you are describing, is a process which is already underway in the aftermath of the introduction of Dynapen by promotional labeling and journal advertising which we get to later.

We found that it might indeed be desirable for the labeling for these three dicloxacillin products, as they entered the market, to be tighter

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HEARING DATES*

*The testimony for May 15, 16, 17, June 7 and 8, 1967, appears in part 1 of these hearings; the testimony for June 27, 28, 29, July 24, and Aug. 8, 10, 1967, appears in part 2 of these hearings; the testimony for Sept. 13, 14, 29, and Oct. 13, 1967, appears in part 3 of these hearings; the testimony for Oct. 31, Nov. 9, 15, 16, and 28, 1967, appears in part 4 of these hearings; the testimony for Dec. 14, 19, 1967, Jan. 18, 19, and 25, 1968, appears in part 5 of these hearings; the testimony for Nov. 29, 1967, Feb. 6, 8, 27, 28, and 29, 1968, appears in part 6 of these hearings; the testimony for April 23, 24 and May 1, 1968, appears in part 7 of these hearings; the testimony for May 2, 3, and Sept. 17, 1968, appears in part 8 of these hearings.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, SEPTEMBER 18, 1968

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

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Our first witness this morning is Dr. Harvey Minchew, Acting Director, Bureau of Medicine, Food and Drug Administration.

Dr. Minchew, we are very pleased to have you here this morning. You may proceed to present your statement as you see fit.

STATEMENT OF DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. ROBERT S. McCLEERY, ACTING DEPUTY DIRECTOR, BUREAU OF MEDICINE, FDA; HARRY CHADDUCK, DEPUTY DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FDA; WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA; MORTON M. SCHNEIDER, ASSISTANT DIRECTOR, OFFICE OF LEGISLATIVE AND GOVERNMENTAL SERVICES, FDA; AND DR. ALAN SMITH, DEPUTY DIRECTOR, DIVISION OF ANTI-INFECTIVE DRUGS, BUREAU OF MEDICINE, FDA

Dr. MINCHEW. Mr. Chairman: I appreciate this opportunity of appearing before you this morning to discuss the marketing approval and the promotion of Vibramycin, Chas. A. Pfizer & Co.'s brand name for doxycycline. For the sake of brevity, with your permission, I will submit for the record a statement of my educational and professional background.

Senator NELSON. It will be printed in the record at this point.

(The biographical data follow:)

BIOGRAPHICAL SKETCH OF B. HARVEY MINCHEW, M.D.

Date of Birth: May 1, 1932.
Place of Birth: Waycross, Georgia.

EDUCATIONAL AND PROFESSIONAL EXPERIENCE

A.B.—Emory University 1953.
M.D.—Emory University School of Medicine 1957.
Intern—University of Arkansas Medical Center 1957–1958.
USPHS–CDC–EIS (Epidemic Intelligence Service) Fellowship in the Division of Allergy and Infectious Diseases, Johns Hopkins Hospital 1958–1960.
Residency in Internal Medicine—University of Washington 1960–1962.
Private Practitioner, Internal Medicine 1962–1963.
Medical Officer, Food and Drug Administration, Bureau of Medicine, Division of Antibiotic Drugs June 1963–February 1965.
Medical Officer, Division of New Drugs, Investigational Drug Branch February 1965–July 1966.
Deputy to the Assistant for Drug Coordination, Bureau of Medicine, May 1965—July 1966.
Acting Deputy Director, Bureau of Medicine, July 1966—September 1966.
Assistant to the Director for Professional Development, September 1966—January 1967.
Deputy Director, Bureau of Medicine, January 1967—Present.
Director, Antibiotic Task Force, Bureau of Medicine 1966.
Clinical Instructor in Medicine, Georgetown University Medical School.
Physician, Group Health Association, 1964—present.

SOCIETIES

American Association for the Advancement of Science of Washington, D.C.
Academy of Medicine of Washington, D.C.
The American Public Health Association, Inc.

Dr. MINCHEW. The application for approval for marketing of Vibramycin (called a form 5 application for antibiotics) was submitted by Chas. Pfizer & Co. on June 22, 1966.

It was reviewed by the Office of New Drugs and by the Division of Antibiotics and Insulin Certification.

The original submission was inadequate and additional data were required. On October 13, 1966, we received further analytical data and on the next day, October 14, additional clinical reports were submitted.

By January 11, 1967, the preclinical studies in pharmacology had been reviewed. Our conclusions were that liver toxicity was shown in the dog, gastrointestinal toxicity was exhibited in the dog and the monkey, and thyroid changes were found in the monkey, the rat, and the dog. Nonetheless, the pharmacologist felt that the animal data did not preclude approval, so long as the package insert described the toxicity noted to alert the physician to the possibility of comparable effects in man in clinical use. A final review in May of a longer rat study confirmed these conclusions.

Senator NELSON. Confirmed what conclusions?

Dr. MINCHEW. The conclusions of the animal toxicity that had been seen on the shorter term studies.

By February 15, 1967, the chemical controls review had been completed. Manufacturing controls were considered adequate.

The medical review was concluded the same day. The evaluation was that the drug was another tetracycline similar in safety and effectiveness to the previously approved tetracyclines. Its distinguishing characteristics were more rapid absorption and a longer half life, permitting the drug to be given once or twice a day (rather than the usual four times), in smaller doses, to achieve similar clinical results as those seen in higher and more frequent doses of the older tetracyclines.

Mr. GORDON. Doctor, you talk about toxicity studies in animals. Do

you do any toxicity studies in humans before a drug is released for general use?

Dr. MINCHEW. Toxicity observations or observations for toxicities in humans would be a routine part of investigational phases of the drug. Even though a similar product in the form of other tetracyclines would have been marketed previously, this being a new molecule, it would technically have a phase I period when it was first introduced into man, so that during the phase I, phase II and phase III studies, observations would be made for human toxicity.

The competitive situation in tetracycline marketing is intense. The company sought to include in the labeling for Vibramycin features that would emphasize its safety and effectiveness in comparison with established products. To do this, Pfizer sought to feature the lower, once-a-day dosage, a broader antibiotic spectrum, and an advantage in not causing tooth discoloration—a side effect particularly important for pediatric age groups.

Senator NELSON. When you are referring to tooth discoloration, are you referring to permanent deposits of color?

Dr. MINCHEW. The teeth that would be discolored, Mr. Chairman, would be dependent upon which teeth were being calcified at the time the drug was administered. If the drug were being administered at a time when permanent teeth were in fact calcifying, then the permanent teeth could be discolored.

Senator NELSON. Permanently?

Dr. MINCHEW. The observations on this are not so sound that one can say unequivocally permanently, but certainly they have persisted for as long as some people have been observed.

Senator NELSON. Is this a very dramatic coloration?

Dr. MINCHEW. Yes, sir; it is. It is a very noticeable cosmetic defect. It is not the same in every person, and probably depends upon how much of the drug is deposited and combined with the calcium as the calcification occurs. It is certainly a noticeable and disadvantageous cosmetic defect.

Senator NELSON. And this is a characteristic of all tetracyclines?

Dr. MINCHEW. Yes, in general that is true. I can't say that unequivocally for each and every molecule of the tetracyclines that are available it has been specifically observed. Our position is that until proven otherwise, any tetracycline is capable of causing tooth discoloration because they all will combine with calcium this way.

Senator NELSON. Are there any preparations of tetracycline that has any noticeably less effect than others?

Dr. MINCHEW. I don't know that any studies have been done in terms of the actual incidence of tooth discoloration with each particular dosage form of tetracycline that would give a sound answer to your question.

Our conclusion was that the antimicrobial spectrum of this drug was very similar to that of the other tetracyclines, that the small differences in antibiotic sensitivity were of no practical significance, that the animal studies should be called to the prescriber's attention, and that the drug had the single advantage of less frequent dosage.

Labeling changes were requested—to delete a sentence implying greater effectiveness against Staphylococcus aureus, and to modify a claim for efficacy in treatment of genitourinary infection to state

that "certain strains of Proteus and Pseudomonas have responded to Vibramycin." A claim for acne was regarded as unacceptable. A cautionary statement against use in pregnancy was needed. Under "Adverse reactions," we recommended that the effects on the nails be added, that the observations in animals of liver and thyroid changes of undetermined significance be included, and that rare adverse effects on blood be reported.

We had discussed some of this tentatively in January, when Pfizer representatives called to inquire about progress on the application, and we met with them again on February 14, 1967, to go over the points I have noted.

The company disagreed strongly with our recommendations that the observations regarding animal thyroid effects should be in the labeling. They felt that this would place them at a competitive disadvantage in relation to other products whose labeling included no such discussion. They also did not want to delete the statement regarding efficacy in the treatment of Staphylococcus aureus infections.

Senator NELSON. May I interrupt a moment? The sentence above that, "They felt that this would place them at a competitive disadvantage in relation to other products whose labeling included no such discussion." Are you referring to other tetracyclines?

Dr. MINCHEW. Yes.

Senator NELSON. Did the other tetracycline products indicate the same animal thyroid effects?

Dr. MINCHEW. Yes, sir; in general they do show similar effects in the animals, and the inequity which is described here as having been emphasized by Pfizer is a result of evolutionary changes that are always going on in terms of package inserts.

Senator NELSON. Did you require the other types of tetracycline to refer to the animal thyroid effects?

Dr. MINCHEW. We have not to date, but we are currently actively revising the labeling of all tetracyclines. This was initiated in the spring of 1967.

Senator NELSON. So that all of them will be required to have the same reference to the animal thyroid toxicity?

Dr. MINCHEW. This is our intention; yes, sir.

Senator HATFIELD. What is your intention? How do you implement your intention? I think that the way you describe it, it sounds like there is a certain inequity here that you are imposing upon one company that you are not imposing upon other companies. Why haven't you taken steps already?

Dr. MINCHEW. We have taken steps to discuss with them revisions in the package insert.

Senator HATFIELD. Are they still marketing under the old methods?

Dr. MINCHEW. Yes, sir.

Senator HATFIELD. What is your time factor?

Dr. MINCHEW. The time factor in this one has now been drawn out to over a year now since we began negotiations and discussions with the companies about changing the package inserts of all of the tetracyclines.

Senator HATFIELD. I am not quite certain as to your procedure. It sounds like you are rather negligent in not taking faster action, if you think it is important enough to have it put on Pfizer. Why haven't you taken immediate steps to have it included in the others?

Dr. MINCHEW. We have taken immediate steps in terms of initiating an effort to get this done. At the same time, we could not——

Senator HATFIELD. How long has it taken?

Dr. MINCHEW. This is a highly variable thing. There are several manufacturers of the tetracyclines. We wrote all of the manufacturers, I believe in the spring of 1967 or the winter, I would have to check that date, requested a meeting with them to discuss class labeling of the tetracyclines.

Senator HATFIELD. December 1967.

Dr. MINCHEW. I would have to check the date. It was either in the winter or early spring of 1967.

Senator HATFIELD. You get worse mail delivery and mail service than we do, don't you?

Dr. MINCHEW. I don't know the condition of yours. Ours does have problems.

Senator HATFIELD. You mean you are almost a year involved in this thing?

Dr. MINCHEW. In changing the class labeling of tetracylines, yes, sir.

Senator HATFIELD. Is this typical of your bureaucracy?

Dr. MINCHEW. I would not say it is typical. It certainly is an example of our efforts to handle a large number of manufacturers with a very complex question of making uniform labeling.

Senator HATFIELD. How much longer do you think it will take?

Dr. MINCHEW. I can't say because it will be dependent upon some degree of concurrence being reached by a variety of people, and I could not honestly give you an estimated date of completion.

Senator HATFIELD. In other words, you want Pfizer under this special regulation that you have not yet implemented on these other pharmaceutical houses.

Dr. MINCHEW. For this particular product, yes, sir. I think, for example——

Senator HATFIELD. But these other products of these other houses have been on the market and are still on the market.

Dr. MINCHEW. And including some of Pfizer's; yes, sir.

Senator HATFIELD. And you claim some of the same factors are involved in their product that should be labeled as you now require Pfizer; is that correct?

Dr. MINCHEW. And I just would like to make a point also——

Senator HATFIELD. And you have been almost a year in not getting this implemented on the other houses; is that correct?

Dr. MINCHEW. And Pfizer; yes, sir.

Senator NELSON. May I ask a question here? Does the Pfizer package insert include this specific reference to animal thyroid effects now?

Dr. MINCHEW. In the Vibramycin. Pfizer has other tetracycline products currently on the market that do not have it, which will have to have it when we are able to implement across-the-board changes.

Senator NELSON. So Pfizer with its other tetracyclines along with all the other companies with their dosage forms, do not now——

Dr. MINCHEW. Have this animal pharmacology section, that is correct.

Senator NELSON. But in this Vibramycin, issue is raised prior to approval of marketing of the drug?

Dr. MINCHEW. That is correct.

Senator NELSON. The dosage form.

Dr. MINCHEW. It is our feeling that when a new product is becoming available, even though it may have factors in common with already marketed products, that we must at the time of approval of this new drug put the very best labeling into effect which we can. In this case, it does create an inequity until the products which are already marketed, including Pfizer's others, can all be put in a similar labeling position.

Senator HATFIELD. Mr. Chairman, I understand that, and I think that is a very proper action that you take on the new products as they come on to the market. What I don't understand is the length of delay that is involved here in bringing up to standard or up to the same requirements all of the existing products of other pharmaceutical houses. That is the point that I am trying to get at here. Why is there this—you wrote letters in December of 1967, and you are still dillydallying around on this. Why haven't they been brought up to standard as to the new product? How much longer is it going to take?

Dr. MINCHEW. The only honest answer which I can give you is the total volume of work which the Bureau handles is such that these delays are sometimes inevitable, particularly in an instance where so many different manufacturers are involved, and it has to be discussed with them.

Senator HATFIELD. Are you telling me that you are inadequately staffed?

Dr. MINCHEW. To handle everything as promptly as we would like to, yes.

Senator HATFIELD. Well, what do you consider a reasonable time to update these other products in line with these new products, the requirements you impose upon the new products? What is a reasonable time? What is your bureoucratic time? Let me ask you that question.

Dr. MINCHEW. I don't understand.

Senator HATFIELD. I can tell you what I think a reasonable time is, but what is your standard?

Dr. MINCHEW. I don't understand the bureaucratic time.

Senator HATFIELD. What is it that you find in your own history and your own practices in the FDA as far as the time required on the normal or on the average on updating the existing products to bring them to standard that you have established under a new product that comes into the field as in this instance?

Dr. MINCHEW. This is a highly variable figure. In instances where a labeling change has a very direct implication to human toxicity or is a direct immediate question of public safety, the time period is extremely short.

Senator HATFIELD. Such as?

Dr. MINCHEW. Such as weeks.

Senator HATFIELD. You can do it in a matter of weeks.

Dr. MINCHEW. Yes.

Senator HATFIELD. So it is just a question of how much data is involved, is that right?

Dr. MINCHEW. Not that and that alone though certainly that is a factor.

Senator HATFIELD. What are you doing in the meantime in this case? For instance, if it has taken you almost a year, then it shows there is not very much danger involved evidently. What are you doing? What is the procedure you are involved in now on this case? Are you reading letters or are you holding conferences or what are you doing?

Dr. MINCHEW. The immediate status of this implementation is something on which I would have to check with the operating unit in the Bureau that is handling it. I don't have that information available at this moment. I don't know just exactly where this negotiation is at this point in time.

Senator HATFIELD. I would be very interested in knowing your procedures, if you can do something in a matter of weeks, and then at other times it takes you months. I would like to know what your bureaucratic procedure is on that.

Dr. MINCHEW. What would be the question to which you would like to have a direct answer?

Senator HATFIELD. I would like to know in changing the labeling of existing products to base it upon a new standard that you prescribe, because of your research and determinations arrived at on a new product, you tell me that if there is a great deal of danger involved that you can get all this change brought about in the matter of a few weeks. Now you tell me that in this particular instance that you have been almost a year. My question is simply why the great difference? What are you doing in your procedures in your department that you have to take almost a year in some instances when you can do the same job in weeks, a matter of weeks, in other instances?

Dr. MINCHEW. We can provide the committee with a chronology of the negotiations.

Senator HATFIELD. I don't want a lot of that chronology. I want to know the procedure. I want to know why it takes you so little time in some instances and so much time in other instances. If it is a matter of staffing, then I want to know that. I think the committee should know that. If it is a matter of just poor procedures, administrative procedures, I would like to know that, too. I don't want a lot of papers showing a chronology. I just want to know the basic procedures and administrative practices in which you are engaged.

It seems to me ridiculous that you have got the ability to perform in a few weeks in some instances and it takes you so long in others. These are where you open yourself to criticism, and rightfully so. These companies have every right to criticize your operation, when you put one company under that kind of inequitable economic situations, as you are attempting to do, Pfizer here in this case, and then in almost a year you can't get other companies updated in their labeling.

As I say, you admit here that you can really handle such cases under a danger factor in a matter of weeks, then you open yourself up to bureaucratic charges, and rightfully so, when it takes you so long to get moving in other instances. That is my point.

Senator NELSON. I assume one of the problems in the time factor is that if it is a serious matter, that it takes priority over any other backlog material you have got; is that correct?

Dr. MINCHEW. That is correct.

Senator HATFIELD. Mr. Chairman, then we ought to deal with the question of staffing. I don't think that is any excuse. I think after all that if they have that kind of a problem, that they ought to come in here with the kind of budget that is going to let them maintain a current workload so they can deal in a reasonable time with all of these companies on all of the products.

Senator NELSON. I wouldn't quarrel with that. I think they have been asking for more staff and desired more staff for a long time, but haven't been able to get it out of the Congress. But in any event, in chloramphenicol, for example, you moved forthwith after the hearings here with a letter to 200,000 doctors, and I assume that is because you put aside anything of lesser importance, lesser priority.

The question that still remains, however, and which bothers me, is once you have decided with Vibramycin that in the labeling that would—when did that drug go on the market by the way?

Dr. MINCHEW. August of 1967 it was approved. Now I could not comment when the industry first got it in interstate commerce.

Senator NELSON. Once you made the decision that it was significant enough to require the package labeling of Vibramycin, I think the question raised by Senator Hatfield raises this point. You had already made that decision. It isn't necessary to carry on a dialog back and forth with the rest of the companies on their labeling. It would seem to me he has made the point that once you have made that decision you ought to order the other companies in their future package labeling to make this amendment without any delay. I think that is a valid point raised. Is there any response you have to that?

Dr. MINCHEW. Yes, sir. The only point I would make here, though I certainly in no way disagree with the desire which you obviously have, is that we have also to be as efficient as is possible and as equitable as possible. The particular labeling changes which we are talking about far exceed just the animal pharmacology section. They did involve other matters which we felt that it was fair and equitable to discuss with the industry in terms of a format for presenting the indications for the drug and this type of thing.

It did involve a lot more variables than just simply establishing the edict that animal pharmacology sections shall be present. We did also discuss some of these with our Medical Advisory Board.

Senator NELSON. The point raised here, if there are competing products, and I agree when a New Drug Application is made and you decide upon the package insert, you use the most up-to-date information you have. You notify the doctor. But it seems to me in any competing product, once you have made that decision, you certainly ought to move as expeditiously as possible in directing an amendment to the package insert of the other products, or it is subject to, I think, a valid complaint.

Dr. MINCHEW. And we agree that the time period is certainly longer than we would prefer. In the interest of giving the doxycycline as equitable a treatment as is possible in this regard, the package insert does state that the animal toxicities which are observed and described in their labeling occur with other tetracyclines.

Senator HATFIELD. May I ask one more question? Could you tell me what your requests were in the budget for additional staff for this year that were denied you, the numbers that were denied you or the dollars that were denied you?

Dr. MINCHEW. Not for the coming year, because we have not received that in final yet.

Senator HATFIELD. Have you made requests for specific additional staff in your division, in the Bureau of Medicine?

Dr. MINCHEW. Yes, sir; we have. We are currently operating under a personnel freeze system, under a replacement system where at the present we can only hire one for every two losses, so that even approved figures at this point in time don't enable us to obtain the staff.

Senator HATFIELD. About how much understaffed do you consider yourself at this point?

Dr. MINCHEW. Well, we are currently right now at around 480 people in the Bureau of Medicine, with an approved number last year of somewhere around 560.

Senator HATFIELD. And you made a request for more in the coming——

Dr. MINCHEW. Yes, sir; we have.

Senator HATFIELD. What figure is that?

Dr. MINCHEW. I would have to check that figure. I can't give it to you right now.

Senator HATFIELD. Thank you.

Dr. MINCHEW. The only other point I would make that I think is critically related to the discussion of this specific drug is that, in this area, and that is the area of physicians with specialty training in infectious diseases and antibiotic therapy, they are even much more scarce, much harder to find than a physician in general.

Senator HATFIELD. When do you expect to have your work completed on the insert label updating of these other products in the industry?

Dr. MINCHEW. I would have to check with the operating division, Senator.

Senator HATFIELD. You don't know?

Dr. MINCHEW. I do not know right at this moment, no.

Senator HATFIELD. Yet you have great detail to give us today on everything that Pfizer did or did not do in this whole case, in this whole controversy, and yet you do not know what this whole time schedule is in your own agency on updating these other insert labels?

Dr. MINCHEW. This is something I would have to check with the operating division. I have these details concerning this particular drug because this was the drug I was asked to comment upon.

Senator NELSON. That may be my fault, Senator. I asked them to discuss detailing and promotion of the drug, and I didn't specifically ask this question, but I assume that you can produce it for the record for us.

Senator HATFIELD. I think it would be very important, Mr. Chairman, to see how the agency is moving on the other pharamceutical houses on this drug.

Senator NELSON. Please go ahead.

Dr. MINCHEW. A revised "package insert" received March 10, 1967, still did not contain the animal toxicity data, made claims that Vibramycin had a different spectrum than other tetracyclines, did not list all the warnings and adverse reactions recommended, and included some diseases in the indications section for which efficacy had not been shown. Changes we considered necessary in the labeling were further dicussed with the company in a telephone conversation on March 30, 1967, and at a meeting on April 19.

Revised labeling submitted May 10 was still considered unsatisfactory. There were further meetings and telephone conversations about the labeling held on June 28, July 7, and July 10.

On July 7, 1967, a representative of Pfizer, called the Commissioner to urge prompt action on the application, stating that everything had been approved and that clearance had been too long delayed. Dr. Goddard had previously invited the industry to bring to his personal attention any instances of what is regarded as undue delay in new drug clearance.

The final clearance was in process during the week of July 24. A monograph establishing standards of identity, strength, quality, purity, and safety, and the final labeling describing safe and effective conditions of use were the last parts of the clearance.

This final review developed the fact that we did not have a firm understanding with Pfizer as to the conditions under which the drug would be introduced and promoted to the profession. While the file indicated that all questions had been resolved, the labeling submitted by the firm did not support this.

Three defects were identified:

1. The first page of the insert stated that Vibramycin had several useful properties not observed with previously available tetracyclines.

2. The medical review had noted the importance of adhering to the recommended dosage because of greater absorption and longer persistence, yet the insert said that the drug had been given to volunteers for long periods at high doses without evidence of toxicity, a statement which deemphasized the importance of following the recommended dosage.

3. The insert claimed the drug was useful in acne, whereas the medical review had noted that the studies in acne included only a few cases and lacked objective criteria for evaluating improvement.

Dr. Ley, the then Director of the Bureau of Medicine, called the company, discussed these points, and told them the product would not be approved until these issues were resolved. At a meeting on Monday, July 31, Pfizer representatives continued to protest these changes, contending they had been made after the company had been given informal approval of the package insert. They confirmed their objections in writing. However, the matter was resolved by the company agreeing to make the necessary changes, and on August 10, 1967, the certification monograph was published.

Mr. GORDON. Doctor, may I interrupt at this point?

Dr. MINCHEW. Yes.

Mr. GORDON. The application for Vibramycin, I notice, was submitted on June 22, 1966. The certification monograph was published on August 10, 1967. Now, if the claims for the product had not been so broad, is it reasonable to assume that it could have been put on the market much earlier?

Dr. MINCHEW. I think that is a fair statement, Mr. Gordon. I would not be able to pinpoint exactly at what point the approvability would have been implemented, but I believe the testimony indicates that a significant part of this last few months was dealt in discussing and negotiating over labeling.

Mr. GORDON. It does take a long time to negotiate, is that correct? Could that be the answer to the problem that Senator Hatfield was discussing a short while ago, that the firms make claims which you

try to cut down; the firms then are reluctant to accept your views and all this takes a long time? Is that the way it works?

Dr. MINCHEW. Yes, sir.

Mr. GORDON. And is that the way it is working with the other tetracyclines also?

Dr. MINCHEW. That is the way it is working with the other tetracyclines in that part of the negotiations that I have been involved in.

Again, I would like to check with the operating division involved in terms of where they are at this point in time with it.

Mr. GORDON. I want to push this a little further. Now, if the company had accepted what you wanted it to accept with respect to Vibramycin, then there wouldn't have been any problem; is that correct?

Dr. MINCHEW. There certainly would not have been the delay of these last few months.

Mr. GORDON. Concerning the delay in relabeling the other tetracyclines, if the firms said "OK, we will accept for the other tetracyclines what you suggested for Vibramycin," but they didn't do that; is that right?

Dr. MINCHEW. To date, as far as I am aware, we have not gotten concurrence from the manufacturers of the varieties of tetracyclines. We have not gotten concurrence with all of the changes we believe are necessary. I would, however, have to confirm the latest negotiations between the Bureau and the companies because I was not personally involved.

Mr. GORDON. So it is really the companies who are not accepting the FDA's recommendations and that is causing delay. Is that a fair statement?

Dr. MINCHEW. That is part of the delay. We do have our own problems in terms of staffing and priorities, but that certainly is one of the causes of the delay; yes.

Senator NELSON. As to the question though, of animal thyroid effects that you have required Pfizer to include in its package labeling, there is no necessity for any negotiations with the rest of the companies on that point; is there? You have made the decision that Pfizer must do it. Then I assume it is automatic that the rest of them have to do it.

You don't need to waste any time negotiating. You have settled that issue; isn't that correct?

Mr. GOODRICH. If we took the regulatory step of taking all products off the market immediately.

Senator NELSON. I don't mean taking them off the market. All I am saying is as to this one, I understand there are apparently several points that are involved in revising the package labeling, but you have settled so far, I assume, as all tetracyclines are concerned, you have settled the question of requiring that some notation be made of the animal thyroid effects in Vibramycin. Therefore, you needn't waste any time negotiating with another dosage form of tetracycline, wasting time back and forth with companies as to whether they agree that that ought to go in, do you?

Mr. GOODRICH. But the point is that if you made them make that change, which is a relatively minor change compared with others that are under discussions with the companies, you would not have achieved the rewrite of the total tetracycline package labeling that is now under negotiation.

This drug is also under review by the National Academy of Sciences, National Research Council for effectiveness. This is another factor that enters into the ultimate development of a final package labeling form. These are the procedures that Senator Hatfield asked about.

We could, of course, withhold certification of all the tetracyclines until this labeling change was made. This is what was done, of course, in some other instances with antibiotics. This was not regarded as that type of a hazard that should be called immediately to the attention of the profession through that type of action.

Instead, we thought it justified discussions with the companies with a view of developing a uniform pattern of labeling to be fully informative, accurate, and would have the necessary warnings in it. Of course, all of us will agree it has taken too much time.

Senator NELSON. So if I understand correctly what you are saying, that the requirement in the labeling of Vibramycin, which at the time the issue was raised was a new dosage form——

Mr. GOODRICH. Right.

Senator NELSON. Coming on to the market.

Mr. GOODRICH. Right.

Senator NELSON. For the first time, you had the information then that there were some animal thyroid effects, and you were requiring that that be included in the labeling in the first instance in the marketing of this product, right?

Dr. MINCHEW. Correct.

Senator NELSON. And you are saying that there are a number of other revisions that are apparently going to be made in the package inserts. They are under review. And so you had the choice of requiring everybody to change his package insert as to this one item.

Mr. GOODRICH. Yes, sir.

Senator NELSON. Or waiting awhile until you could settle all the other issues involved?

Mr. GOODRICH. That is correct.

Senator NELSON. And you are saying that you didn't consider it important enough under the pending circumstances to require them to make this specific amendment as to the animal toxicity question, and then a few months later another amendment to the package labeling? Is that what your testimony is?

Mr. GOODRICH. That is correct, sir.

Dr. MINCHEW. However, similar problems developed with the promotion of the drug.

Senator NELSON. Please go ahead.

Dr. MINCHEW. The first promotional material submitted to us for the initial campaign for Vibramycin included a 22-page "visual aid" to be used by detail men in explaining the drug to physicians.

Such a "visual aid" is particularly important because, among other reasons, it sets a proper basis for oral presentation to physicians by the company's detail men.

In preparation for a meeting between Pfizer representatives and members of our Division of Anti-Infective Drugs on August 15, 1967, Pfizer brought in a draft copy of the "visual aid" on August 8. This draft was discussed in a preliminary manner with Pfizer representatives and it was apparent that there remained a number of differences between us as to how Vibramycin should be promoted. The Division of Anti-Infective Drugs indicated to Pfizer representatives that the

material would be reviewed in detail and agreed to meet with Pfizer when the review was completed.

During the August 15 meeting, a number of specific changes in the visual aid were discussed, but not all of the changes that we recommended were reflected in the next draft presented by Pfizer in typewritten form on August 16, 1967, a copy of which I have submitted.[1] Oral tentative acceptance was given by the Division of Anti-Infective Drugs to the revised copy, but it was also pointed out that other FDA approvals would be required.

Senator NELSON. What do you mean by that?

Dr. MINCHEW. That the Division to which this material was submitted and the initial reviewers did not have final approval authority.

Senator NELSON. So the Division of Anti-Infective Drugs gave a tentative oral approval of the proposed promotional advertising with a caveat that the final approval would be required by what other department?

Dr. MINCHEW. If it's promotional labeling or promotional advertising or general advertising, it also is reviewed by the Division of Medical Advertising. Final approval for either a New Drug Application or a supplement to a New Drug Application has been vested in the Office of the Director of the Bureau.

Senator NELSON. Well, at this stage in history, had there been an approval of the NDA?

Dr. MINCHEW. Yes. The monograph had been approved on August 10 and the labeling in the package insert was disapproved. Once the monograph is published in the Federal Register, the company is then free to submit for certification batches of the antibiotic.

Senator NELSON. But we are talking about some promotional material.

Dr. MINCHEW. Right.

Senator NELSON. That has nothing to do—is that right?

Dr. MINCHEW. Yes.

Senator NELSON. So what is the practice? Once there is an approval of the NDA, and they are certified to go into the market, are they required then to submit to you, they are required to meet your standards for the package labeling, but you are talking about some other promotional material, aren't you?

Dr. MINCHEW. Correct.

Senator NELSON. Are they required to submit to you all other types of promotional material for approval?

Mr. GOODRICH. What we are talking about, Senator, as pointed out in the statement, is a visual aid used for detailing. This is a piece of material the company brought in just at the final stages to go over with us, to make sure that this visual aid would be all right.

Senator NELSON. This is after the NDA.

Mr. GOODRICH. That is right. This was after the NDA had been approved for this antibiotic and the visual aid was brought in to be reviewed. They are required under the recordkeeping and reporting provisions to submit to us on a regular basis all of the promotional material used.

[1] See information beginning at p. 3568, infra.

They are not required to submit duplicative pieces that are substantially the same as one that has been previously submitted and approved. But this was a new piece which was submitted. It was examined by the Division of Anti-Infective Drugs, examined later by the Division of Medical Advertising, as the statement shows, and examined by the Director of the Bureau.

Senator NELSON. The law requires that all of this type of promotional material be submitted prior to its use?

Mr. GOODRICH. The law requires that the company submit such records and reports as are required by regulations. Our regulations do require that the companies submit on a regular basis for certified antibiotic promotional materials that are being used and that they obtain approval.

Now after a piece has been approved, the companies are entitled to use substantially the same presentation without reclearance to keep us from getting smothered in a mass of promotional material, but if the marketing piece has any significant change in it, they are required to submit that for approval. These are in accordance with the record-keeping and reporting regulations.

Senator NELSON. So at this stage in the testimony, they have had oral approval; is that correct?

Mr. GOODRICH. No; the drug had been approved. We had gone over the package insert labeling with them carefully. The monograph had been published, I believe; had it not, Dr. Minchew?

Dr. MINCHEW. Correct.

Mr. GOODRICH. And the product was ready for marketing. The company was concerned in August with going over with us this visual aid that would be used to launch the drug with the medical profession. As it turned out, it was quite important that we did have an opportunity to go over this with them to make sure that the drug was promoted to the profession in the way that we had agreed upon with the company. As the testimony develops here, there were still, notwithstanding the points that we had had differences with the company during July, there were still some differences over this visual aid, which were worked out.

Senator NELSON. Please go ahead.

Dr. MINCHEW. The draft submitted by Pfizer on August 16 was further reviewed within the Bureau of Medicine, including the Division of Medical Advertising, and a number of additional changes were found to be necessary. A meeting was held at the Bureau of Medicine on September 5, 1967, to discuss this draft. At this meeting, Pfizer unexpectedly informed us that they had already printed this four-color visual aid in final form on the basis of the tentative acceptance by the Division of Anti-Infective Drugs. A copy of this was also submitted this morning.[1]

Such action on the part of a company to final print material prior to actual approval of a draft creates a subtle type of pressure to approve it, or at least to hold the required changes to an absolute minimum.

Senator NELSON. What were these changes? I had thought that there was tentative acceptance given by the Division of Anti-Infective Drugs to the visual aid; is that correct?

[1] See information beginning at p. 3574, infra.

Dr. MINCHEW. Yes; I will go into the types of changes. On the documents that I have submitted, you will notice the types of changes required as paste-ons.

Senator NELSON. These weren't proposed changes, then, that were called to the attention of the company by the Division of Anti-Infective Drugs?

Dr. MINCHEW. Not at that point; no, sir. The Division of Anti-Infective Drugs does not have the responsibility for the comment on the promotional material per se. It is only reviewed there because this is where the medical expertise reviewed the New Drug Application and the package insert. The promotional implications of the material itself, however, is the primary responsibility of the Division of Medical Advertising.

Senator NELSON. So at this stage the Division of Anti-Infective Drugs apparently discovered——

Dr. MINCHEW. They did not raise any——

Senator NELSON. Did not discover any claims—medical claims—over and beyond what they thought there ought to be? Is that assumption correct?

Dr. MINCHEW. I think the types of problems that we asked for correction will be seen better as we go on.

Senator NELSON. All right.

Dr. MINCHEW. We explained that the visual aid was not acceptable as submitted and that it would need revision. We pointed out that our comments regarding this promotional piece were parallel, and in principle similar, to those previously made by us to the firm in connection with Pfizer's advertising activities for a similar product, Rondomycin. We proceeded to discuss with Pfizer representatives specific objections to the visual aid copy, page by page.

Among the important changes we requested were, that it be clearly specified that the once-a-day dosage was only a maintenance dose and that this dosage must be doubled in initiating therapy and for serious infections; that Vibramycin should be properly identified as another new member of the tetracycline family; that it be clearly stated that the antimicrobial spectrum of Vibramycin is comparable to other tetracyclines; that the need for culture and sensitivity of infecting organisms be pointed out; that use of data from clinical studies be limited to those cases in which sufficient cultures and sensitivity studies were carried out to demonstrate the effectiveness of the drug; and that a claim be dropped that suggested that less Vibramycin would be bound to bones or teeth than is the case with older tetracyclines since there was insufficient data to show this.

However, Pfizer informed us that they had already arranged for its detail men to gather for training sessions in preparation for the later marketing of the antibiotic. Many were en route to these sessions as we were meeting on September 5. They requested that they be permitted to use the uncorrected visual aid for these sessions. We agreed to this, provided Pfizer made clear to its staff the important revisions that were to be made before the aid could be used in detailing.

Mr. GORDON. Is there any evidence that Pfizer did actually make this clear to its staff?

Dr. MCCLEERY. Dr. Minchew is reluctant to comment on this because I was involved directly in these negotiations, and as a general answer

to your question I would say yes. If you want to go into the details of why we think so, it will take some development, but I would say yes.

Mr. GORDON. There is evidence that they did make it clear to the detail men?

Dr. MCCLEERY. There is indirect evidence that they did make it clear, yes.

Dr. MINCHEW. We were assured that this would be done. At the end of the meeting the senior Pfizer executive present, stated that in general the firm accepted FDA's proposals, and that the firm would prepare corrected copy for the visual aid and submit it to the Bureau of Medicine for approval as soon as possible.

Senator NELSON. This visual aid was to be used in detailing to physicians?

Dr. MINCHEW. Yes. Now, at this point in time the visual aid was going to be presented to the detail men themselves for instructional purposes for them, and then subsequently the visual aid would be used for the detail man's presentation to the physician.

Senator NELSON. All right.

Dr. MINCHEW. On September 11, 1967, Pfizer submitted a copy of the four-color printed visual aid with only some of the requested corrections pasted over the original copy. Several additional changes were considered necessary. Notable among these were: (1) The need to reduce from 754 to 454 the number of cases cited in a chart showing clinical success rate, since a number of the cases included by the company were not regarded as sufficiently documented; and, (2) The need to state clearly that claims for lower binding of calcium with Vibramycin were based only on in vitro studies.

These additional changes were discussed with Pfizer representatives, and they agreed to all of them. They were told that other promotional material, such as the file card, a booklet, and dosage calculator that Pfizer had presented, would have to be similarly revised before they were distributed.

In a letter dated September 14, 1967, Pfizer reflected its agreement with the changes we felt were necessary.

This submission is presented to you, and the paste over will show the necessary changes.[1]

A revised, final printed copy of the visual aid was submitted on October 6, 1967, and a copy of this has been submitted.[2] It was reviewed and found to contain all changes requested in the prior negotiations.

Let me again note two of the major corrections Pfizer was required to make in the Vibramycin visual aid: First, the company was required to indicate that the antibacterial spectrum of Vibramycin was not significantly different from other tetracyclines; second, the company was required to omit, because of a lack of supporting clinical evidence, any inference that the depicted in vitro test indicated there was less chance that Vibramycin will be deposited in the teeth and bones of children.

Very soon after the introduction of the new antibiotic, a pediatrician reported to the FDA by letter that at the American Academy of Pediatrics annual meeting at the Washington Hilton Hotel, on October 25, 1967, a Pfizer representative had stated that Vibramycin in vitro had the least calcium binding capacity, and that, based on this

[1] See information beginning at p. 3596, infra.
[2] See information beginning at p. 3619, infra.

test, there was predictably less chance of human tooth staining with Vibramycin than with any of the other tetracyclines. This episode was followed up by the FDA and on December 8, 1967, an affidavit was obtained in which the physician stated, in addition to the above, that the detail man also stated that Vibramycin was more effective over a larger spectrum of bacteria, including certain staphylococcal and psuedomonal species, than were other tetracyclines.

A Bureau of Medicine physician, who is also a pediatrician, was in attendance at the American Academy of Pediatrics (AAP) meeting on October 25, 1967. He, too, was told by Pfizer representatives that there was predictably less chance of tooth staining with the Vibramycin and that Vibramycin was effective against certain organisms which were not susceptible to other tetracyclines. Staphylococcus and pseudomonas were specifically mentioned.

In addition, a letter was sent to the FDA from an assistant professor of pediatrics of a university medical school. He stated that at the American Academy of Pediatrics meeting in October it had been suggested to him by a Pfizer representative that Vibramycin would not cause tooth staining in children.

On December 22, 1967, the then Commissioner, James L. Goddard, called the president of Chas. Pfizer & Co., Inc., and informed him of these reports. This was followed by a letter from Dr. Goddard explaining FDA's objections in detail.

On December 22, 1967, a telegram was sent by the general manager of Pfizer Laboratories Division to all district managers, regional managers, and regional operations managers. The telegram, which was to be read to the company's field force, stated in part that:

1. "There is no evidence that Vibramycin does not cause tooth staining. To the contrary, as a tetracycline it must be assumed it does though no cases have been reported to date."

Senator NELSON. No cases of discoloration from Vibramycin?

Dr. MINCHEW. From Vibramycin.

2. "As a tetracycline, Vibramycin has essentially the same spectrum of antimicrobial activity as other tetracyclines. Claims of broader spectrum are not in accord with the evidence known to us at this time."

Vibramycin illustrates three problems which confront the FDA in approving a new drug for marketing. They are: first, the necessity for a most careful and critical evaluation of the data offered to establish the parameters of safe and effective use; second, the proper translation of the scientific data into labeling claims and warnings that will provide adequate prescribing information; and, third, the problem of improper promotion through oral detailing, despite extensive efforts in arriving at a complete understanding between FDA and the company as to the proper scope of the basic printed detailing piece.

Thank you for your attention. My associates and I will gladly attempt to answer any questions you may have.

Senator NELSON. We have had over the past year and a half at various times testimony about claims made by detail men that go beyond the approved claims authorized by the FDA in its package inserts and so forth. There have been studies that indicate that the detail man is a very influential force on the prescribing practices of the physician. This recognizes that some physicians don't have anything to do with detail men. I know some. It also recognizes that many

physicians rely very heavily upon the information given to them by detail men. We have had some dramatic cases including testimony here by a doctor who was told by a detail man that chloramphenicol did not have any serious side effects, when the same detail man had given notice to the community pharmacist that there had been something.

I think it presents a very serious problem. If the detail man is as influential on the prescribing practices of a large number of physicians as it appears he is, what method of control over what he presents to the physician can the FDA have, or what method should they have, or what should we do about it?

Referring once again to chloramphenicol, here is a most dramatic case of overpromotion through advertising and through the detail man had been called to my attention, achieving a situation in which distinguished experts testified that 90 percent and as high by one witness, as high as 99 percent of the people receiving chloramphenicol are receiving it for nonindicated cases, acne, infected gums, infected toenails, upper respiratory diseases, sore throats, headaches, all of them nonindicated, all of these cases exposing the patient to aplastic anemia, and a number died who received it for insignificant minor infections.

Yet the company was able to move into the marketplace through promotional advertising, through claims of the detail man, and sell at least 90 percent at the smallest estimate of its drugs for nonindicated cases. There were lawsuits with big claims, big judgments for misprescribing.

Dr. Goddard testified that he was at wit's end, to use his phrase, as to how to persuade the doctors to stop misprescribing this drug. The American Medical Association apparently was absolutely ineffective if it had any interest in trying to dissuade the doctors at all. It has been a great tragedy. Nobody knows how many thousands of people died from aplastic anemia that were not reported, because in those cases where chloramphenicol was prescribed for a minor infection, and the patient got aplastic anemia and died, they aren't reported. There is a good reason for not reporting them. There is no record-keeping. There is no central reporting. The physician who did it and discovered he had made a mistake is not going to report it. So we don't know how many thousands and thousands of people died from it that were unreported, and how many more thousands ended up with a suppression of the capacity for producing blood cells, and remain ill the rest of their lives.

This can happen with the next drug and the next drug and the next drug. In this case the medical profession, the American Medical Association in particular, should have been screaming at the top of its voice. Nothing was done; nothing effective, anyway. Nothing effective happened until we had extensive hearings on it and until there was widespread publicity.

The FDA sent out 200,000 letters, and stories were appearing all over the country, and then from that the batch certification dropped, January 30 through June 1967 it was 20 million grams, and January through June of this year 4 million grams. It is just an incredible story to me. It took a congressional hearing to dramatize the case, and if there hadn't been a congressional hearing on this thing, there would be 4 million people a year getting chloramphenicol, 90 percent at least, according to Dr. Dameshek and as high as 99 percent, according

to others, getting this very potent, dangerous drug. It wouldn't have been stopped by FDA; it wouldn't have been stopped by the AMA, which would continue to take ads for chloramphenicol saying, "When it counts, use chloramphenicol."

I think the whole business is a disgrace and a real shocker that ought to scare every person in the United States.

Now, what has the FDA got in mind about suggesting what we do about controlling the advertising so it does not overpromote and controlling what the detail man says to the physician? On that aspect of it, at least, we ought to get some recommendations from FDA.

Now, the continuing education of the doctor, that is something that I don't expect is your business. That tremendous failure is the fault of the medical profession, and it is a terrible indictment in my judgment. But I would like to know what we are going to do to keep another chloramphenicol case from occurring in this country, and with the present company saying, "Well, the usage of the drug dropped off because of the hearings but it will come back again." What he means to say is, "We will promote it again, and we will have people dying from aplastic anemia for a prescription of chloramphenicol for an infected tooth or acne or hangnail." That is what was happening, and the company is willing to do it again. I don't know what kind of standard of ethics is followed by this company, by business people, but it seems to me the FDA has got some positive responsibility to take this fight head on, if you are going to protect the public interest. I don't know who else is going to do it.

The Congress isn't qualified to do it. It is just by accident that this chloramphenicol case came up at these hearings, but it takes the expertise of the people in the field to do this, and I don't know how it is going to be done. It seems to me the FDA ought to do something about it. You have the expertise. I would like to know what you think ought to be done about it. The advertising of this drug is ridiculous. The FDA knows about the testimony before this subcommittee by Parke, Davis that: "We don't list any side effects at all of Chloromycetin in England because the law doesn't require it. We don't list any other country because the law doesn't require it."

When we asked "Why not," the company's representative said, "We comply with the law of the country in which we sell," all of which means, "We can promote it over there and make a profit on the deaths of other people."

I think something has got to be done about this business, and I would like to know if FDA has some ideas about controlling the promotion of these drugs so the doctor isn't misled, because the fact is, the hard, cold, sad fact is, that the great, distinguished American medical profession in substantial numbers is being misled by promotional advertising and detail men, and the proof is in the record abundantly. This is a grave reflection on the American medical profession, not all of them of course, but it is a reflection on the medical profession just in the chloramphenicol case alone. How do we know that there isn't another case like this coming?

I would like to know what the FDA's ideas are for legislation or something, regulations to be proposed to the Congress. You have got the expertise. We don't.

Maybe that isn't your function. It may be an unfair question. I address it to the whole of FDA. I suppose it is Dr. Ley's responsi-

bility, but I don't think anybody who knows the facts, any American citizen, can help but be shocked and ashamed at what is going on in the promotion of drugs for purposes for which they should not be used, just for the purpose of making a profit. I think that is a terrible, terrible thing.

When I look at that stack of letters in my office from parents whose kids got chloramphenicol, 18-year-olds, infected tooth, hangnail, sore throat, my heavens, what are we coming to if that is what we will do to make a profit? And what is happening to regulations in this country, if the FDA with all of its physicians can't come up with some recommendations as to what we should do? Maybe we ought to get rid of all detail men. If that is the result, maybe we ought to stop it, just not have it. If this is the best we can do, we ought to stop them. Maybe you ought to stop this type of promotional advertising; make the physician go to a source to find out what that drug does; he should go to a reliable, unbiased source. Make them take some educational courses, continuing education of the physician. But I don't see out of the promotional practices—I see a negative in the detail man and the promotional advertising.

It shocks me, the stuff I have looked at, but I don't expect you to respond to that. That isn't what I called you up here for. But I expect to be calling upon the FDA for some ideas about this because I think it has got to be corrected.

Mr. GOODRICH. May we respond just very briefly, Senator, to that. You know what our program was on Chloromycetin. We did send out the letters as you know, and we sent letters to the physicians and to the hospitals and others.

Senator NELSON. Are you talking about the Chloromycetin letters?

Mr. GOODRICH. Yes, sir; after the hearings, and it did have an effect. This matter of oral detailing of Chloromycetin was reviewed by Senator Kefauver's committee back in 1961. At that time we did not have inspection authority over this kind of information. Nonetheless the Commissioner did take it up with Parke, Davis and within the limits of what he could do with voluntary compliance efforts were made to stop this. This is not to say that oral detailing isn't a problem.

You asked what has Food and Drug Administration done and implied that the total picture or presentation of information to the physicians is totally bad. With that of course we must disagree.

Senator NELSON. I didn't say it was totally bad, but all I am saying, if I may interrupt, Mr. Goodrich, is that in the promotion of chloramphenicol, through advertising and detail men, 4 million people a year were being prescribed that drug when it shouldn't have been—well, the highest figure by Dr. Damashek was 100,000, maybe, and that was the effect of the promotion and advertising.

If you will look at the sales record over the years, after the Kefauver hearings and at various times, it fluctuated up and down a bit, but the first time it dramatically dropped was after our subcommittee's hearings, and in comparing the first 6 months of last year versus the first 6 months of this year. What are you going to do if it gets back up to 40 million grams a year again?

Mr. GOODRICH. What the Commissioner committed himself to do, and I am certain that it will be done, is to follow the production and certification of that drug in a regular way, on a regular basis, so that if its certification and sales do grow again, then the message must be put out

again, or we will have to reconsider whether or not the product should remain on the market. But the agency is alert to Chloromycetin, and has exercised efforts over the years to hold its prescribing within bounds. There is no question that it did get out of bounds.

I was trying to address myself to the broader question of what have we done on the overall issue of promotion. In 1961, we put out requirements for full, complete disclosure to physicians on all promotional pieces. This made a drastic change in the information that went to the prescriber.

In 1962, Congress gave us authority over effectiveness claims, that was a program to review all the claims that had been approved over the years. The program of reviewing the claims is underway. Soon after the enactment of the 1962 amendments, we required drastic changes in the advertising. That is still a matter of controversy with us, but some steps have been taken to improve this, not enough, of course.

Senator NELSON. All I am saying, however, is the great and dramatic failure was chloramphenicol, because it continued to be prescribed indiscriminately. Nine out of 10 people for whom it was prescribed shouldn't have gotten it.

Mr. GOODRICH. Dr. Goddard could see to that when it came up.

Senator NELSON. What I am concerned about now is by what mechanics do we prevent it from happening again. The FDA, maybe through no fault of its own—whatever it required on the package labeling—was not effective. It didn't work. And I would have thought, knowing what the FDA did know, that your "Dear Doctor" letter should have gone out saying that nine out of 10 of you fellows prescribing this drug are prescribing it for nonindicated cases, and you had better stop. That is what I think should have been done. I assume that the FDA knew that people were dying from a drug that they shouldn't have received in the first place, and this went on for years and years and years. Just think of the tragedies. But FDA did nothing effective about it.

Yesterday we had Indocin, and the usage is contraindicated in children on the label clearly as can be. Yet 10 percent of pediatricians in a poll said they used it in children. They are misprescribing that drug. There is something wrong here, tragically wrong.

Senator HATFIELD. I have a couple of questions on the matter of restricting these drugs once they have been determined by your agency that they do not represent the truth, or to provide all the therapeutic value they claim. Take chloramphenicol.

Let's say that they decided to promote this drug again, and on the second go around you determine that it still lacks safeguards that you had prescribed or that you wanted placed on them. What would FDA do, negotiate, or what kind of action would FDA take against an industry or against a pharmaceutical house that violated what you considered to be appropriate safeguard requirements?

Dr. MINCHEW. Does your question pertain to total promotion or medical journal advertising or oral detailing?

Senator HATFIELD. Anything, any part of the promotional field which would tend to cause people to expect more and to submit themselves thereby to certain dangers than that which really exists?

Mr. GOODRICH. We have a variety of sanctions to deal with that, Senator. If the company made representations contrary to what had

been approved in advertising or promotion, it would be a criminal offense. We also have an administrative mechanism for discontinuing the certification of an antibiotic, where it is being promoted for conditions contrary to what has been agreed upon between us and the company in certifying the lot. Chloramphenicol is an antibiotic, so there are rapid mechanisms for dealing with such a problem.

Senator HATFIELD. Have you used that power that you have?

Mr. GOODRICH. Yes; we have.

Senator HATFIELD. Frequently?

Mr. GOODRICH. Not frequently, but it has been used decisively in a number of instances.

Senator HATFIELD. Have you used it more or less than opportunities provide? In other words, have you been conservative in the exercise of this authority, or have you been liberal?

Mr. GOODRICH. Quite conservative.

Senator HATFIELD. Do you feel that perhaps if you were a bit more aggressive or less conservative in your application of this power, it might be helpful in policing the industry that you are required to police?

Mr. GOODRICH. I expect the drug industry would say that we have been quite liberal in the exercise of the authority, but I think that, we hope that, we have struck the proper level of enforcement, but maybe we haven't been strong enough at some and perhaps too strong at other times. But there are mechanisms for dealing with the problem.

Senator HATFIELD. You feel you have adequate authority?

Mr. GOODRICH. Yes.

Senator HATFIELD. At this time, to deal with any situation that might arise in which you are called upon to protect the public?

Mr. GOODRICH. We think so. We examined our authority in great detail, when the Kefauver investigation was on, and made our recommendations. Now, since then, as you know, the President has recommended the enactment of legislation to provide for the issuance of a compendium which will provide one of the points Senator Nelson was talking about, that is, an on-the-desk, authoritative unbiased viewpoint of drug prescribing information.

Congress hasn't acted on that yet. But we are hopeful that something can be done.

Senator HATFIELD. On the matter of keeping control over the promotional program of these pharmaceutical houses, what is and what is not included in your review as far as promotion materials are concerned?

Mr. GOODRICH. Both the package material, all direct mailing, catalogs, movies, tape recordings.

Senator HATFIELD. Charts?

Mr. GOODRICH. All that, charts, visual aids, all that material which has been classified, as we were authorized to classify it by the Kefauver-Harris amendments, as labeling requiring full disclosure.

We also have authority to regulate the advertising of prescription drugs, but not the advertising of over-the-counter preparations. We initiated our prescription drug advertising program early in October of 1963, soon after the Kefauver-Harris amendments were passed. The regulations were placed into effect, I believe, in January of 1964. They have been successful in bringing about significant changes in

general advertising for prescription drugs, but they still pose some problems.

Last year we took the initial steps to improve the quality of advertising messages. We received objections from pharmaceutical manufacturers and the advertisers and a lot of other people.

Senator HATFIELD. This was on a continuing basis?

Mr. GOODRICH. Right.

Senator HATFIELD. As well as on——

Mr. GOODRICH. To bring these regulations up-to-date to deal with the problems that had emerged under our experiences with the regulations placed in effect in 1964.

We highlighted in the revised regulations those points of most concern and the points of failure that we had seen in actual practice.

Now PMA opposed that, and notwithstanding, we have taken efforts to resolve our difficulties. The matter now stands that they have objections in and it will have to go to a public hearing.

Senator HATFIELD. So that you have both the initial authority to deal with their advertising and promotional material as they introduce a drug, and then the continuing responsibility.

Mr. GOODRICH. Yes.

Senator HATFIELD. To review any additional or modified or changed——

Mr. GOODRICH. Yes.

Senator HATFIELD (continuing). Modifications or changes in their advertising and promotional materials.

Mr. GOODRICH. Yes.

Senator HATFIELD. Then as I understand it, you have control over everything except what may be stated orally by the detail men?

Mr. GOODRICH. Well, the opinion that Senator Nelson put into the record yesterday from the Library of Congress indicates some doubt about our authority to deal with oral detailing of this kind. I have no such doubts.

As Senator Nelson's opening statement said, in 1961 when we promulgated the full disclosure regulations, we provided that a drug, a prescription drug would be regarded as misbranded unless its labeling contained adequate directions for professional use for all the conditions for which it was advertised or represented. Now, that included oral detailing. That regulation has been in effect since 1961, was specifically called to the attention of the Congress in 1962, and was recently sustained in a criminal case in Chicago on whether we had the authority to promulgate such a regulation. So I don't have the doubts and fears that the Library of Congress opinion does. I will be glad to supply the committee with our views, if you would like to have them in detail.

Senator HATFIELD. But the point I am trying to get at is, that actually unless there is evidence shown from the oral presentation by say, a detail man that he has misrepresented the drug to the doctor, it is difficult then to enforce or police other than that which you have as now the existing authority on the printed and visual and all the other kinds of——

Mr. GOODRICH. Sure it is difficult. There is no question at all about that.

Senator HATFIELD. Yes.

Mr. GOODRICH. And this is why we have put our priorities first on making all the public promotion that goes in such great volume, both

believable and informative. This was our advertising and full disclosure regulations.

Now, as we move into problems of detailing, no detail men sent us any bulletins. Senator Nelson sent us the bulletins. If some detail men would be good enough to send us the bulletins, we would know how to react to them.

Senator HATFIELD. Do you feel you have enough authority then in the area of——

Mr. GOODRICH. Of inspection.

Senator HATFIELD. Of inspection and review of promotional and advertising materials.

Mr. GOODRICH. I think we do, but of course there are going to be controversies over this.

Senator HATFIELD. Yes.

Mr. GOODRICH. We have taken some steps to learn more about detailing. The companies, some of them, take the view that this is a private matter that is none of our business. We, of course, couldn't agree with that. We think it is public business.

Senator HATFIELD. The law doesn't agree either with that viewpoint.

Mr. GOODRICH. Yes.

Senator HATFIELD. Now, in the case of chloramphenicol, did you approve this drug in its original presentation to the market?

Mr. GOODRICH. Yes, Senator.

Senator HATFIELD. Its introduction?

Mr. GOODRICH. That product was approved. We made a full statement on this before the committee.

Senator HATFIELD. Yes.

Mr. GOODRICH. It was approved, I believe, in 1949. By 1952, the first alarm had been sounded about aplastic anemia. We did have a review by the National Academy of Sciences and modified the labeling. That was reviewed again in 1961 at the time of the Kefauver hearings, and a further tightening up of the labeling was considered.

Senator Nelson was good enough to bring out that there were now available incidence figures of aplastic anemia to give us a measure of how often the aplastic anemia side effect occurred. This new information was incorporated into a much stronger warning to the profession, which went out, I believe, last spring.

Senator HATFIELD. So the original introduction of the drug was then under the approval of the FDA?

Mr. GOODRICH. Yes.

Senator HATFIELD. And that included the packaging instructions and claims?

Mr. GOODRICH. Yes, sir.

Senator HATFIELD. Made by the pharmaceutical house, and then you had also review of their promotional and advertising material as it related to this particular drug?

Mr. GOODRICH. Yes.

Senator HATFIELD. There were none of these things along the way then that would indicate to you that there had been misrepresentation?

Mr. GOODRICH. We knew from the oral detailing to one of our own physicians, I mean the issue of oral detailing was divulged by our own experience. One of our physicians on the west coast was detailed for chloramphenicol by one of Parke, Davis' people, and he was told

that notwithstanding what was in the labeling, chloramphenicol was no more dangerous than some other competing product.

The physician reported that back in here, and the Commissioner took it up with Mr. Loynd, the president of Parke, Davis. That exchange is in the hearings on the Kefauver investigation.

Senator HATFIELD. So it was in the oral detailing that the misuse or improper use of this drug was experienced that created some of these ill effects?

Mr. GOODRICH. At least in part, yes.

Senator HATFIELD. What I am trying to get at is, is there a lack of authority or breakdown in the relationship between the industry and the FDA and the doctors and what have you that could be precluded from arising again or finding another similar experience? Do you feel that the pharmaceutical house or the houses chose to promote this drug in an improper way or make this decision on the basis of economics rather than therapeutic value?

Mr. GOODRICH. I wouldn't like to judge their motives. I only know that from what we have seen, this drug, chloramphenicol, was grossly misprescribed. Nonetheless on the broader issue of detailing, we had no authority whatever to get into this in an inspection way prior to 1962. Now we have a lot to learn about detailing. As I said a moment ago, detail men have not favored us with these inside communications. We found, after we saw the material Senator Nelson submitted to us, a need to make some further inquiry into what was going on in the detailing. That project is underway, but is still in the preliminary stages, and we are not prepared yet to discuss it in any final way.

Senator HATFIELD. Could you enjoin an industry or a drug house, say, to stop immediately?

Mr. GOODRICH. Yes.

Senator HATFIELD. Do you have that power?

Mr. GOODRICH. Yes, we have that authority. We don't have the authority to enjoin them. We would have to of course seek——

Senator HATFIELD. Through the court?

Mr. GOODRICH. Court, yes.

Senator HATFIELD. But you have the authority?

Mr. GOODRICH. We do have the authority to seek a statutory injunction.

Senator HATFIELD. It seems like we have two very important problems here to resolve at least in my clear understanding that perhaps would be helpful for the record. We have two specific problems. One is the relationship of FDA to the industry, to the practice of medicine as it relates to the matter of protecting the public against drugs that would be harmful. As I undersand it, you feel you have existing authority sufficient to deal with this.

Mr. GOODRICH. We think so.

Senator HATFIELD. So when something like this arises, then as far as that part of the problem is concerned, you feel you could act upon it adequately and quickly enough to protect the public, such as the choloramphenicol situation?

Mr. GOODRICH. We think we have the authority. Now whether we are alert enough, whether we exercise our authority quickly enough, or whether we are diligent enough in our investigation, are human issues, but the law is there.

Senator HATFIELD. The second point it seems to me then that needs to be clarified is how then do we deal with the problem of oral detailing? Do we do this with new alternatives to oral detailing? Is there some other approach here or some other technique that can be used in order to bring about a tightening up or a greater control, because as I understand it in the chloramphenicol case, you described the oral detailing as one of the bases of this great disaster. How do we correct that or how do we find an alternative to that problem?

Mr. GOODRICH. We are attempting to correct it first by insisting that all of the written, printed, and graphic matter, both the direct mailing, the tapes, and the motion pictures and all the other promotion, give the physician a full disclosure of the good and the bad that can be expected from the drug.

We are proposing to correct it by being sure that the advertising copy, which runs in great volume, tells the physician accurately and adequately what the hazards and the benefits of the drug can be.

We are trying to improve the advertising regulations.

Now, when we get down to the issue of oral detailing, our first program is to learn more about detailing. We have that project underway. If we find bulletins of the sort that were introduced yesterday and found that they were authorized by the company, we would have authority to take immediate action on that.

Senator HATFIELD. In this situation that you bring up, what do you feel about this increasing or at least it appears to me to be an increasing activity on the part of the industry to advertise directly to the public? And it is not perhaps carried in trade journals and other medical publications.

Mr. GOODRICH. Our view, Senator, has been that in general, prescription drugs ought to be advertised to the profession. The oral contraceptives, however, have introduced something new here, in which the companies have an inclination or desire to advertise the products directly to the public.

We issued a statement of policy on this, saying that where a company decided to advertise a prescription drug directly to the public, it would nonetheless have to have a proper disclosure of adverse reactions as well as indications in terms that were understandable to the nonprofessional audience.

We haven't seen a great deal of direct advertising of prescription drugs to the patient, but the oral contraceptives have introduced that problem, and we have a statement of policy on it.

Senator HATFIELD. How long does it take on the average for your agency to stop a certain advertising practice?

Mr. GOODRICH. Not very long. During the last 2 years we have met with companies on, I believe, 26 or 27 occasions to discuss with them advertising failures. Each one of these were episodes involving a Journal ad or, in two or three instances, labeling in the Physicians' Desk Reference, which we regarded as misleading and requiring immediate change.

I believe without any exception at all, the companies were willing to discontinue the advertising at once. We insisted on a mailing to the profession in general to bring about a correction, and in two instances we have called for the production of corrective advertising.

Senator HATFIELD. Do you consider then this case to be an exception,

the case we have had under consideration today, the length of time involved here? Is this exceptional?

Mr. GOODRICH. We were requested to present this case to give the committee something of the feel of what goes on between the agency and the sponsor in first assaying the clinical data to decide how good the clinical drug is and what can be expected of it, and what goes on between us in terms of developing a proper promotion. In this instance, there were two public-spirited physicians who called our attention to detailing that was beyond the appoved labeling. This is not the usual experience for us, but this case was chosen by the committee staff to give some idea of how we were doing our job and what sort of pressures back and forth were involved.

Senator HATFIELD. By this committee staff?

Mr. GOODRICH. Yes.

Senator HATFIELD. But this would not be what you would call a typical case. If I understand you correctly from what you said, if you have a case in which you are concerned about the advertising practice, you could stop it just in the matter of days.

Mr. GOODRICH. This case, Senator, involved a drug about to be introduced into the marketplace. Where we have a drug that has been approved, the regulations on advertising say that you can only advertise an approved drug for the conditions that have been approved.

If we find in our surveillance of the advertising copy, such as we see in journals like the Medical World News or the Journal of the American Medical Association, our technique is to work up in a scientific way what we regard as the defects in it, to communicate with the company and go over with them the failures in that message, and to discuss at that time an appropriate corrective action.

Senator HATFIELD. What length of time does that normally take?

Mr. GOODRICH. That normally takes a very short time, the matter of a few days to a few weeks.

Senator HATFIELD. What I would like to make certain that I understand correctly, and if I do then I want to make certain that it is in the record as such, that this case as it has been presented to me impresses me as one in which the procedures are very clumsy, that it appears to me that there are a lot of examples in here of poor administrative practices. Let me just point out one or two.

When you had something very definitely questionable in your mind about the visual aid, you said to this industry, "Go ahead and present it to your detail men, but warn them." I mean it is like in a court when a witness has said something in front of a jury and the judge says "strike that." Well, it has already heard this. I think this is analogous.

Mr. GOODRICH. Let me just react to that in the real world. We were sitting down with Pfizer to go over this visual aid, and they suddenly present us with a final printed copy. We thought it was still in development. We said to them, "this visual aid is no good. It can't be used."

They say to us, "but we have all of our detail men coming to a meeting. Many of them are en route. Can't we use this as a piece and then explain that changes will be made?"

Whether for good or bad that was the human part of the decision.

Senator HATFIELD. I just couldn't disagree with you more. I think you have not only the authority, you have the responsibility to tell them no. Maybe it is not more law. Maybe it is a little more aggressive attitude toward the law that you now have.

Mr. GOODRICH. Perhaps so.

Senator HATFIELD. I couldn't be less interested in their logistical problem, if this film were inaccurately portraying a drug that you said should not be portrayed that way. You had a responsibility to deny them the use of that film.

I think, too, on the top of page 5, "the final review developed the fact that we did not have a firm understanding with Pfizer." I mean to me this is filled with procedures or practices that showed either lack of a strong position posture in other activities that I hope is not typical of FDA, because frankly from the testimony in this case, and I don't know why the staff chose this one, because it didn't help their side of the case at all in my opinion, this was not a case that would be typical, I would hope would not be typical.

What I would like to see is the aggressive posture of FDA in handling any of this advertising and promotional material on which they have doubts. And then, also, on the basis of equity as it relates to other companies, other competing pharmaceutical houses. But that is just a point of view that I have that I wanted to make sure that I understood and that I held on a certain basis of fact and that it is not an improper or not a factual understanding.

I would like to suggest, too, that on this whole matter, where we do have staff inadequacies, as indicated awhile ago, legal inadequacies or other such, I know that Senator Nelson is keenly interested in this matter. I, too, share his interest. There are many other Senators on the Appropriations Committee, and others, who would share the interests that we have.

We certainly would feel very pleased if you would indicate to us that we could become an ally to you in behalf of your financial needs before the Appropriations Committee, because we are interested in a policy and in the policing and the other activities of this agency. If you are inadequately staffed, you can't come before us and fulfill your responsibilities here. We have no reason to demand anything more than you are capable of performing.

But if you do have the law, and as you indicate to me, you have the adequacy of law to enforce, to administer, to police, then it seems to me there might be a review as to the philosophy of your agency's attitude toward these laws, philosophy and attitude toward these laws and administrative responsibilities, because I do feel that we should be most aggressive in this field, most aggressive.

Mr. GOODRICH. I would agree with you. Vibramycin, the big, the salient point that comes through, however, is that here is a drug which was introduced on the proper basis, once all these negotiations went through. Perhaps there was some laxity or unsatisfactory procedures as you see it, where we did not have a firm understanding. But the critical fact is that before this drug was launched to the medical profession, an accurate, informative, reliable statement of its place and its hazards was presented both in the labeling and in the promotional material.

Dr. MINCHEW. I would like to make one comment in regards to the first paragraph on page 5. The impact of this statement was not that it just all of a sudden dawned on us that we didn't have a final understanding. It was when this visual aid material was presented that the promotional thrust of the material did not reflect that we had reached this understanding in the negotiation of the package insert.

Senator HATFIELD. As I say, the implications may be in error, but it does seem to me that we have here an awful lot of negotiations, discussions, and involvement that I am sure are very technical and very difficult to handle, but I do think that the agency was in error in permitting the films shown, the visual aids shown, when it had to be predicated on a modification, oral modification by those who were showing it. It is just one of the, I think, sloppy procedures.

Dr. MCCLEERY. It may well be true, Senator, but I think you might for your own sake, in talking in terms of reality, want to be aware of what it is we are talking about. I don't think you have seen and, therefore, couldn't understand what it is we are talking about. We are not talking about a film at all.

We have submitted the visual aid for the record, which I am afraid you haven't had the opportunity to see. The agreement to which you are taking some exception, is the agreement by the agency to allow the company to use it in the training session of their detail men. It was not an approval to use the visual aid when the product was on the market to be detailed to physicians.

What they were requesting was that since they had their detail men en route to a series of company meetings across the country, that, rather than to take some typewritten copy, they be permitted to use the printed visual aid. The men would later get corrected copies before they went out to detail physicians. This is the nature of what we are talking about.

Senator HATFIELD. You have not impressed me with your comment at all, because I think, and I stand corrected on whether it is a film or a visual aid, they should have received nothing, or they should have received something mimeographed. I mean a film certainly takes a lot longer to produce. If we are dealing now with just pieces of paper here, I mean that is all we are dealing with, it is attractively presented in color, and so forth.

But to let them go ahead and present this, I think, is even less excusable, less excusable when you found it objectionable. They should have either totally corrected it——

Dr. MCCLEERY. They did.

Senator HATFIELD (continuing). Or eliminated it.

Dr. MCCLEERY. They did totally correct it, Senator Hatfield. Let me just say that there is no film in this problem at all. There were very specific negotiations.

Senator HATFIELD. Well, we are in a judgment area rather than a factual area.

Dr. MCCLEERY. If we are in a judgment area it would be nice to have the facts on which to base a judgment.

Senator HATFIELD. Yes; we have the facts here, and I think the judgment is still wrong on the part of the agency.

Dr. MCCLEERY. You may be correct, but it might be helpful to get the facts before a judgment is made.

Senator HATFIELD. We have the facts here and the judgment has been made on the basis of facts, so the record will show that, too.

Any other comments or questions?

Dr. MCCLEERY. Yes; I have a comment.

Senator HATFIELD. I think Mr. Gordon has some questions he would like to ask.

Mr. GORDON. In view of the care that the FDA exercised in regard to the detailing of misleading statements by Pfizer detail men, do you regard the matter as serious?

Dr. MINCHEW. The matter of the details over which we were discussing?

Mr. GORDON. Yes.

Dr. MINCHEW. Yes; I do. The difference of opinion that we had in regard to the antibacterial spectrum, I would consider serious. Any misinformation which the physician might have that this drug would be effective in treating staphylococcal infections which indicated resistance to other tetracyclines could be very serious.

I would also consider the tooth staining problem certainly serious. If the physician were misled into thinking that this were a tetracycline which did not stain teeth and he used it without this consideration, I think it would be a serious matter.

Mr. GORDON. If you believe this matter was serious why did you select the kind of regulatory action you took rather than some other forms of action?

Dr. MINCHEW. From the medical standpoint, the seriousness of this was such that we felt the most important corrective measure was to take steps to be certain that the physician did not get this misinformation, or it did not continue. It apparently had taken place at the American Academy of Pediatrics. This is why we took this step to most expeditiously determine as far as we could that the misinformation and oral detailing did not continue.

Now in terms of other legal steps that might have been available, I would like Mr. Goodrich to comment, if he cares to.

Mr. GOODRICH. The decision in this case was made by Dr. Goddard to call the president of Pfizer about the detailing. The Pfizer president immediately reacted to say that he would send a telegram the same day to all of this force to bring about correction.

That was done, and that was satisfactory to Dr. Goddard, who was responsible for the agency at that time. It was concurred in by me and by others.

Senator HATFIELD. Who made the decision to permit this visual aid material to be used?

Dr. MINCHEW. For the purpose of informing the detail men?

Senator HATFIELD. Yes.

Dr. MINCHEW. This was a decision made in the Bureau of Medicine.

Senator HATFIELD. By whom?

Dr. MINCHEW. Dr. Ley and me.

Dr. MCCLEERY. Mr. Gordon, may I have the microphone again?

Senator HATFIELD. Just a minute. He had a series of questions. Just 1 second.

Dr. MCCLEERY. Yes. I asked him if he would yield the microphone, Senator.

Senator HATFIELD. Well, I happen to be chairman.

Dr. MCCLEERY. May I ask you?

Senator HATFIELD. Just a moment. Just as soon as Mr. Gordon completes. Will you finish your questions first and then we will be happy to.

Dr. MCCLEERY. Thank you.

Mr. GORDON. What would be your attitude regarding new legislation that would make it a misdemeanor for any detail man or other representative of a firm to make a false or misleading oral statement about a drug?

Mr. GOODRICH. We wouldn't have any recommendation on legislation and couldn't until it went through the regular system, you know, through the agency, and so forth. But in terms have we considered that as a legislative need; we have not.

We have in regulations already the authority to classify a drug as misbranded if it is orally represented for a condition for which it is not labeled, and that would result in the product being misbranded and it would be a misdemeanor. So we would think that legislation you are talking about would not be necessary.

Mr. GORDON. You think it is covered now?

Mr. GOODRICH. I think so.

Mr. GORDON. How many legal actions has the FDA initiated in the last 5 years based on violations of section 502(f)(1) in advertising of prescription drugs?

Mr. GOODRICH. None, I believe.

Mr. GORDON. Can you tell us why?

Mr. GOODRICH. Because we have been concerning ourselves with the higher priority problems, one, with the full disclosure regulations, second with the advertising, third with review of effectiveness for all drugs approved between 1938 and 1962.

We have initiated an exploratory program into the field of detailing, and when those results are in, we will be ready to move into that area.

But we considered our first priority to deal with the adequacies and the truthfulness of the claims, and second, the kind of promotion that was going to the physician in great volume both in direct mailing and in advertising. That has occupied our attention in terms of priorities. We did learn about this oral detailing in the case of Vibramycin by a report from a physician, and the Commissioner took it up with the president of the firm.

Senator HATFIELD. Would you state your name, please?

Dr. MCCLEERY. I am Dr. Robert S. McCleery. At the moment, I am Acting Deputy Director of the Bureau of Medicine, Senator Hatfield.

At the time of the events in question, I was in charge of the Division of Medical Advertising. I, too, am interested that the record be correct, and show the events and the nature of what it is we are discussing.

For the sake of the record, I think it should be pointed out in relation to your last statement, Senator Hatfield, that we this morning submitted a series of documents which I have reason to believe you have not had the opportunity to see.

The judgment that you reached as to the quality of the decision of the Bureau of Medicine in its agreement to allow Pfizer to use this in their training sessions I think could not be well informed until you had a chance to study the documents.

We feel that the record would show that the company made an agreement and that we have documentary evidence to show that we have reason to believe that the top management of the company kept its commitment to make sure that this improper detail piece was not used by their detail men.

Senator HATFIELD. Doctor, are these the documents you are referring to as it related to the involvement here as to whether there was judgment used in letting the company go ahead? Are these the documents you are referring to?

Dr. MCCLEERY. Yes, but there are also some letters there which you have not had the opportunity to see, and I just wanted the record to show that I feel you have not had a chance to study the record.

Senator HATFIELD. These will be carefully studied.

Dr. MCCLEERY. Thank you.

Senator HATFIELD. They have been studied enough to understand that they are visual aid materials that were not correct in their presentation, that is in their original presentation to you, and that you required certain changes to be made if they were to use them in their detail men's conference to introduce this drug.

Dr. MCCLEERY. That is not correct, Senator, but go ahead.

Senator HATFIELD. And that they were to correct or make the corrections according to your requirements, according to Mr. Gordon, our man here, our counsel.

I am saying to you that based on the fact that these were materials which were presented even though they were in corrected form, as you have pasted little things in here, that I feel that there was a judgment, a poor judgment used in making these materials, using these materials that would not be a permanent part of the promotional program.

That is all I am saying, and I would hold the opinion that it was poor judgment by your agency or maybe by you personally, I don't know. But we are not dealing here with facts but a matter of judgment. I am just indicating to you in my judgment, you have obviously indicated to me what your judgment has been.

Dr. MCCLEERY. Thank you.

Senator HATFIELD. Are there any other questions now or statements or comments?

Mr. Gordon, do you have anything else?

Mr. GORDON. No.

Senator HATFIELD. We will adjourn until tomorrow morning at 9:30 in the same room.

(The supplemental information submitted by Dr. Minchew follows:)

CHAS. PFIZER & CO., INC.,
New York, N.Y., August 16, 1967.

Re Vibramycin, § 148z.3 and § 148z.4.

ALAN E. SMITH, M.D.,
Acting Deputy Director, Division of Anti-Infective Drugs, Office of New Drugs, Bureau of Medicine, Food and Drug Administration, Washington, D.C.

DEAR DR. SMITH: We are submitting for your review the proposed Vibramycin visual aid and the Vibramycin Dosage Calculator, which we intend to utilize in the promotion of Vibramycin.

Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.

[Cover]

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NEW FROM PFIZER RESEARCH

Vibramycin® doxycycline once-a-day dosage.

Vibramycin is the newest advance in tetracycline research . . . a unique homolog of oxytetracycline and methacycline.

In dosage and absorption (caption for art) developed for efficiency.

Vibramycin® (doxycycline)—an efficient oral broad-spectrum antibiotic in terms of . . .

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection indicating the great absorption from the G.I. tract.

Long half-life and slow urinary clearance of Vibramycin allow you to prescribe it on a one-dose-a-day basis after the first day.

The lowest daily dose of any oral tetracycline.

Minimal dose related G.I. side effects.

May be administered with meals or milk without loss of activity.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms.

The broad-spectrum range of Vibramycin® (doxycycline) activity:

Site of infection	Indications	Pathogens (susceptible strains)
Ear, nose, and throat	Pharyngitis	Pneumococcus
	Tonsillitis	Beta-hemolytic streptococcus
	Otitis Media	Staphylococcus
	Sinusitis	H. influenzae
Lower repiratory tract	Single-lobe pneumonia	Pneumococcus
	Multilobe pneumonia	Streptococcus
	Bronchopneumonia	H. influenzae
	Bronchitis	Klebsiella pneumoniae
Soft tissue	Impetigo	Staph. aureus
	Furunculosis	Staph. albus
	Cellulitis	Streptococcus
	Abscess	E. coli
	Infected wounds	Klebsiella-Aerobacter group
	Paronychia	
Genitourinary tract	Pyelonephritis	Klebsiella-Aerobacter group
	Cystitis	E. coli
	Urethritis	Enterococcus
		Staphylococcus
		Streptococcus
		Neisseria gonorrhoeae
Other areas:		
Ophthalmic infections	Gonococci	
	Staphylococci	
	H. influenzae	
Gastrointestinal infections	E. histolytica	Salmonella
	Shigella	Pathogenic E. coli
Miscellaneons	Bacteroides	Donovania granulomatis
	Brucella	
	Listeria	Pasteurella
	Mycoplasma pneumoniae (Eatonagent, PPLO)	Psittacosis
		Rickettsia
	B. anthracis	H. pertussis
	N. meningitidis	C. welchii
	Proteus	Treponema
		Pseudomonas

[1] In combination with streptomycin.

Note: Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

With Vibramycin® (doxycycline) the lowest effective dose.

The Key: Efficient absorption . . . as reflected in high blood levels—even in the critical first hour.

After 45 minutes, Vibramycin blood levels are higher than those provided by I.M. injection of tetracycline [1] in 15 human subjects:

[1] During passage through the body a fraction of each antibiotic is metabolized thus lowering the amount of active antibiotic recoverable after an oral dose.

	Vibramycin 100 mg. (oral) mcg./ml.	Tetracycline 100 mg. (I.M.) mcg./ml.
After 30 minutes	0.727	1.111
After 45 minutes	1.013	.866
After 60 minutes	1.244	.751
After 75 minutes	1.405	.715
After 90 minutes	1.562	.702
After 105 minutes	1.494	.657
After 120 minutes	1.462	.842

As demonstrated by excretion studies in test animals urinary excretion study [1] indicates significantly greater G.I. absorption of Vibramycin—The percentage of the oral dose recovered in urine of mice relative to the amount recovered after an I.V. dose is 3.5—5 times greater than these other tetracyclines. Oral and I.V. doses were equivalent.

RELATIVE ABSORPTION VALUES

	Percent
Doxycycline	70
Methacycline	21
Demethylchlortetracycline	19
Tetracycline	13

With Vibramycin, antibacterial effect demonstrated in experimental animal studies—Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin® (doxycycline) in the critical first hour of therapy.

THE TEST

1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either Staph, aureus or Past. multocida). The two groups were kept separate.
2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival $Time_{50}$ was calculated. (Survival $Time_{50}$ is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

THE RESULTS

Pathogen: *Staph. aureus.*
Percent of animals surviving after 4 days.

Time in hours from inoculation to administration of drug:	*Oral Dose (mg./Kg.)*
☐ Vibramycin	6.25
☐ demethylchlortetracycline	12.5
☐ tetracycline	12.5

Note: Tetracycline was not administered at the one-half hour interval.
Pathogen: *Past. multocida.*
Percent of animals surviving.

Time in hours from inoculation to administration of drug:	*Oral Dose (mg./Kg.)*
☐ Vibramycin	12.5
☐ demethylchlortetracycline	50
☐ tetracycline	50

[1] During passage through the body a fraction of each antibiotic is metabolized thus lowering the amount of active antibiotic recoverable after an oral dose.

The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

The conclusion:

1. An important factor in protecting test animals is the rapidly attained therapeutic concentrations of Vibramycin. (Mice infected with *Staph. aureus* are generally moribund about four hours after inoculation.)

2. Even at a fraction of the dosage of other tetracycline antibiotics tested, Vibramycin provided a greater and more persistent chemotherapeutic effect.

With Vibramycin® (doxycycline)—Excellent therapeutic results in humans [over 90% clinical success rate]:

Diagnostic group	Clinical response			Percent success
	Favorable	Poor	Total	
Lower respiratory infections	172	11	183	94
Upper respiratory infections	143	11	154	93
Soft-tissue infections	133	8	141	94
Genitourinary infections	57	19	76	75
Venereal (gonococcal infections)	175	14	189	93
Miscellaneous infections	31	3	34	91
Total	711	66	777	92

Note: For criteria used in evaluating results of therapy, see end of brochure.

Summary of side effects in patients treated with Vibramycin® (doxycycline) not all of whom met the criteria established for efficacy:

Side Effect	*Number of cases*	Side Effect—Continued	*Number of cases*
Nausea	24	Flare-up of colitis	1
Vomiting	13	Glossitis	1
Diarrhea	8	Stomatitis	2
Photosensitivity	7	Nail discoloration	1
Dermatitis	4		

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

With Vibramycin®—Minimal untoward reactions in the lower G.I. tract as confirmed by the occurrence of only 8 cases among the patients treated,

The Key: efficient absorption:

Since absorption of Vibramycin is high, a minimal quantity of antibiotic is left in the G.I. tract. This would suggest the possibility of a lesser likelihood of monilial or bacterial overgrowth.

Vibramycin:

With Vibramycin® (doxycycline)—Lowe degree of binding with calcium than any other tetracycline analogue.

Per cent of binding with calcium[1] (Based on *in vitro* studies) with equal amounts of each antibiotic:

Vibramycin	19.0
Oxytetracycline	36.0
Methacycline	39.5
Tetracycline	39.5
Demethylchlor-tetracycline	74.5

This study would suggest that less Vibramycin is bound to bones or teeth.

With Vibramycin® (doxycycline)—The lowest effective dose—once a day after the first day

The Key: Long half-life:

Half-life of Vibramycin is significantly longer than that of other agents—based on single dose studies:

Doxycyline 15.1[1] hours (4)
Demethylchlortetacycline, 12.7 hours (4)
Tetracycline, 8.2 hours (5)

[1] With multiple dosing, the cumulative half-life has been reported to be approximately 22 hours.

Vibramycin owes its long half-life to slow renal clearance—½ that of DMCT, ⅕ that of tetracycline.

Average renal clearance (As a percent of creatinine clearance):

Vibramycin, 12.0(4)
Demethylchlortetracycline, 26.8(4)
Tetracycline, 61.0(5)

With Vibramycin—Serum levels are therapeutic around the clock(1)

The Key: Efficient absorption and long half-life.

Average serum levels of Vibramycin in humans.

And Vibramycin levels usually persist 24–36 hours after cessation of therapy

With Vibramycin—absorption relatively unaffected in the presence of food or milk.

Plasma levels of doxycycline and DMCT after oral ingestion of the drugs, fasting, and with foods in human subjects.

(Adapted from Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.(4)

After the first day of therapy . . . the only one-dose-a-day tetracycline in oral form.

Vibramycin[R] doxycycline once-a-day dosage. In dosage and absorption . . . developed for efficiency.

VIBRAMYCIN[R] HYCLATE CAPSULES DOXYCYCLINE HYCLATE

	Day 1	Day 2	Day 3	Subsequent days
Usual adult dosage..	2 caps. b.i.d. (200 mg.).	2 caps/day (100 mg.)...	2 caps/day (100 mg.)...	2 caps/day (100 mg.)

Note: Vibramycin[R] Hyclate Capsules contain doxycycline hyclate equivalent to 50 mg. doxycycline. Available in bottles of 50.

Vibramycin[R] Monohydrate for Oral Suspension doxycycline monohydrate.

Recommended dosage for children:

First day of treatment—2 mg./lb. of body weight divided into two doses.

Subsequent days—1 mg./lb. of body weight given as single daily dose or divided into two doses.

For more severe infections—up to 2 mg./lb. of body weight.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry power for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant tasting, raspberry flavor: 2 oz. bottles.

Vibramycin[R] (doxycycline)—an efficient oral broad-spectrum antibiotic in terms of . . .

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The lowest daily dose of any oral tetracycline.

Minimal dose related G.I. side effects.

May be administered with meals or milk without loss of activity.

In dosage and absorption . . .
Developed for Efficiency

REFERENCES

1. Research data on file, Pfizer Medical Department, Pfizer Laboratories.
2. English, A.R. and Lynch, J.E.: Proc. Soc. Exp. Biol. Med.: to be published.
3. Clinical data submitted to F.D.A. Available to physicians on request, Medical Department, Pfizer Laboratories.
4. Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.: Antimicrobial Agents and Chemotherapy—1966. pp. 134–141.
5. Kunin, C. M., Dornbush, A .C. and Finland, M.: J. Clin. Invest. 38:1950, Nov., 1959.

CRITERIA FOR EVALUATING CLINICAL RESULTS

UPPER AND LOWER RESPIRATORY INFECTIONS

Soft-tissue Infections

Miscellaneous infections

Favorable responses: Includes those designated as "good" or "satisfactory."

Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.

Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses: Cases in which it was felt there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

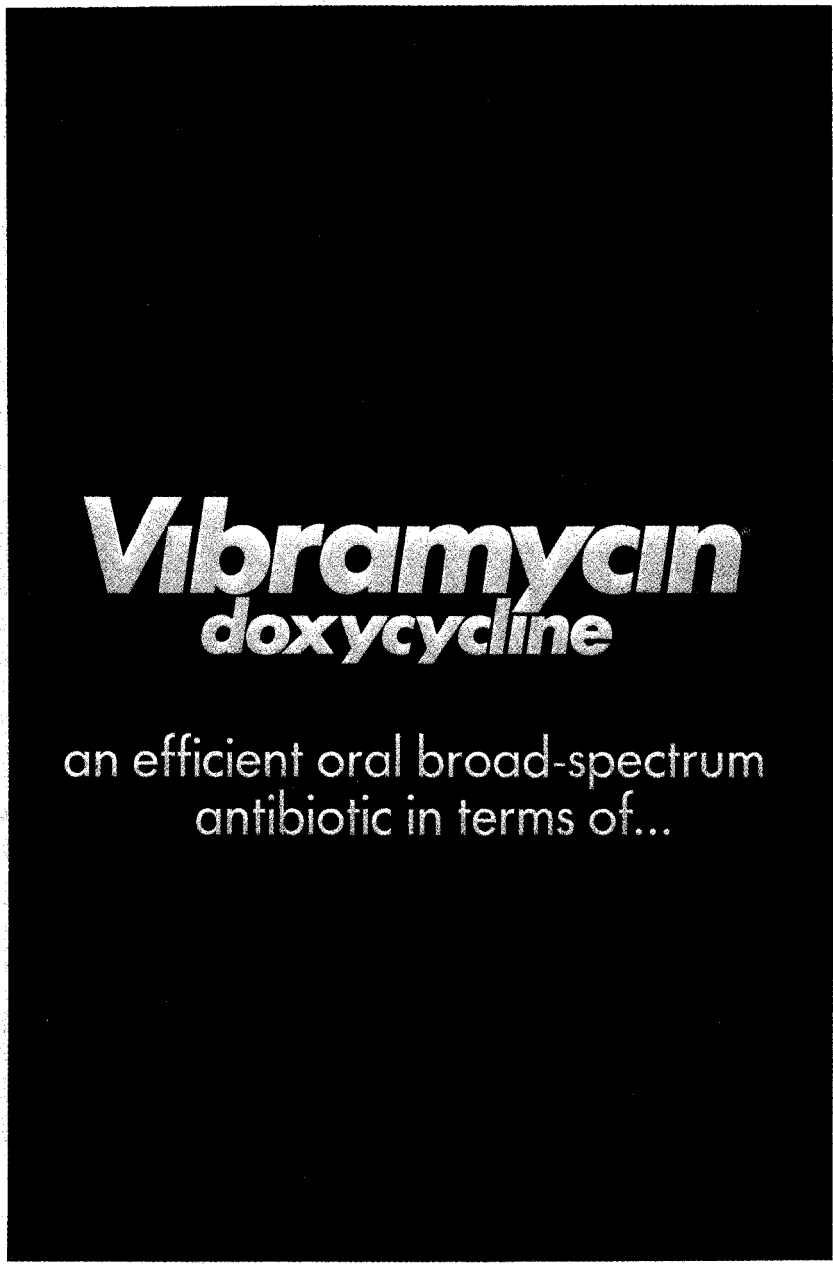
Favorable responses: Includes those designated as "good" or "satisfactory."

Good responses: Those in which *clinical* symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

Satisfactory responses: Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses: Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

Science for the world's well-being® (Pfizer logo) *Since 1849* Pfizer Laboratories Division, Chas. Pfizer & Co., Inc. New York, New York 10017 p159X67 (c) 1967, Chas. Pfizer & Co., Inc. Printed in U.S.A. Issued ----------

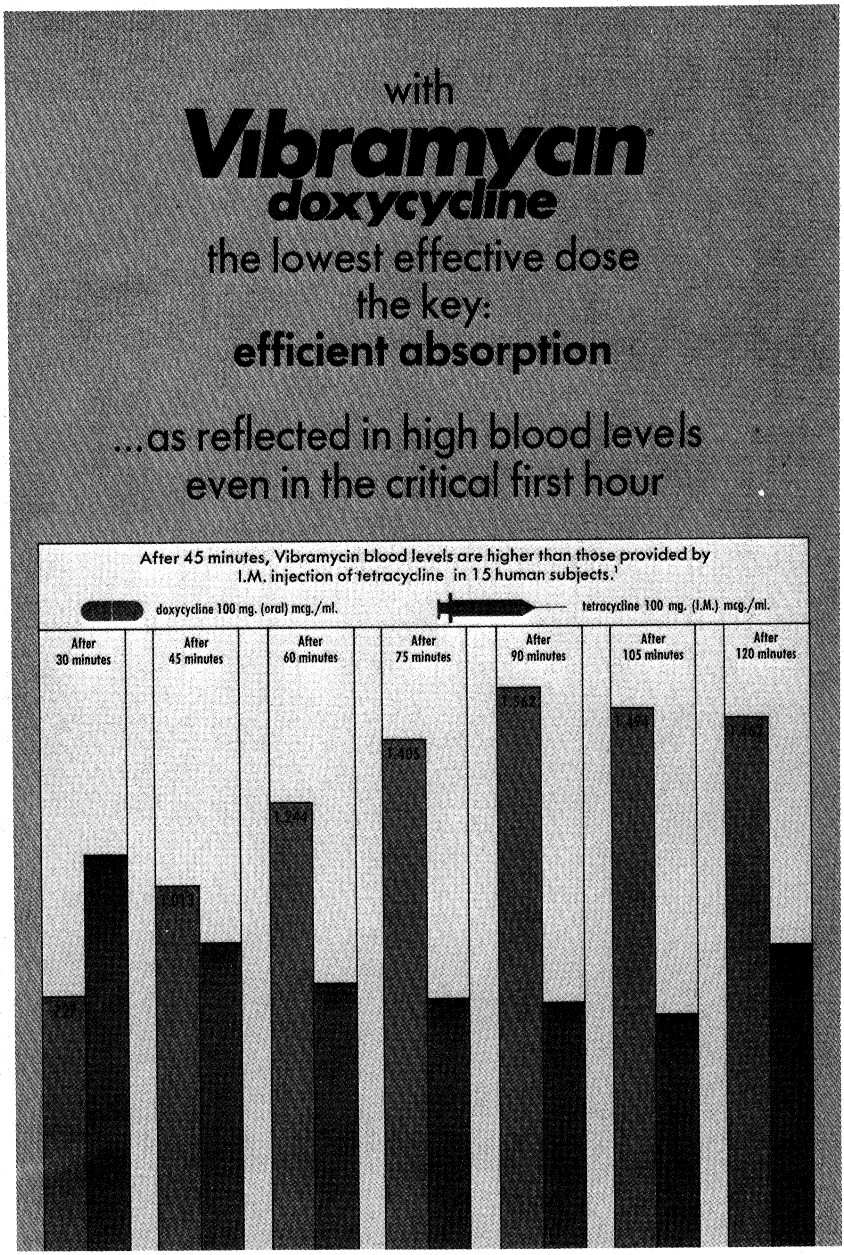

Vibramycin
doxycycline
an efficient oral broad-spectrum
antibiotic in terms of...

Site of Infection	Indications	Pathogens (Susceptible Strains)
Lower Respiratory Tract	Single-lobe pneumonia Multilobe pneumonia Bronchopneumonia Bronchitis	Pneumococcus Streptococcus H. influenzae Klebsiella pneumoniae
Soft Tissue	Impetigo Furunculosis Cellulitis Abscess Infected wounds Paronychia	Staph. aureus Staph. albus Streptococcus E. coli Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis Cystitis Urethritis	Klebsiella-Aerobacter group E. coli Enterococcus Staphylococcus Streptococcus Neisseria gonorrhoeae

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms:

Site of Infection	Indications	Pathogens (Susceptible Strains)	
	Gastrointestinal Infections	E. histolytica Shigella	Salmonella Pathogenic E. coli

Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.


with
Vibramycin®
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the lowest effective dose
the key:
efficient absorption
...as reflected in high blood levels
even in the critical first hour
After 45 minutes, Vibramycin blood levels are higher than those provided by I.M. injection of tetracycline in 15 human subjects.[1]
doxycycline 100 mg. (oral) mcg./ml.
tetracycline 100 mg. (I.M.) mcg./ml.
After 30 minutes
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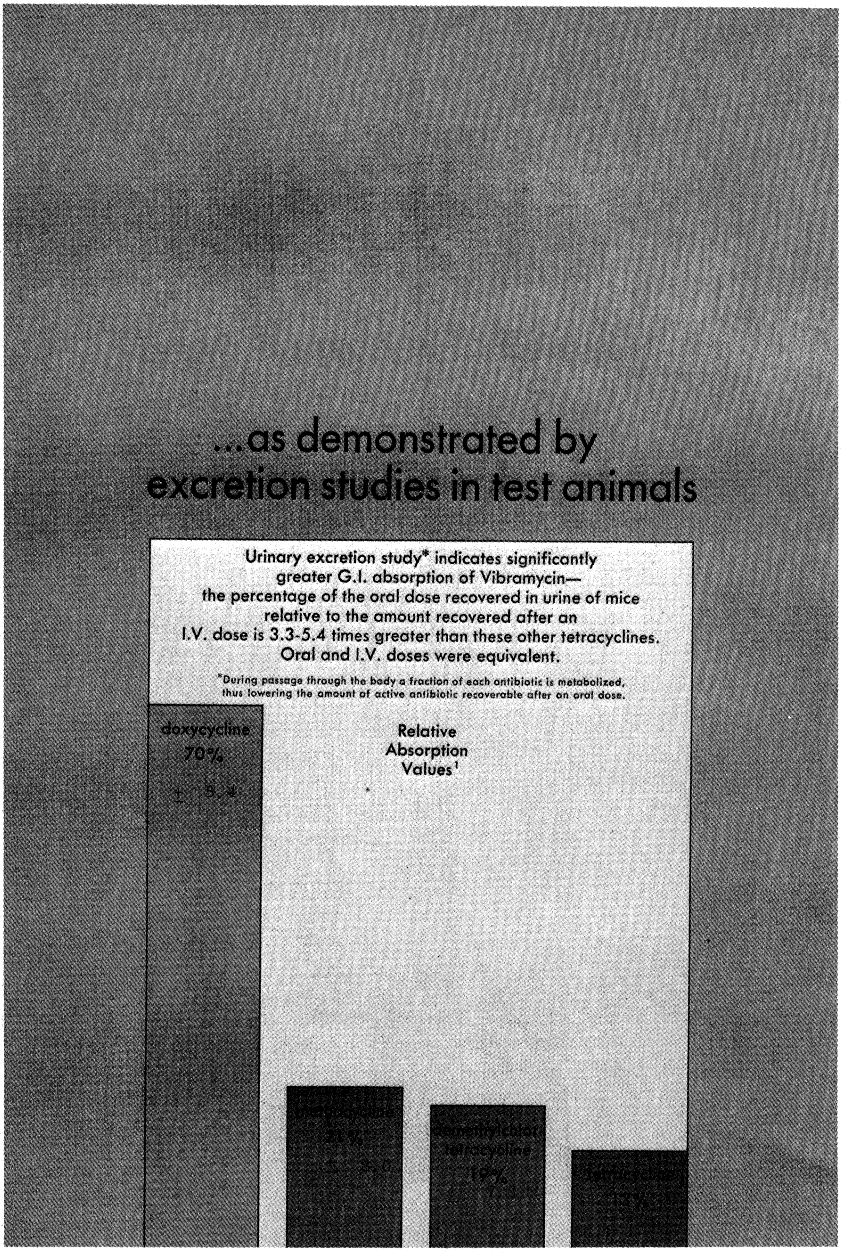
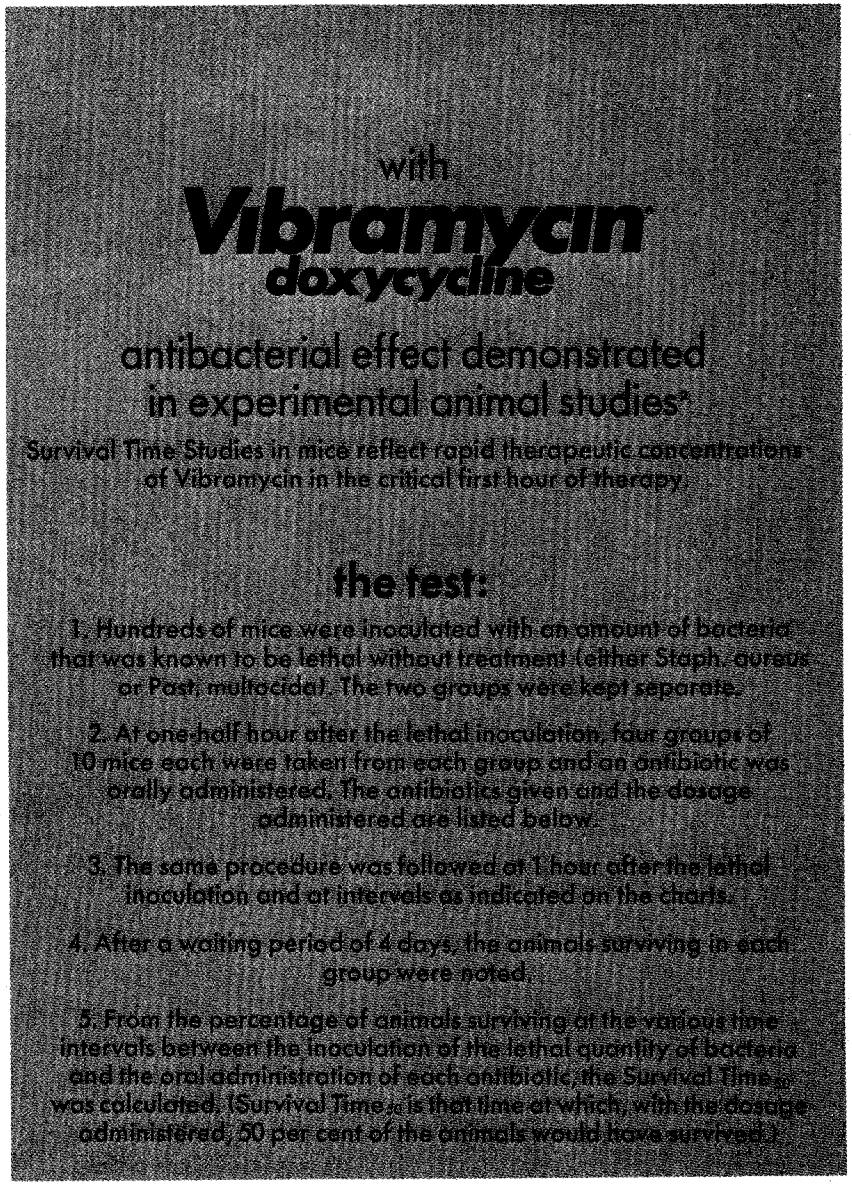

...as demonstrated by
excretion studies in test animals
Urinary excretion study* indicates significantly
greater G.I. absorption of Vibramycin—
the percentage of the oral dose recovered in urine of mice
relative to the amount recovered after an
I.V. dose is 3.3-5.4 times greater than these other tetracyclines.
Oral and I.V. doses were equivalent.
*During passage through the body a fraction of each antibiotic is metabolized,
thus lowering the amount of active antibiotic recoverable after an oral dose.
doxycycline
70%
Relative
Absorption
Values[1]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Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin in the critical first hour of therapy.
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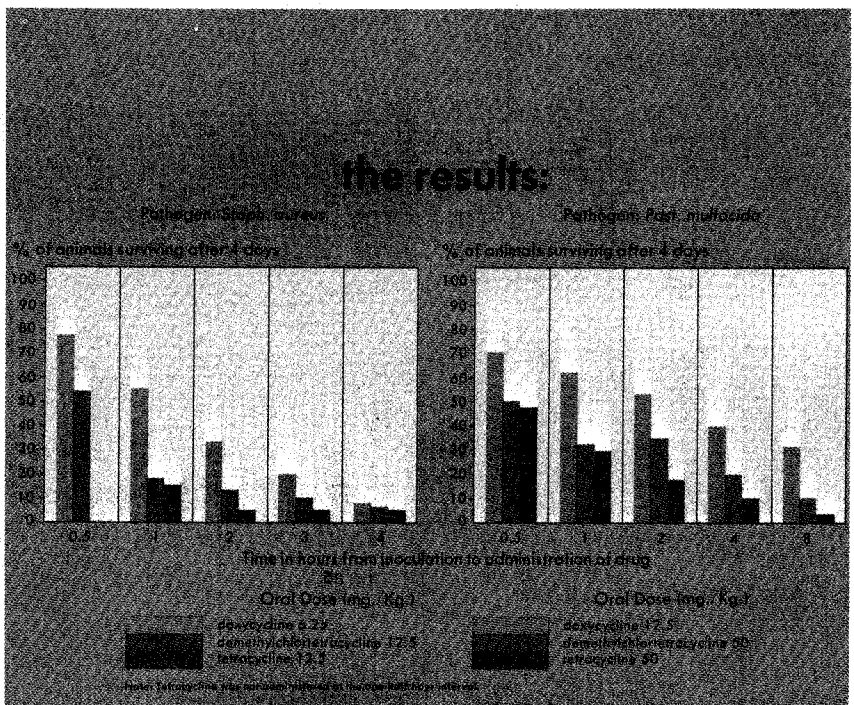
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time50 was calculated. (Survival Time50 is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

the results:



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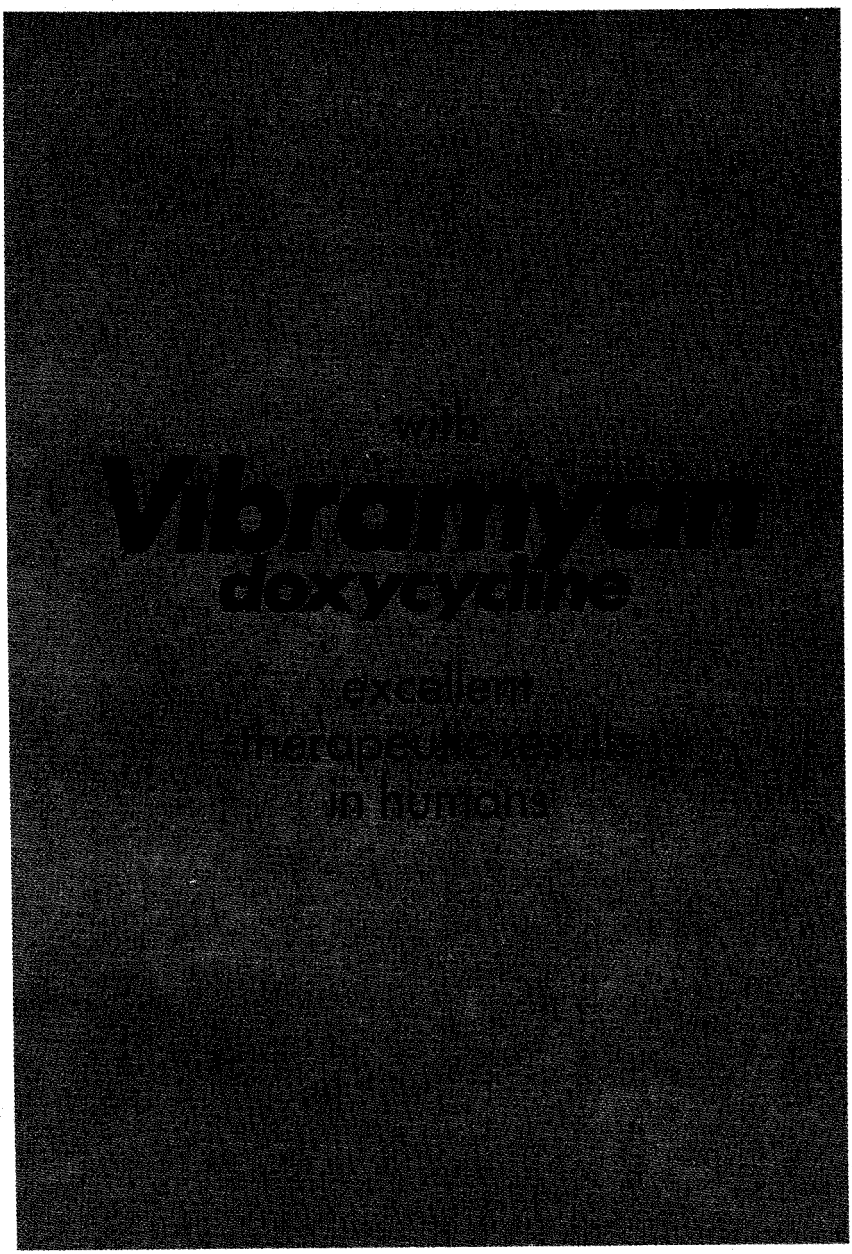
with
Vibramycin
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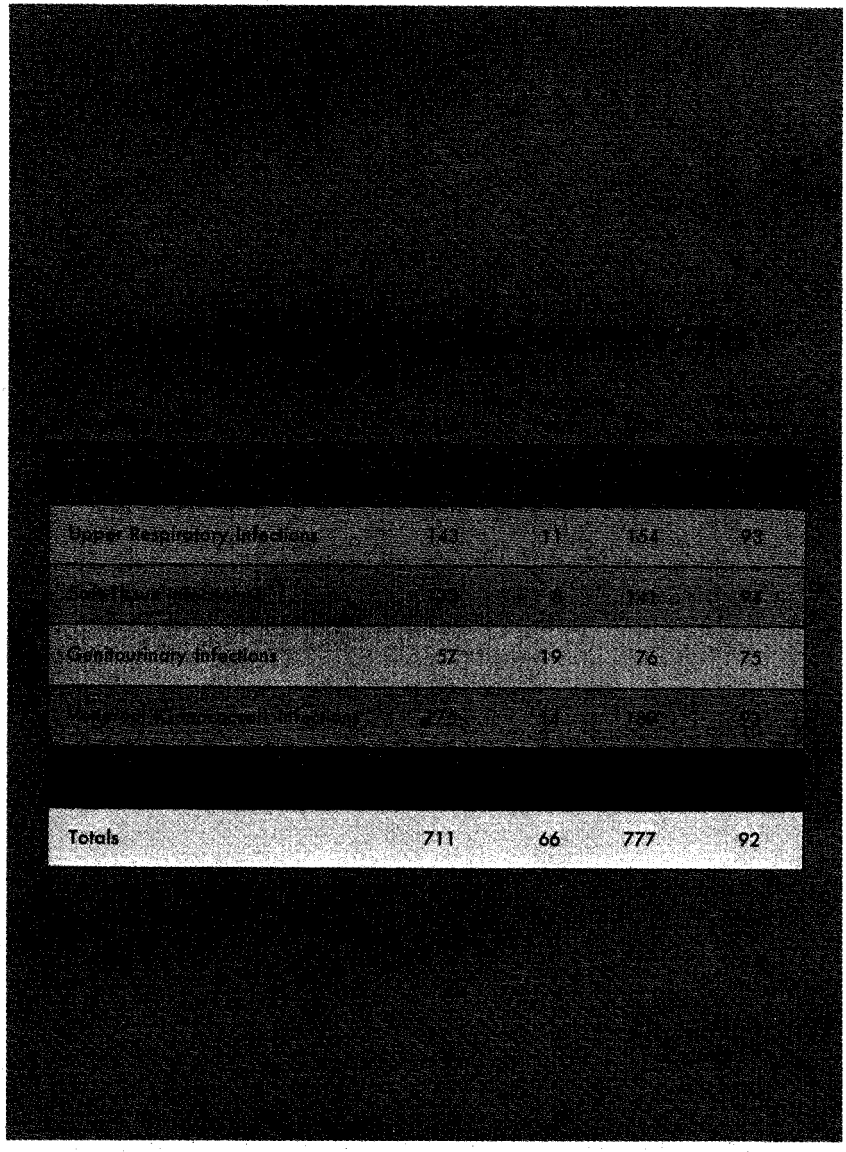
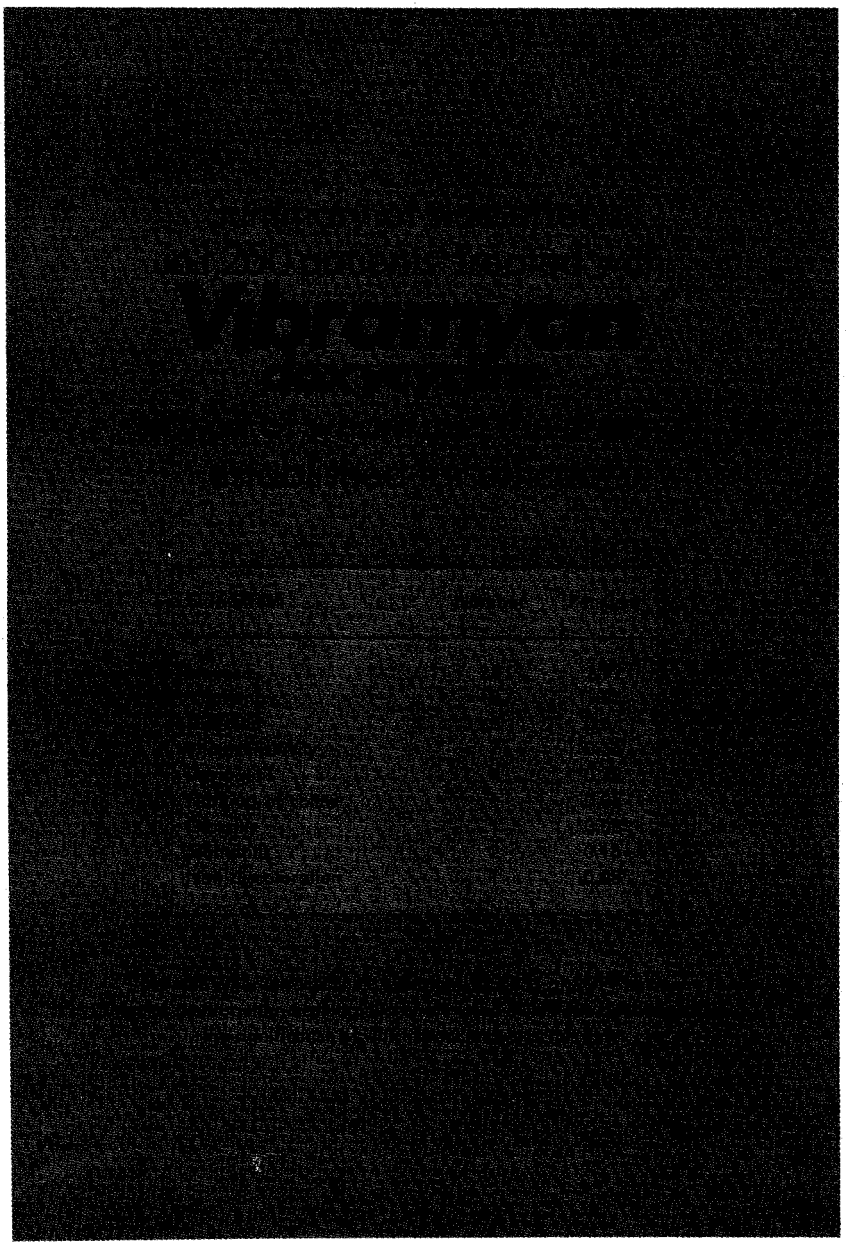
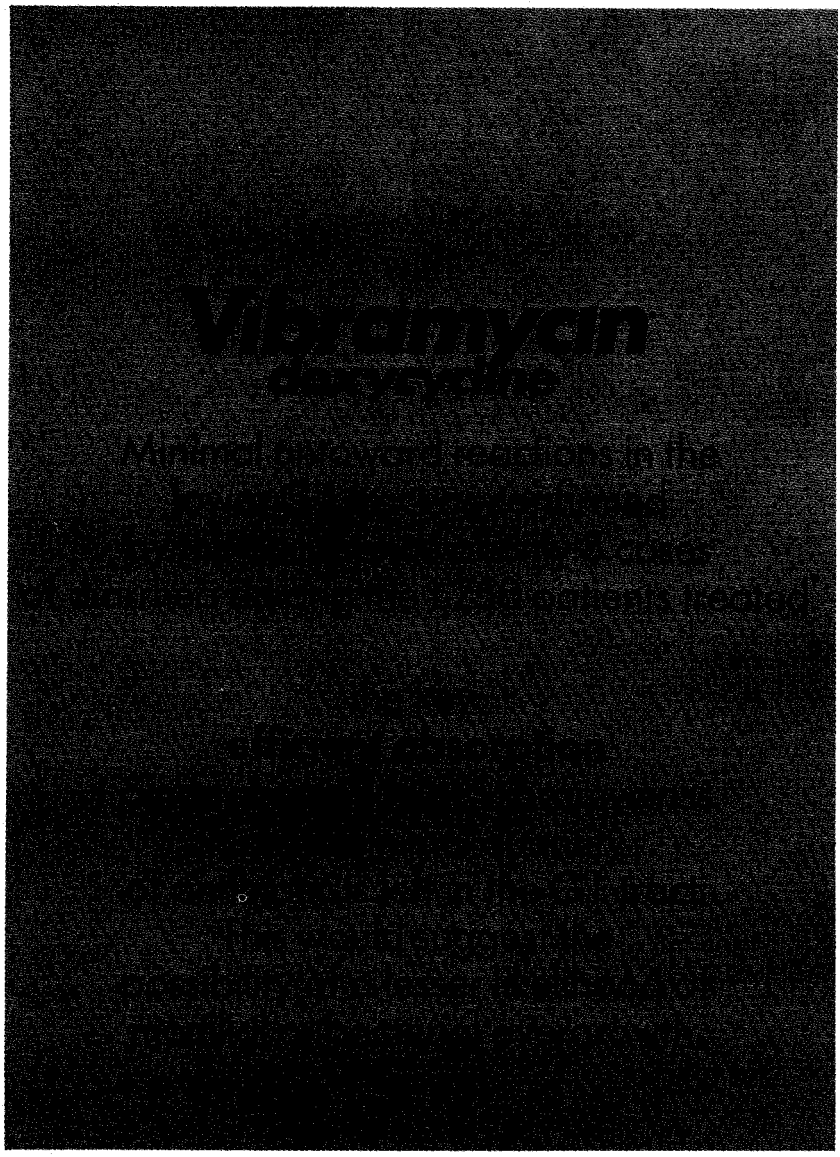
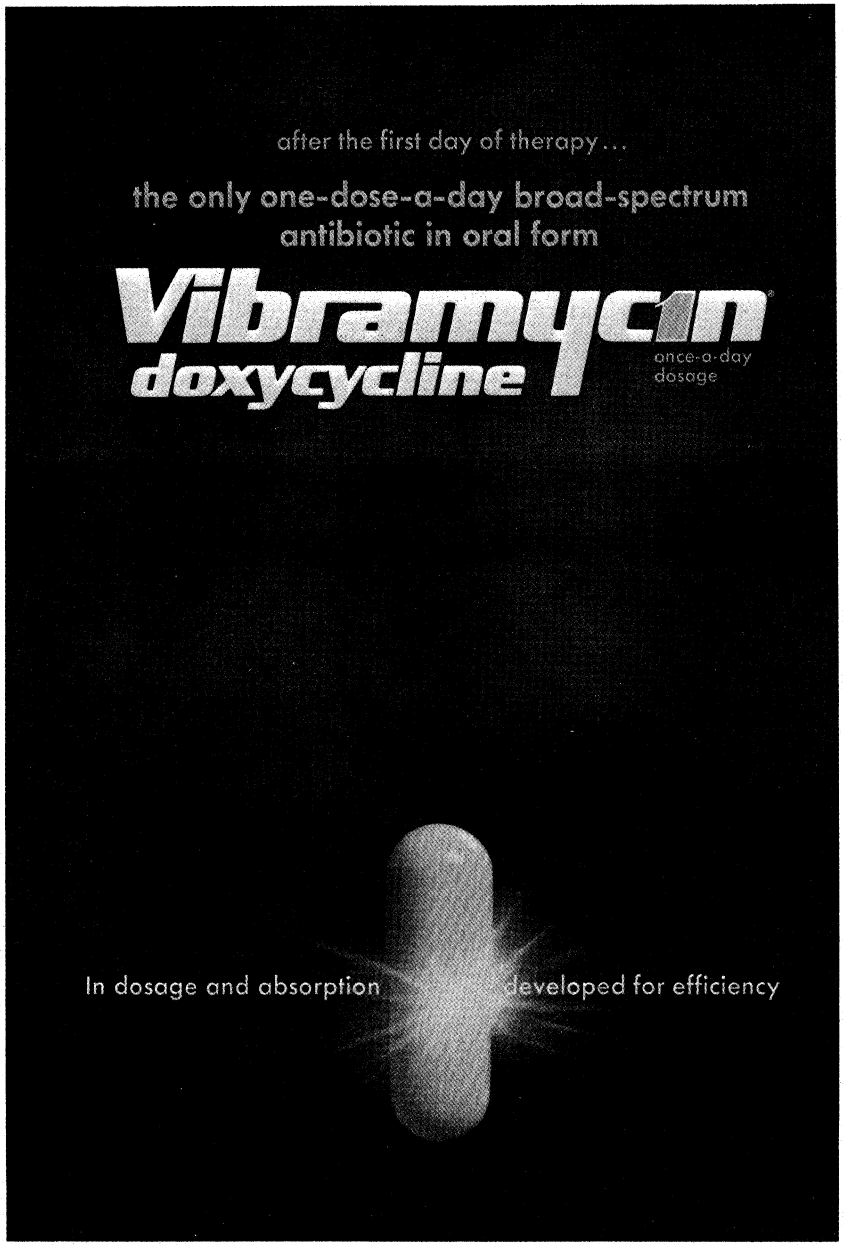


Upper Respiratory Infections	143	11	154	93
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Genitourinary Infections	57	19	76	75
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Totals	711	66	777	92


Vibramycin


Vibramycin
doxycycline


after the first day of therapy...
the only one-dose-a-day broad-spectrum antibiotic in oral form
Vibramycin
doxycycline
once-a-day dosage
In dosage and absorption
developed for efficiency

Criteria for evaluating clinical results:

Upper and lower respiratory infections
Soft tissue infections
Miscellaneous infections

Favorable responses:
Includes those designated as "good" or "satisfactory."
Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.
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Vibramycin® (doxycycline)

Product Information

Description: Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from methacycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is α-6-deoxy-5-oxytetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active in vitro against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD_{50}) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus, Streptococcus, Staphylococcus, H. influenzae,* and *Klebsiella pneumoniae.*

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β-hemolytic Streptococcus, Staphylococcus, Pneumococcus, and *H. influenzae.*

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the Klebsiella-Aerobacter group, *E. coli,* Enterococcus, Staphylococcus, Streptococcus, and *Neisseria gonorrhoeae.* Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus,* Streptococcus, *E. coli,* and the Klebsiella-Aerobacter group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of Gonococci, Staphylococci, and *H. influenzae.*

Gastrointestinal Infections: Due to susceptible strains of such organisms as E. histolytica, pathogenic *E. coli,* and species of Shigella and Salmonella.

Miscellaneous: Other infections due to susceptible strains of Bacteroides, Pasteurella, Brucella (in combination with streptamycin), Psittacosis, Listeria, Rickettsia, *Mycoplasma pneumoniae* (Eaton agent, PPLO), *H. pertussis, B. anthracis, C. welchii, N. meningitidis,* spirachetes (Treponema), *Donovania granulomatis,* and prostatitis and trigonitis due to Proteus or Pseudomonas.

Vibramycin (doxycycline) may be useful in the treatment of acne *vulgaris* and *acne conglobata.*

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long-term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, anycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline: bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor. 2 oz. bottles.

Pfizer **LABORATORIES DIVISION**
New York, N.Y. 10017

Issued September 1967

CHAS. PFIZER & CO., INC.,
New York, N.Y., September 14, 1967.

Re Vibramycin.

ROBERT S. MCCLEERY, M.D.,
Director, Division of Medical Advertising, Bureau of Medicine,
Food and Drug Administration, Washington, D.C.

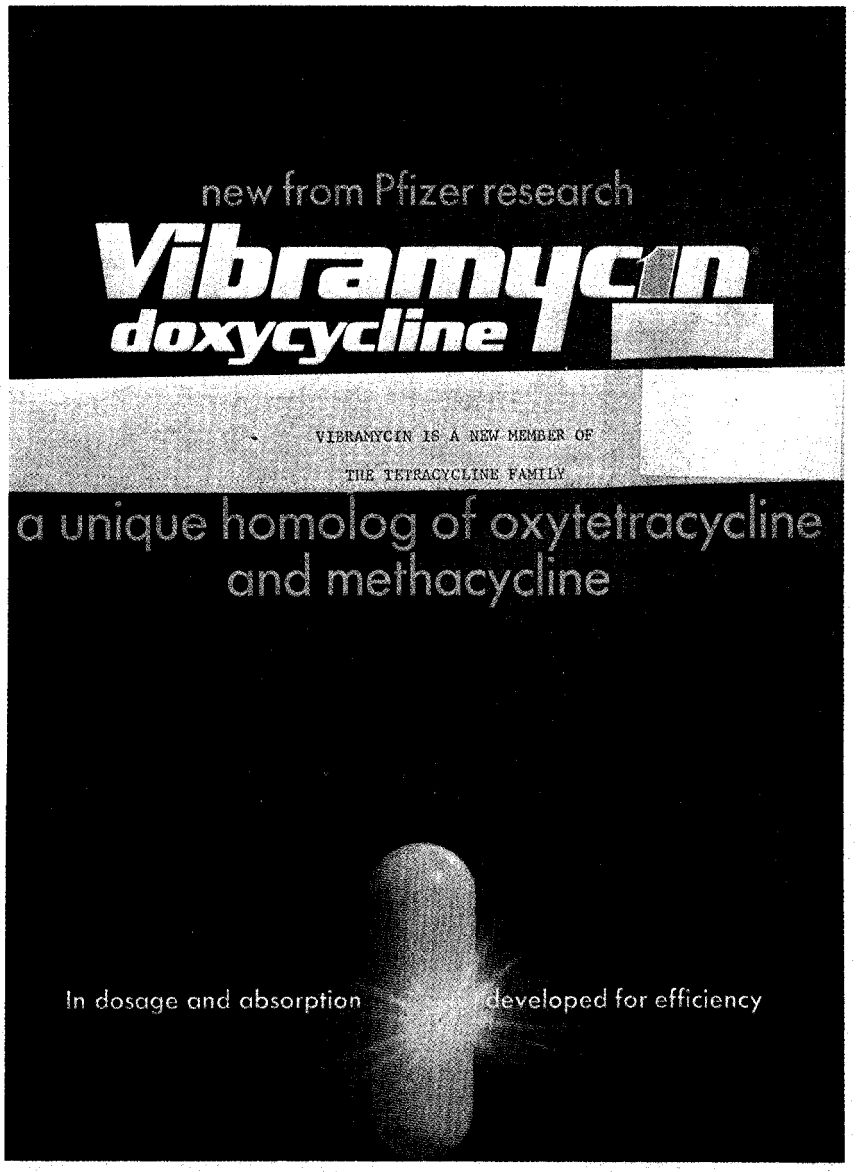
DEAR DR. MCCLEERY: Pursuant to our telephone discussion of September 13, 1967, we are submitting herein the visual aid for Vibramycin as clarified in accordance with our discussion. Also included herein is the dosage calculator which we feel is in line with our discussions concerning the visual aid.

In our telephone conversation you suggested that I indicate to you what course of action we would take concerning the previously submitted, but not now approved, promotional material. With regard to the original file card, which you have in draft copy and which we printed, you will recall that Mr. G. B. Stone stated that it would not be used by our Sales Representative in the form in which it is now printed. We have taken further steps to clarify certain statements in the file card in order to have it coincide with the information in the visual aid. Because of the need to leave something with the physician, under separate cover we are submitting another file card which consists of the package insert and dosage statement page which you have reviewed in our visual aid.

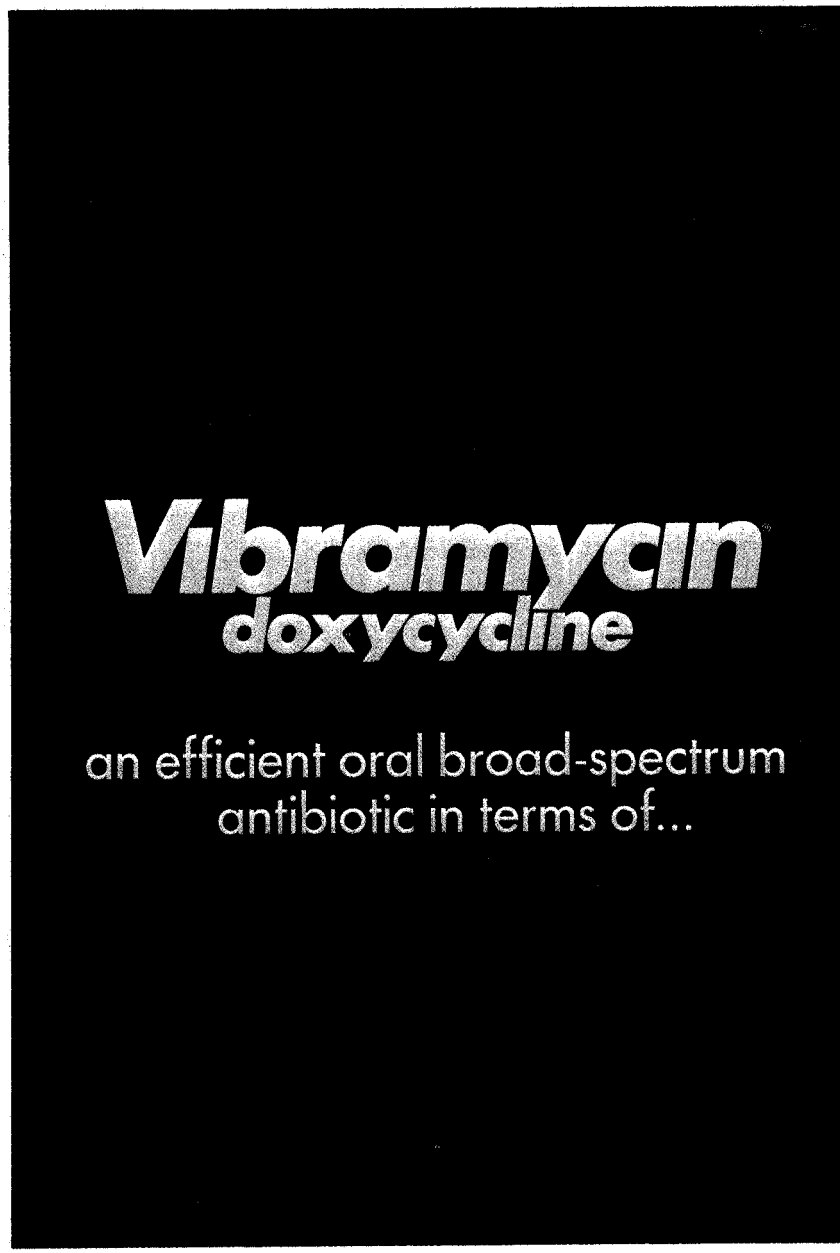
With regard to the compendium which we submitted, I have been requested to state that we would request your concurrence that we be permitted to use this compendium for the same period of time that we are now using the original visual aid. This compendium is primarily for use by the Professional Sales Representative for use in discussion with hospital representatives. It is not to be left with the physician until we have clarified the points in question and have received your approval for its use.

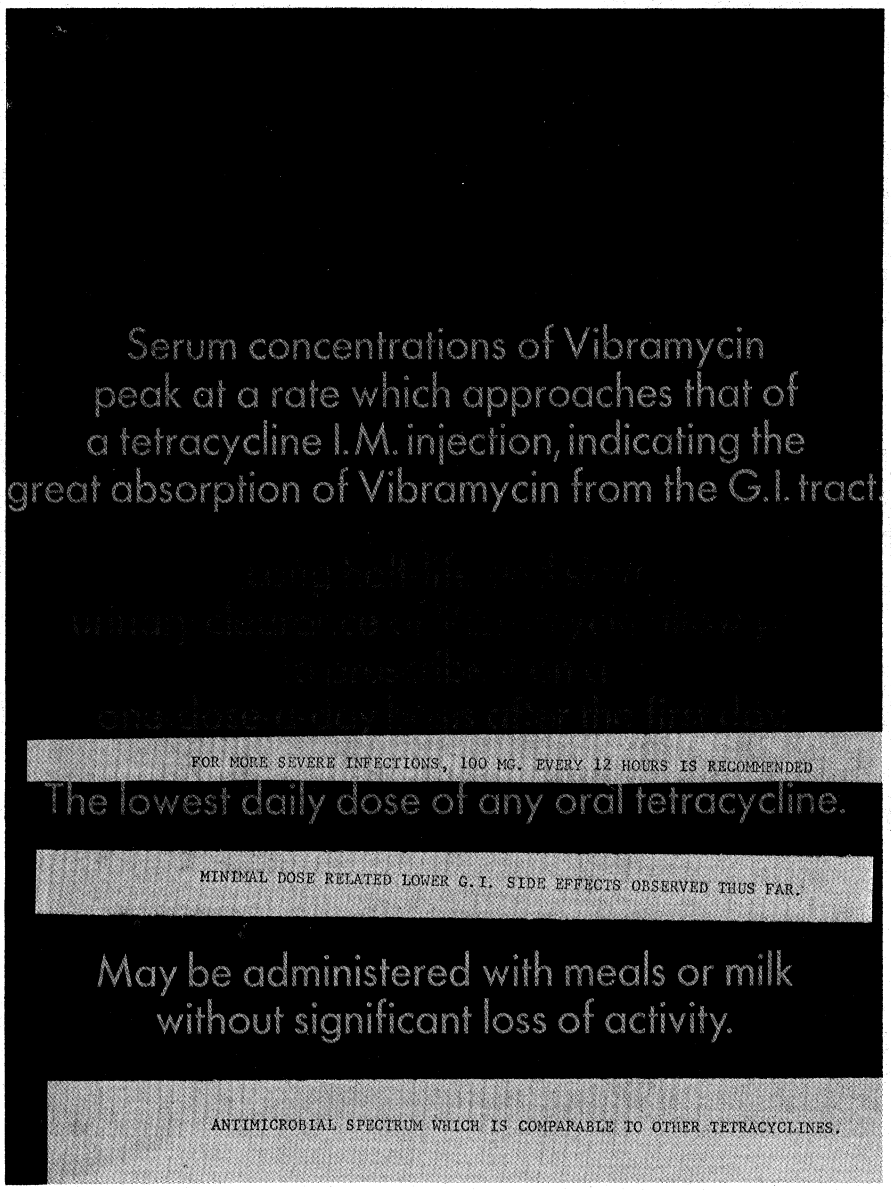
Sincerely yours,

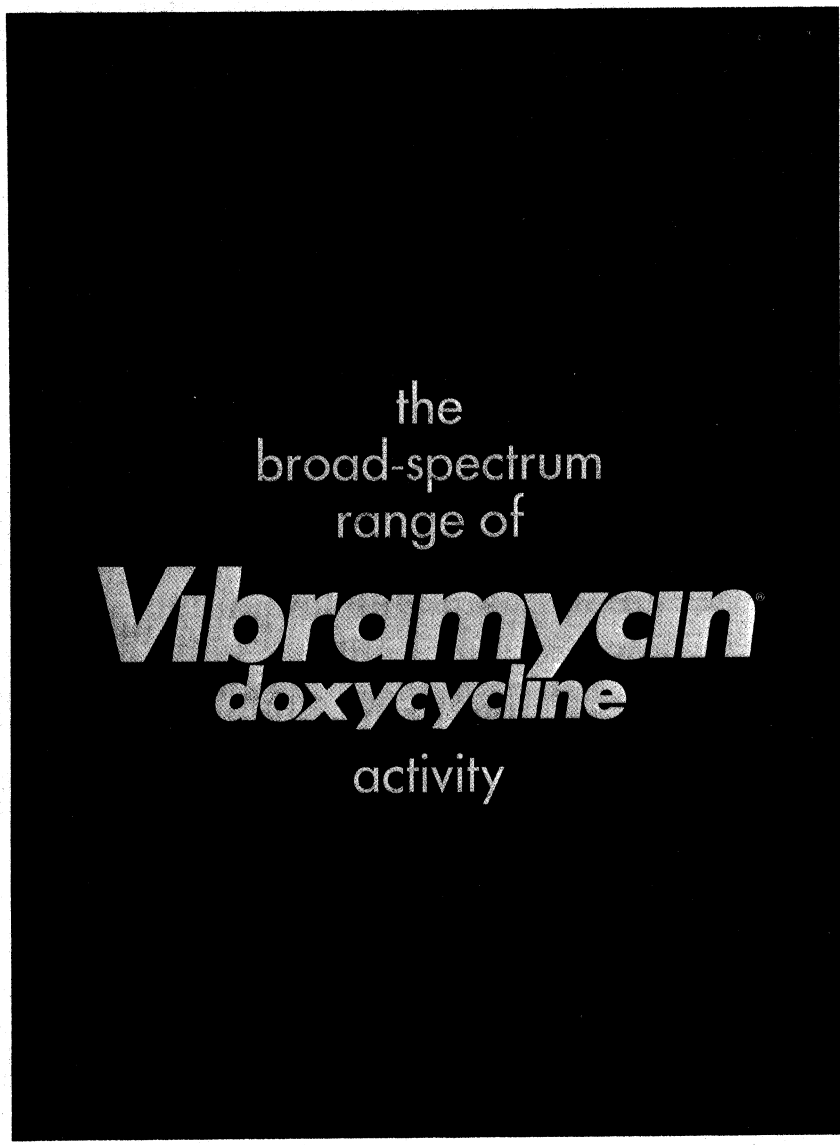
J. P. ATERNO,
Manager, FDA Liaison Department.

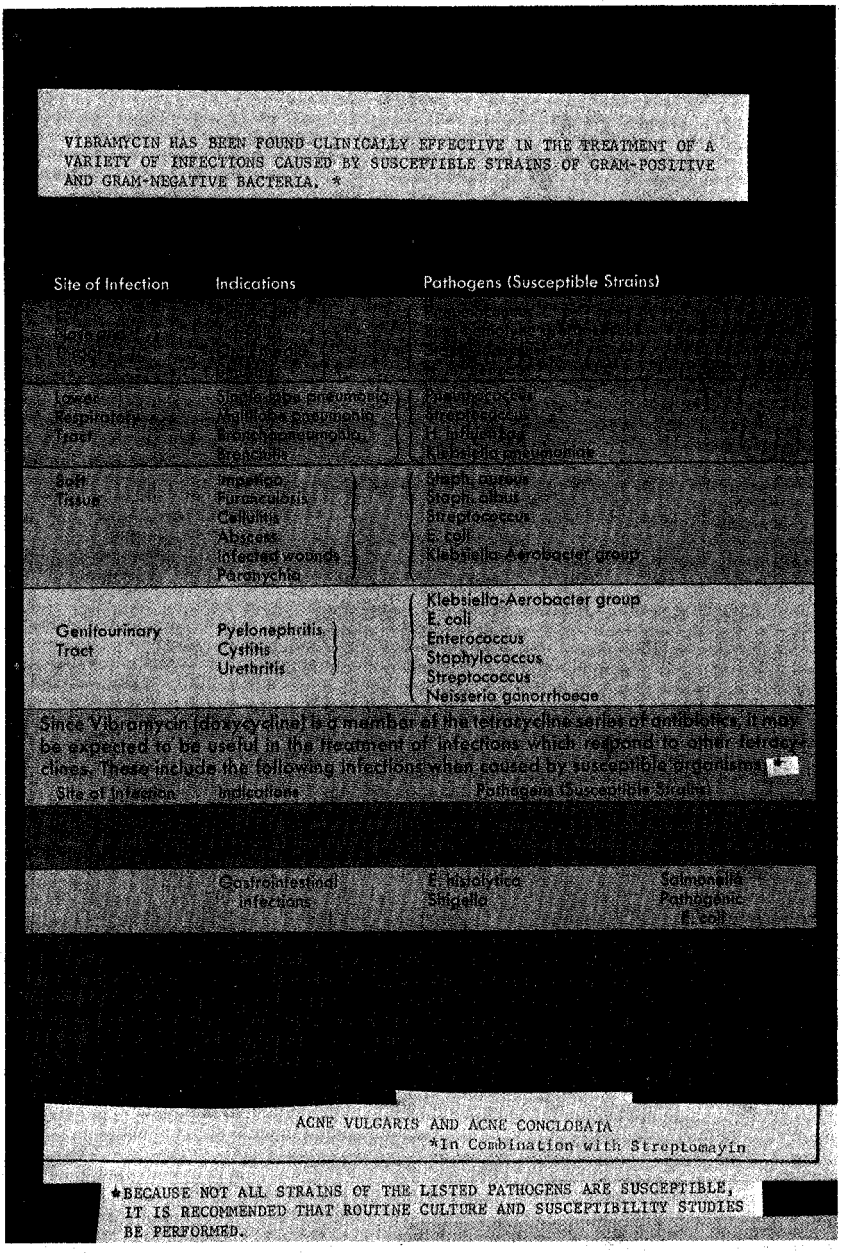


81-280 O-68-pt. 9—5


Vibramycin
doxycycline
an efficient oral broad-spectrum
antibiotic in terms of...


Serum concentrations of Vibramycin
peak at a rate which approaches that of
a tetracycline I.M. injection, indicating the
great absorption of Vibramycin from the G.I. tract.
FOR MORE SEVERE INFECTIONS, 100 MG. EVERY 12 HOURS IS RECOMMENDED
The lowest daily dose of any oral tetracycline.
MINIMAL DOSE RELATED LOWER G.I. SIDE EFFECTS OBSERVED THUS FAR.
May be administered with meals or milk
without significant loss of activity.
ANTIMICROBIAL SPECTRUM WHICH IS COMPARABLE TO OTHER TETRACYCLINES.


the
broad-spectrum
range of
Vibramycin®
doxycycline
activity



VIBRAMYCIN HAS BEEN FOUND CLINICALLY EFFECTIVE IN THE TREATMENT OF A VARIETY OF INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA. *

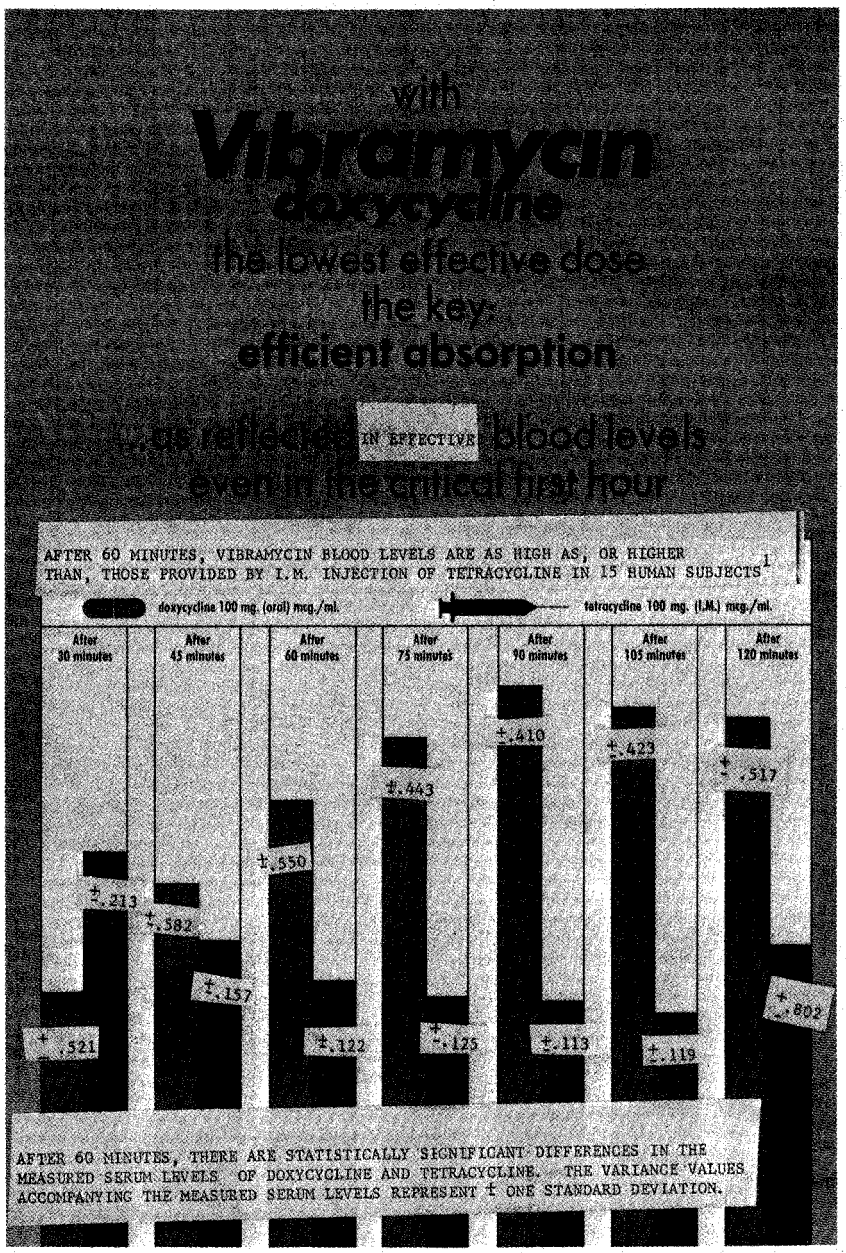
Site of Infection	Indications	Pathogens (Susceptible Strains)
Lower Respiratory Tract	Bronchopneumonia, Bronchitis	Pneumococci, Streptococci, H. influenzae, Klebsiella pneumoniae
Soft Tissue	Impetigo, Furunculosis, Cellulitis, Abscess, Infected wounds, Paronychia	Staph. aureus, Staph. albus, Streptococcus, E. coli, Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis, Cystitis, Urethritis	Klebsiella-Aerobacter group, E. coli, Enterococcus, Staphylococcus, Streptococcus, Neisseria gonorrhoeae

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms:

Site of Infection	Indications	Pathogens (Susceptible Strains)
	Gastrointestinal infections	E. histolytica, Shigella, Salmonella, Pathogenic E. coli

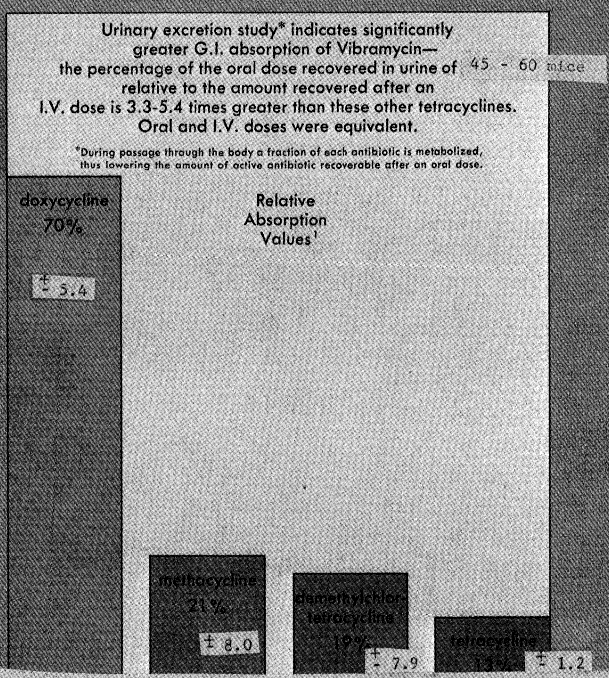
ACNE VULGARIS AND ACNE CONGLOBATA
*In Combination with Streptomycin

*BECAUSE NOT ALL STRAINS OF THE LISTED PATHOGENS ARE SUSCEPTIBLE, IT IS RECOMMENDED THAT ROUTINE CULTURE AND SUSCEPTIBILITY STUDIES BE PERFORMED.

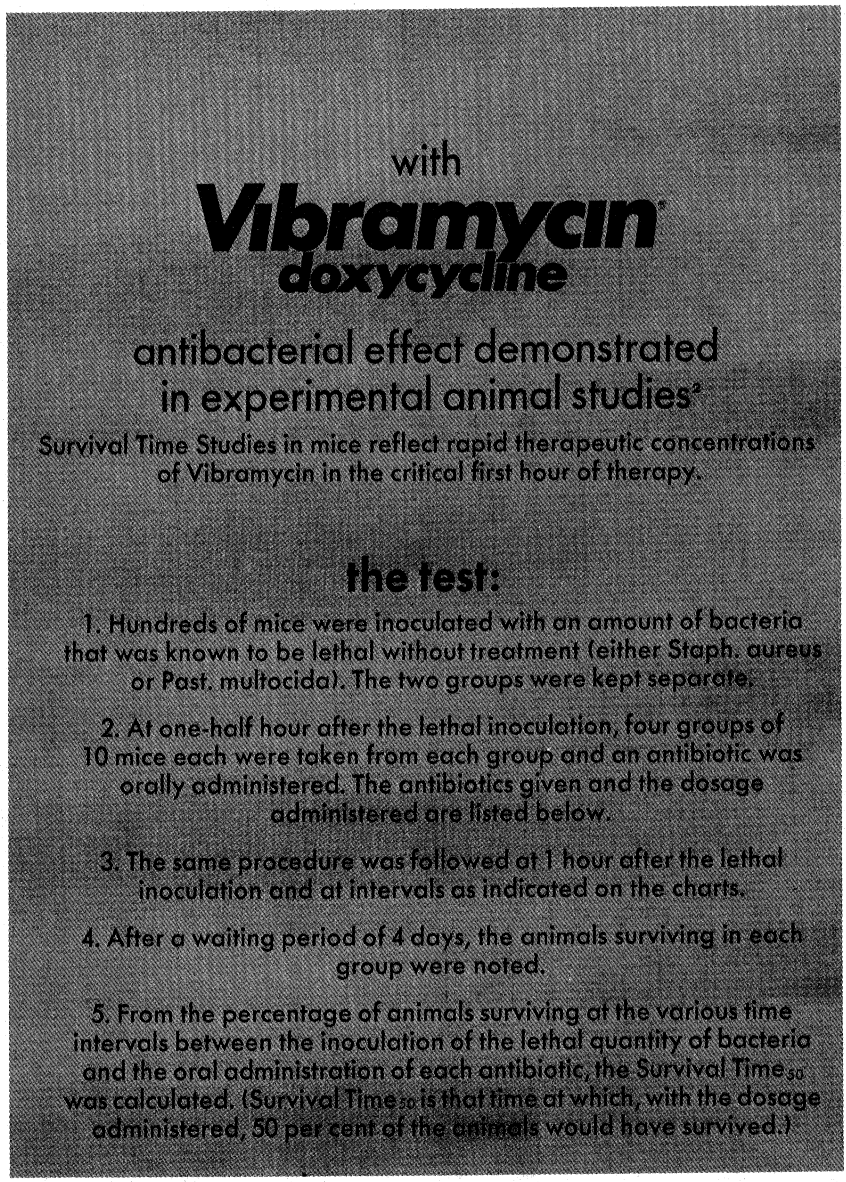

with
Vibramycin
doxycycline
the lowest effective dose
the key:
efficient absorption
as reflected in effective blood levels
even in the critical first hour
AFTER 60 MINUTES, VIBRAMYCIN BLOOD LEVELS ARE AS HIGH AS, OR HIGHER THAN, THOSE PROVIDED BY I.M. INJECTION OF TETRACYCLINE IN 15 HUMAN SUBJECTS[1]
doxycycline 100 mg. (oral) mcg./ml.
tetracycline 100 mg. (I.M.) mcg./ml.
After 30 minutes
After 45 minutes
After 60 minutes
After 75 minutes
After 90 minutes
After 105 minutes
After 120 minutes
±.213
±.521
±.582
±.157
±.550
±.122
±.443
±.125
±.410
±.113
±.423
±.119
±.517
±.802
AFTER 60 MINUTES, THERE ARE STATISTICALLY SIGNIFICANT DIFFERENCES IN THE MEASURED SERUM LEVELS OF DOXYCYCLINE AND TETRACYCLINE. THE VARIANCE VALUES ACCOMPANYING THE MEASURED SERUM LEVELS REPRESENT ± ONE STANDARD DEVIATION.

A SIMILAR COMPARISON IN DOGS SHOWED LESS PRONOUNCED DIFFERENCES BETWEEN THE DRUGS TESTED, BUT SUPPORTED THE CONCLUSION THAT, IN THE DOG, THE PERCENTAGE OF AN ORAL DOSE WHICH IS ABSORBED BY THE GASTROINTESTINAL TRACT IS FROM 2 TO 4 TIMES AS LARGE FOR DOXYCYCLINE AS FOR OTHER DRUGS TESTED. (Bottom of page)

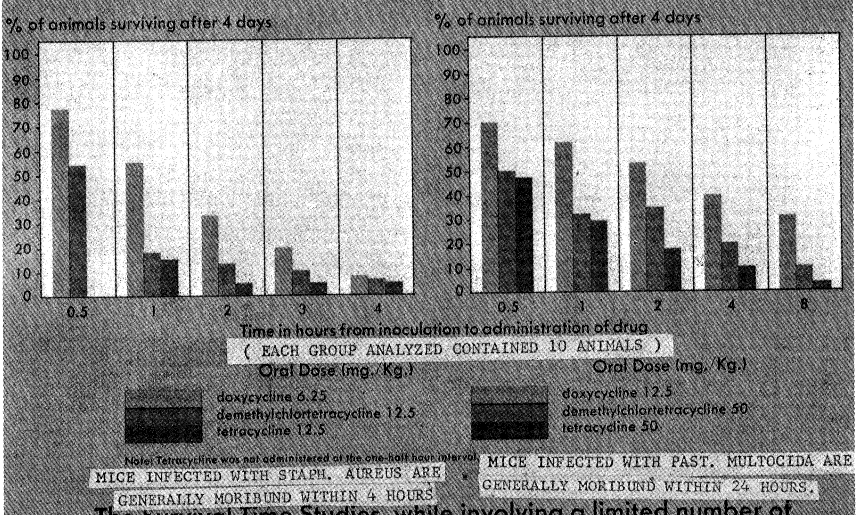
...as demonstrated by excretion studies in test animals



THE VARIANCE %'s ACCOMPANYING THE RELATIVE ABSORPTION VALUES REPRESENT ± ONE STANDARD DEVIATION.


with
Vibramycin®
doxycycline
antibacterial effect demonstrated
in experimental animal studies[2]
Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin in the critical first hour of therapy.
the test:
1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either Staph. aureus or Past. multocida). The two groups were kept separate.
2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time50 was calculated. (Survival Time50 is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

the results:

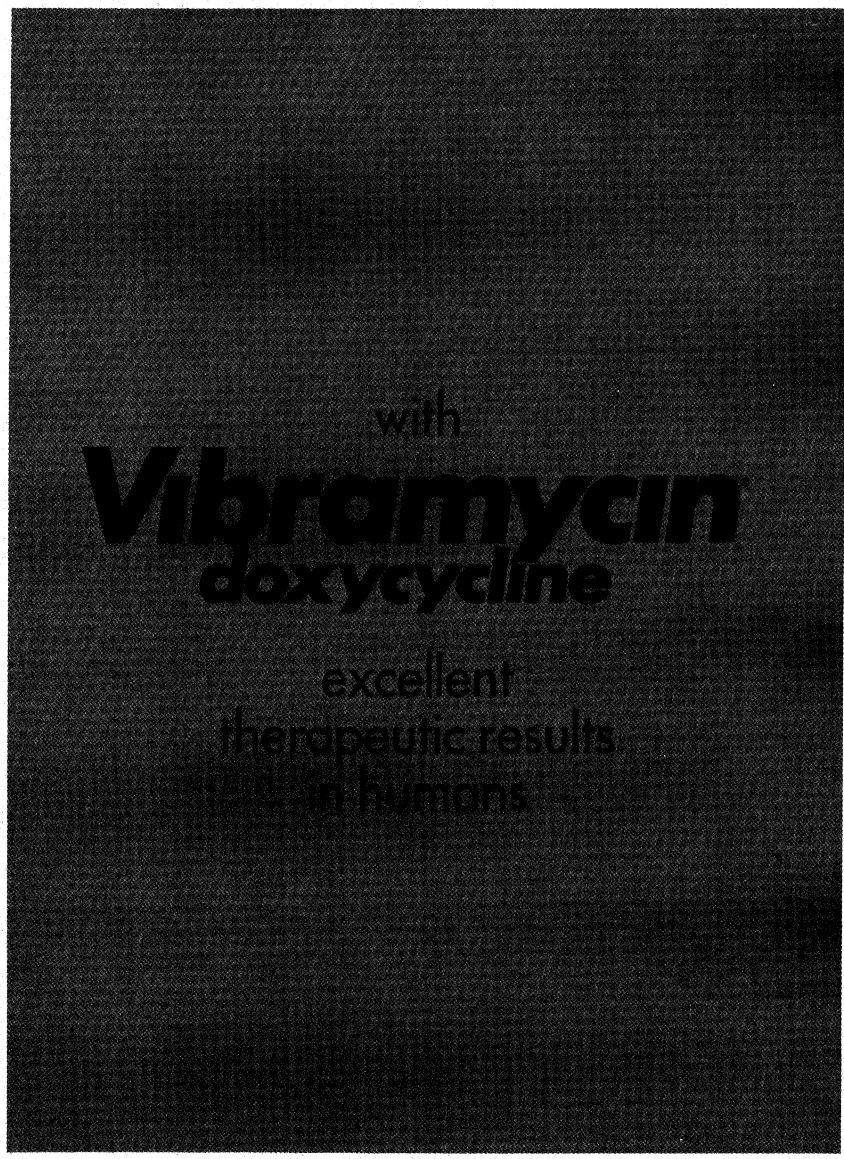


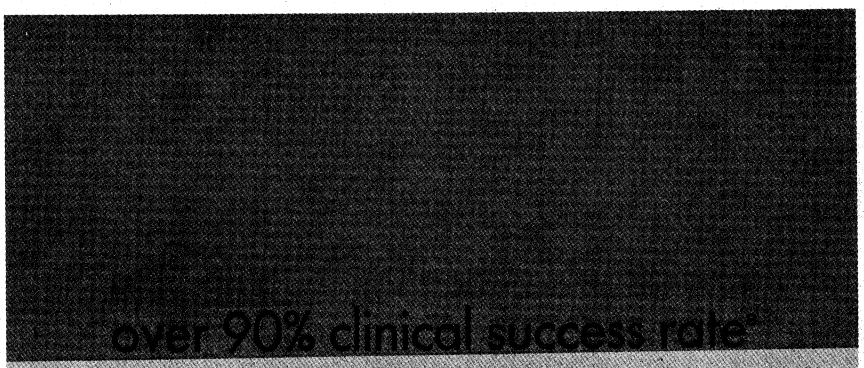
The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

the conclusion:

EVEN AT A FRACTION OF THE DOSAGE OF OTHER TETRACYCLINE ANTIBIOTICS TESTED, VIBRAMYCIN PROVIDED A GREATER AND MORE PERSISTENT CHEMOTHERAPEUTIC EFFECT.

(THE RESULTS OBTAINED CANNOT BE DIRECTLY EXTRAPOLATED TO THE CLINICAL SITUATION.


with
Vibramycin
doxycycline
excellent
therapeutic results
in humans



OF 1250 PATIENTS TREATED WITH VIBRAMYCIN® (doxycycline), THIS ANALYSIS OF THE CLINICAL SUCCESS RATE ~~SPECIFICALLY~~ INCLUDES THOSE CASES IN WHICH THE BACTERIOLOGIC ETIOLOGY WAS DETERMINED AND SENSITIVITY TESTING INDICATED ORGANISM SUSCEPTIBILITY. SENSITIVITY TESTING IS RECOGNIZED TO BE IMPORTANT FOR THE SELECTION OF THE MOST APPROPRIATE ANTIBIOTIC FOR A SPECIFIC PATIENT'S INFECTION.

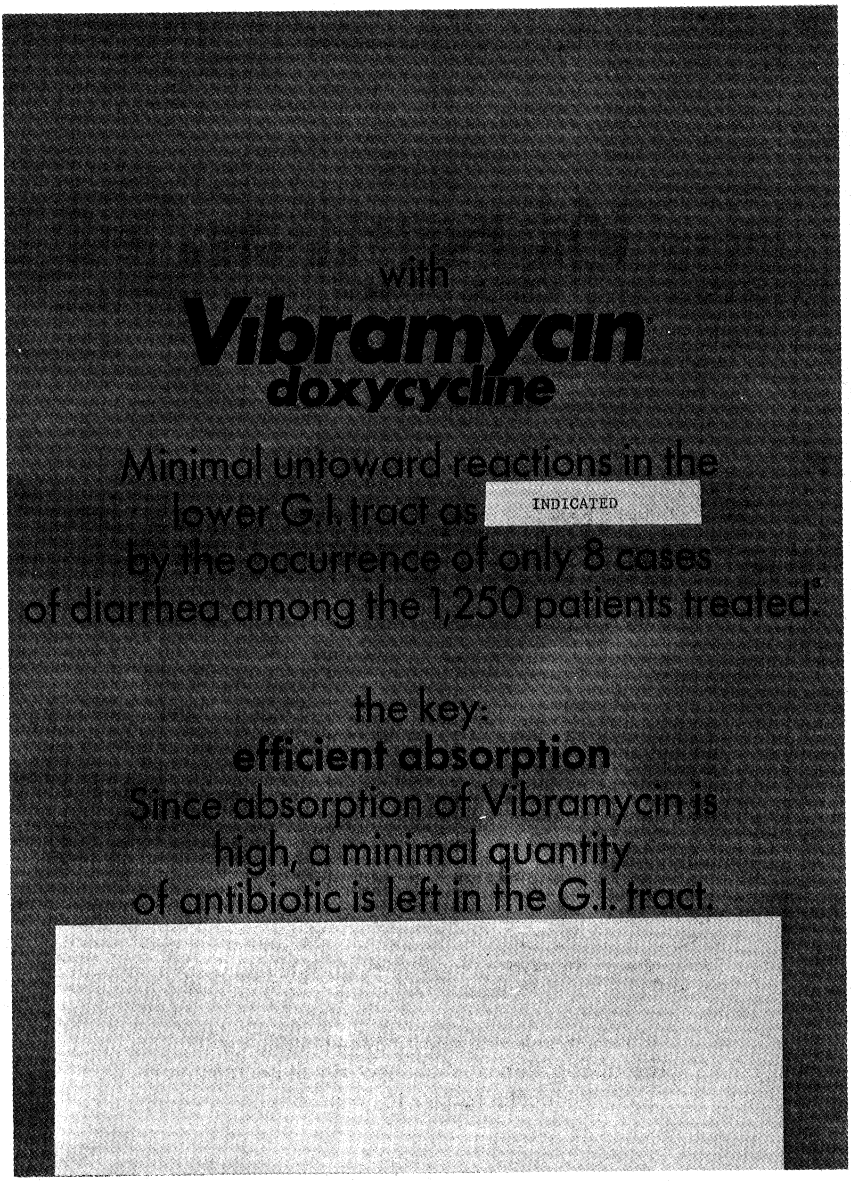
DIAGNOSIS GROUP	CLINICAL RESPONSE FAVORABLE	POOR	TOTAL	PER CENT SUCCESS
LOWER RESPIRATORY INFECTIONS	77	6	83	93
UPPER RESPIRATORY INFECTIONS	123	4	127	97
SOFT-TISSUE INFECTIONS	104	4	108	96
GENITOURINARY INFECTIONS	39	16	55	71
VENEREAL (GONOCOCCAL) INFECTIONS	66	2	68	97
MISCELLANEOUS INFECTIONS	12	1	13	92
TOTALS	421	33	454	

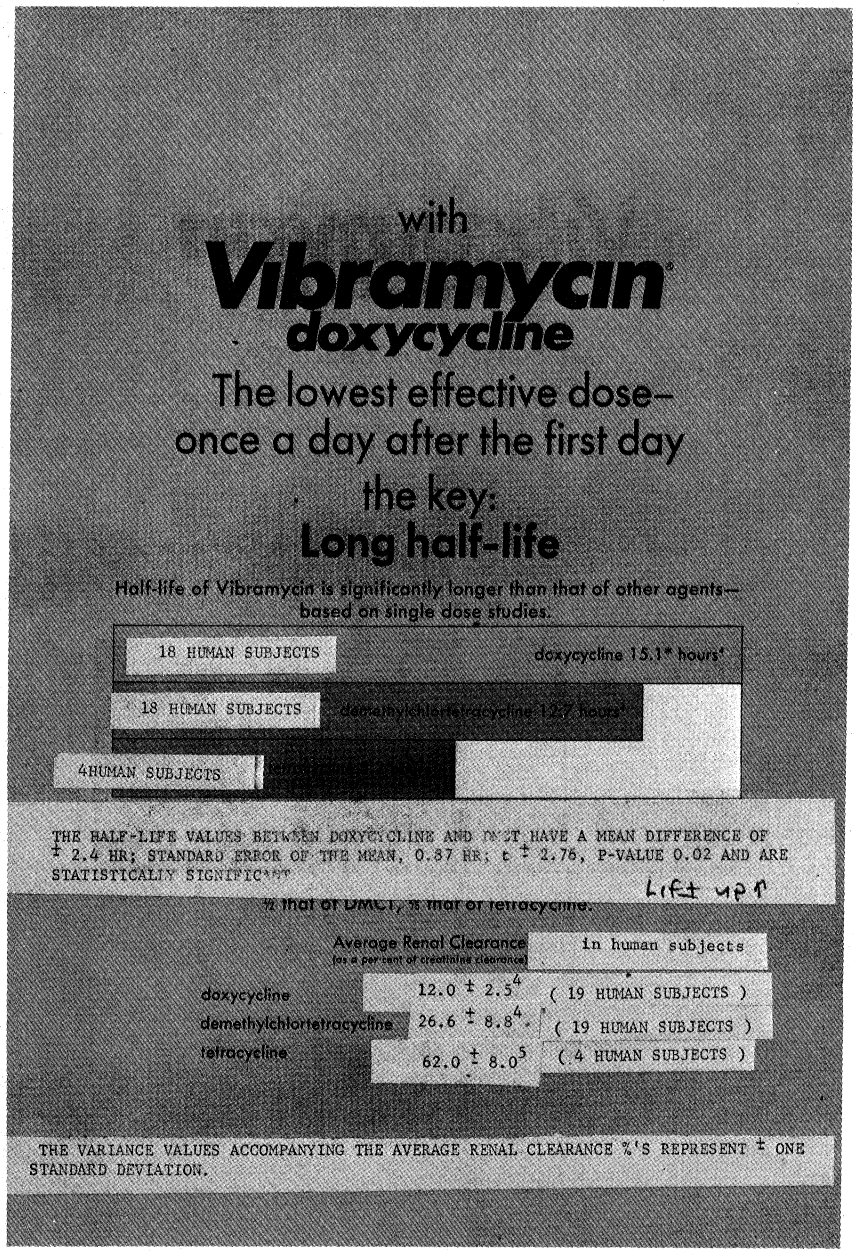
For criteria used in evaluating results of therapy, see end of brochure.

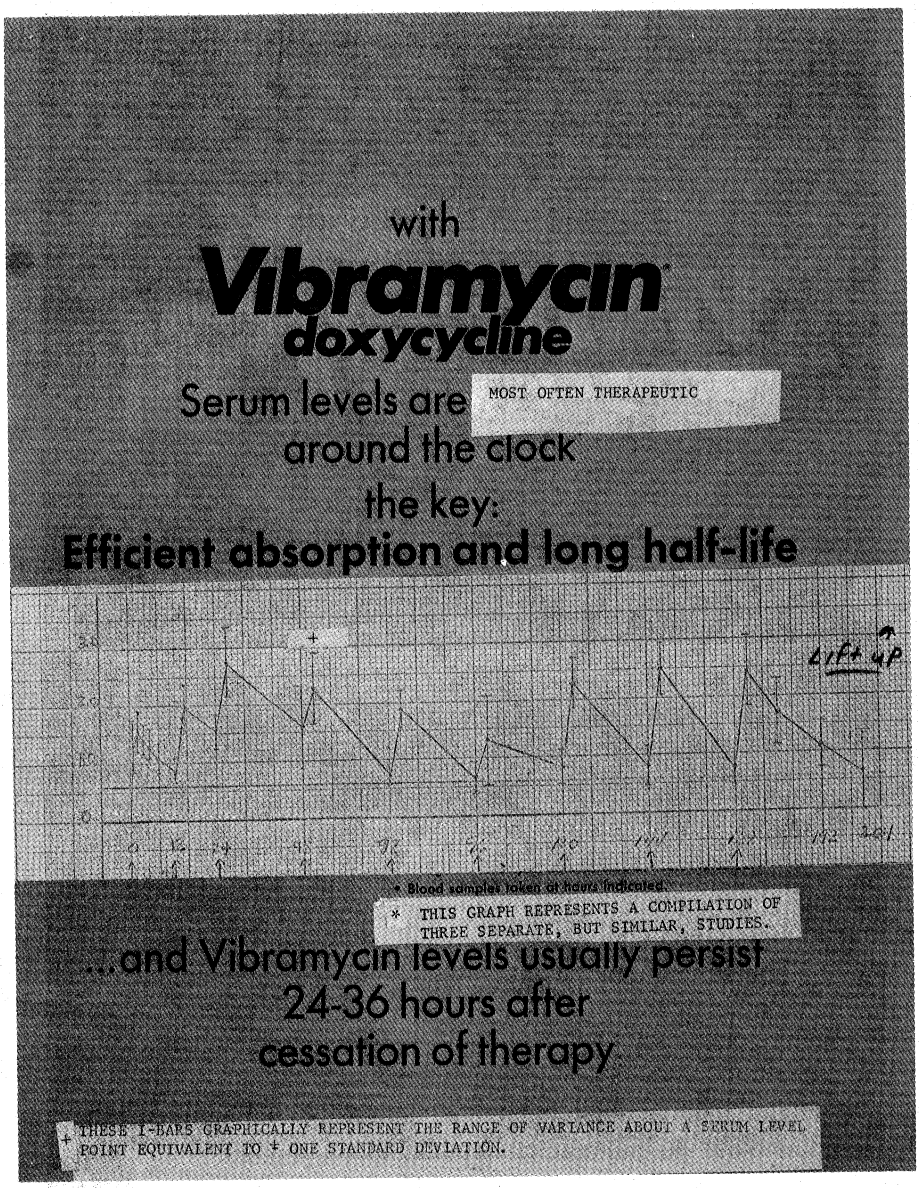
Summary of side effects
in 1,250 patients* treated with
Vibramycin
doxycycline
not all of whom met the criteria
established for efficacy

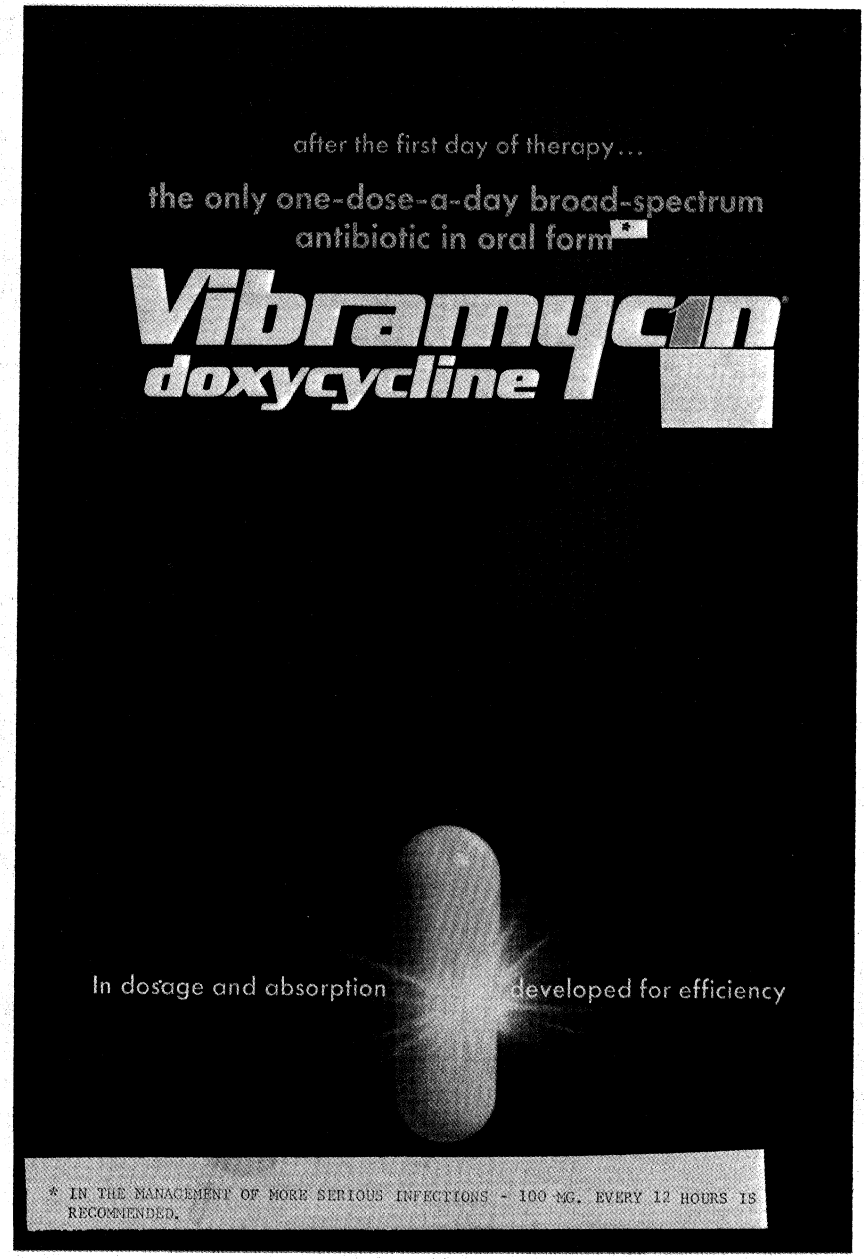
Side Effect	Number	Per Cent
Nausea	24	1.92
Vomiting	13	1.04
Diarrhea	8	0.64
[illegible]	7	0.56
[illegible]	4	0.32
[illegible]	1	0.08
Glossitis	1	0.08
Stomatitis	2	0.16
Nail discoloration	1	0.08

As with other tetracyclines, elevation of SGOT or SGPT values,
anemia, neutropenia, [illegible] or elevated BUN have been reported;
the significance of [illegible] at this time.


with
Vibramycin
doxycycline
Minimal untoward reactions in the lower G.I. tract as INDICATED by the occurrence of only 8 cases of diarrhea among the 1,250 patients treated.
the key:
efficient absorption
Since absorption of Vibramycin is high, a minimal quantity of antibiotic is left in the G.I. tract.


with
Vibramycin®
doxycycline
The lowest effective dose–
once a day after the first day
the key:
Long half-life
Half-life of Vibramycin is significantly longer than that of other agents—
based on single dose studies.
18 HUMAN SUBJECTS
doxycycline 15.1* hours†
18 HUMAN SUBJECTS
demethylchlortetracycline 12.7 hours†
4HUMAN SUBJECTS
THE HALF-LIFE VALUES BETWEEN DOXYCYCLINE AND DMCT HAVE A MEAN DIFFERENCE OF ± 2.4 HR; STANDARD ERROR OF THE MEAN, 0.87 HR; t ± 2.76, P-VALUE 0.02 AND ARE STATISTICALLY SIGNIFICANT
% that of DMCT, % that of tetracycline.
Average Renal Clearance
(as a per cent of creatinine clearance)
in human subjects
doxycycline 12.0 ± 2.5[4] (19 HUMAN SUBJECTS)
demethylchlortetracycline 26.6 ± 8.8[4] (19 HUMAN SUBJECTS)
tetracycline 62.0 ± 8.0[5] (4 HUMAN SUBJECTS)
THE VARIANCE VALUES ACCOMPANYING THE AVERAGE RENAL CLEARANCE %'S REPRESENT ± ONE STANDARD DEVIATION.


with
Vibramycin
doxycycline
Serum levels are
around the clock
the key:
Efficient absorption and long half-life
MOST OFTEN THERAPEUTIC
Life up
• Blood samples taken at hours indicated.
* THIS GRAPH REPRESENTS A COMPILATION OF THREE SEPARATE, BUT SIMILAR, STUDIES.
...and Vibramycin levels usually persist
24-36 hours after
cessation of therapy
+ THESE I-BARS GRAPHICALLY REPRESENT THE RANGE OF VARIANCE ABOUT A SERUM LEVEL POINT EQUIVALENT TO + ONE STANDARD DEVIATION.


after the first day of therapy...
the only one-dose-a-day broad-spectrum antibiotic in oral form*
Vibramycin
doxycycline
In dosage and absorption developed for efficiency
* IN THE MANAGEMENT OF MORE SERIOUS INFECTIONS - 100 MG. EVERY 12 HOURS IS RECOMMENDED.

Criteria for evaluating clinical results:

Upper and lower respiratory infections
Soft tissue infections
Miscellaneous infections

Favorable responses:
Includes those designated as "good" or "satisfactory."
Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.
Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses:
Cases in which it was felt that there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses:
Includes those designated as "good" or "satisfactory."

Good responses:
Those in which clinical symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

Satisfactory responses:
Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses:
Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

Vibramycin® (doxycycline)

Product Information

Description: Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from methocycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is α-6-deoxy-5-oxytetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD_{50}) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus, Streptococcus, Staphylococcus, H. influenzae,* and *Klebsiella pneumoniae.*

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β-hemolytic Streptococcus, Staphylococcus, Pneumococcus, and *H. influenzae.*

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the Klebsiella-Aerobacter group, *E. coli,* Enterococcus, Staphylococcus, Streptococcus, and *Neisseria gonorrhoeae.* Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus, Streptococcus, E. coli,* and the Klebsiella-Aerobacter group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of Gonococci, Staphylococci, and *H. influenzae.*

Gastrointestinal Infections: Due to susceptible strains of such organisms as *E. histolytica,* pathogenic *E. coli,* and species of Shigella and Salmonella.

Miscellaneous: Other infections due to susceptible strains of Bacteroides, Pasteurella, Brucella (in combination with streptomycin), Psittacosis, Listeria, Rickettsia, *Mycoplasma pneumoniae* (Eaton agent, PPLO), *H. pertussis, B. anthracis, C. welchii, N. meningitidis,* spirochetes (Treponema), *Donovania granulomatis,* and prostatitis and trigonitis due to Proteus or Pseudomonas.

Vibramycin (doxycycline) may be useful in the treatment of *acne vulgaris* and *acne conglobata.*

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long-term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline: bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor: 2 oz. bottles.

Pfizer **LABORATORIES DIVISION**
New York, N.Y. 10017

Issued September 1967

CHAS. PFIZER & CO., INC.,
New York, N.Y., October 6, 1967.

Re Vibramycin—§ 148z. 3 and § 148z. 4.

ROBERT S. MCCLEERY, M.D.,
Director, Division of Medical Advertising, Bureau of Medicine, Food and Drug Administration, Washington, D.C.

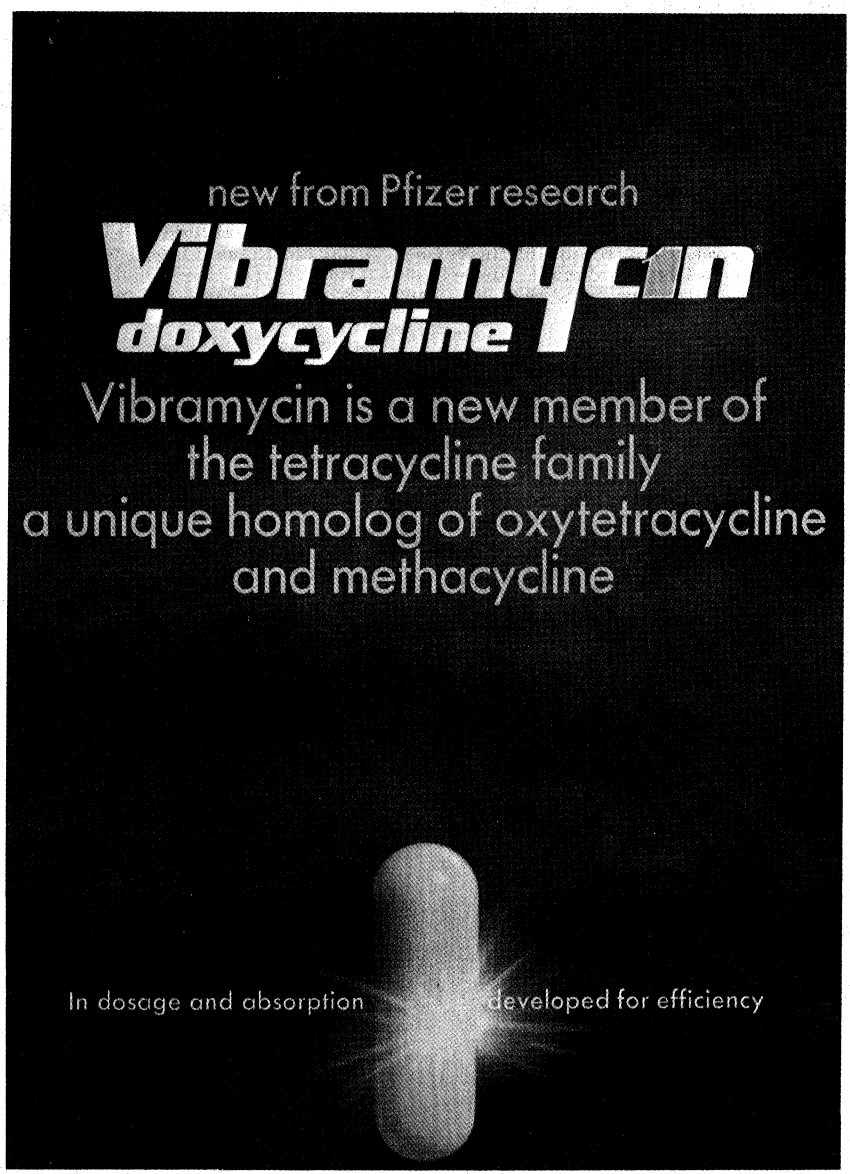
DEAR DR. MCCLEERY: We refer you to your meetings with Mr. Aterno and Dr. Trout on September 5 and September 6, 1967 in regard to Vibramycin.

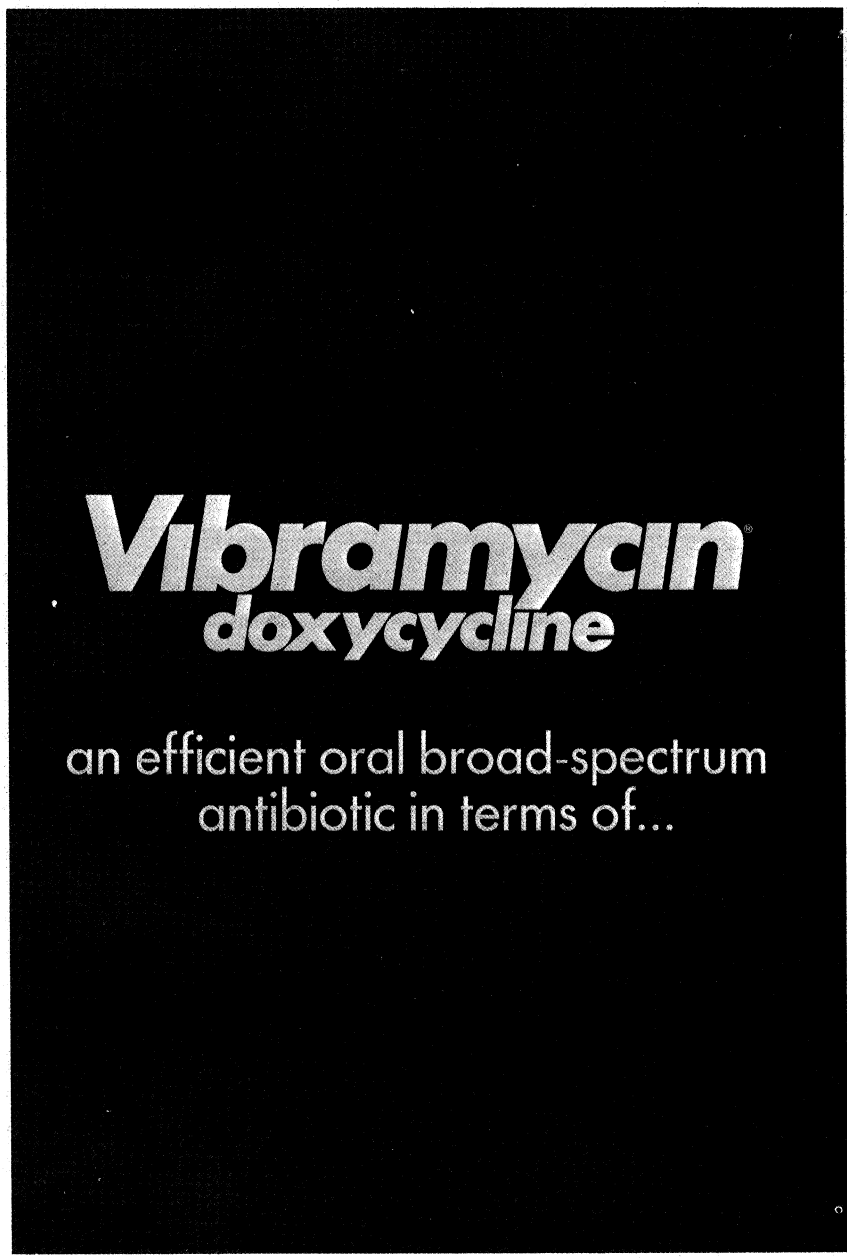
As a result of these meetings Dr. Ley gave us permission to use the existing Vibramycin visual aid and compendium for a period of one month from the date of approval (September 14, 1967) and we were then to replace that visual with the new revised visual aid.

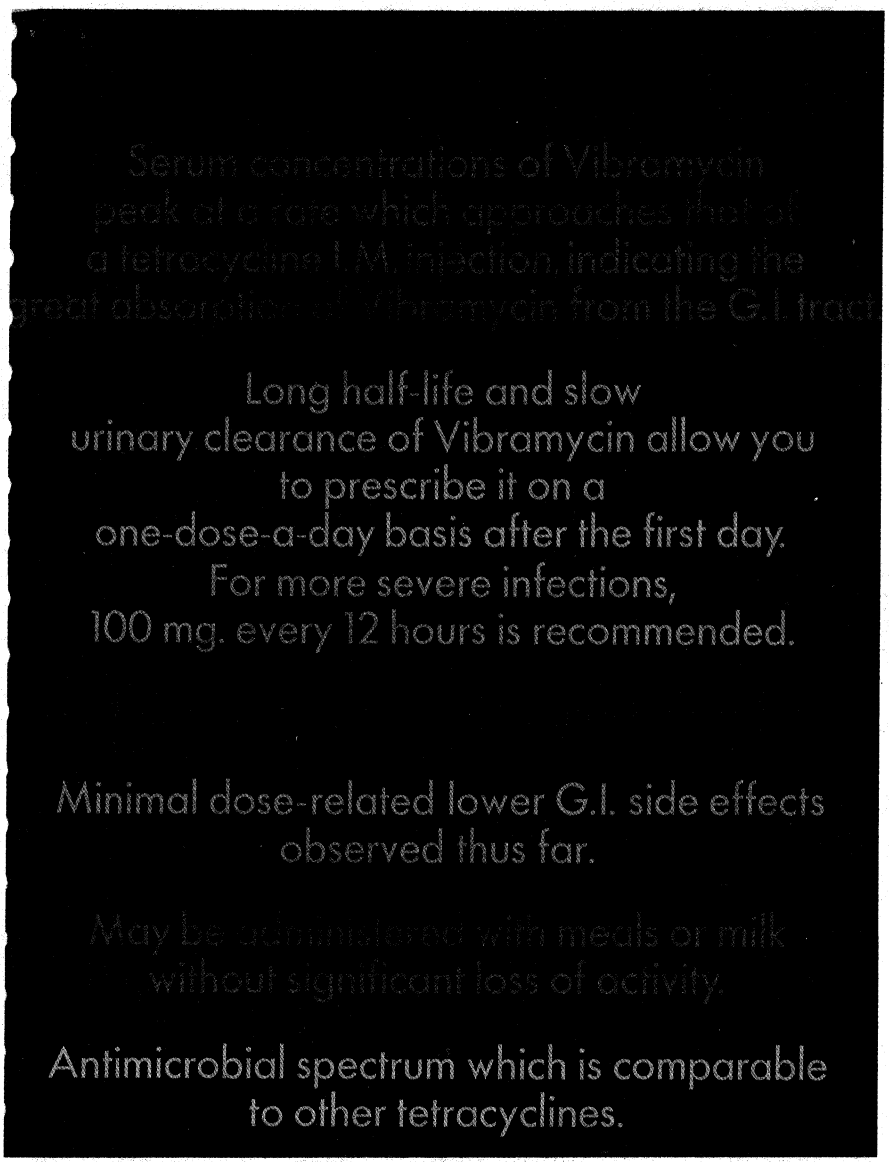
During the coming week of October 9, 1967 the new visual aids will be sent to our sales force. Upon receipt of the revised visual aid the detailman will return his copy to his District Manager and will sign a return sheet. The visual aid, along with the compendium, will then be returned to the company where they will be destroyed.

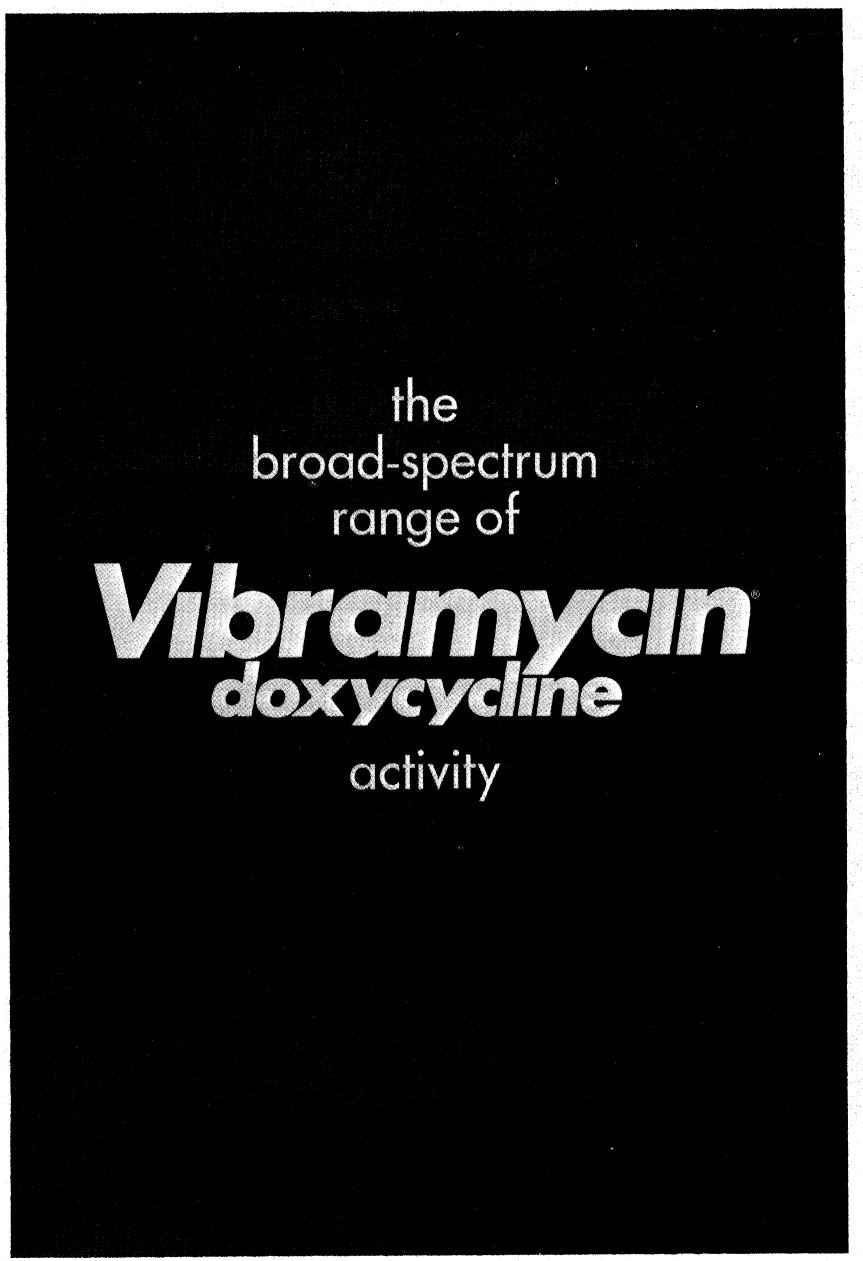
Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.


new from Pfizer research
Vibramycin
doxycycline
Vibramycin is a new member of
the tetracycline family
a unique homolog of oxytetracycline
and methacycline
In dosage and absorption
developed for efficiency


Vibramycin®
doxycycline
an efficient oral broad-spectrum
antibiotic in terms of...


Serum concentrations of Vibramycin
peak at a rate which approaches that of
a tetracycline I.M. injection, indicating the
great absorption of Vibramycin from the G.I. tract
Long half-life and slow
urinary clearance of Vibramycin allow you
to prescribe it on a
one-dose-a-day basis after the first day.
For more severe infections,
100 mg. every 12 hours is recommended.
Minimal dose-related lower G.I. side effects
observed thus far.
May be administered with meals or milk
without significant loss of activity.
Antimicrobial spectrum which is comparable
to other tetracyclines.


the
broad-spectrum
range of
Vibramycin®
doxycycline
activity

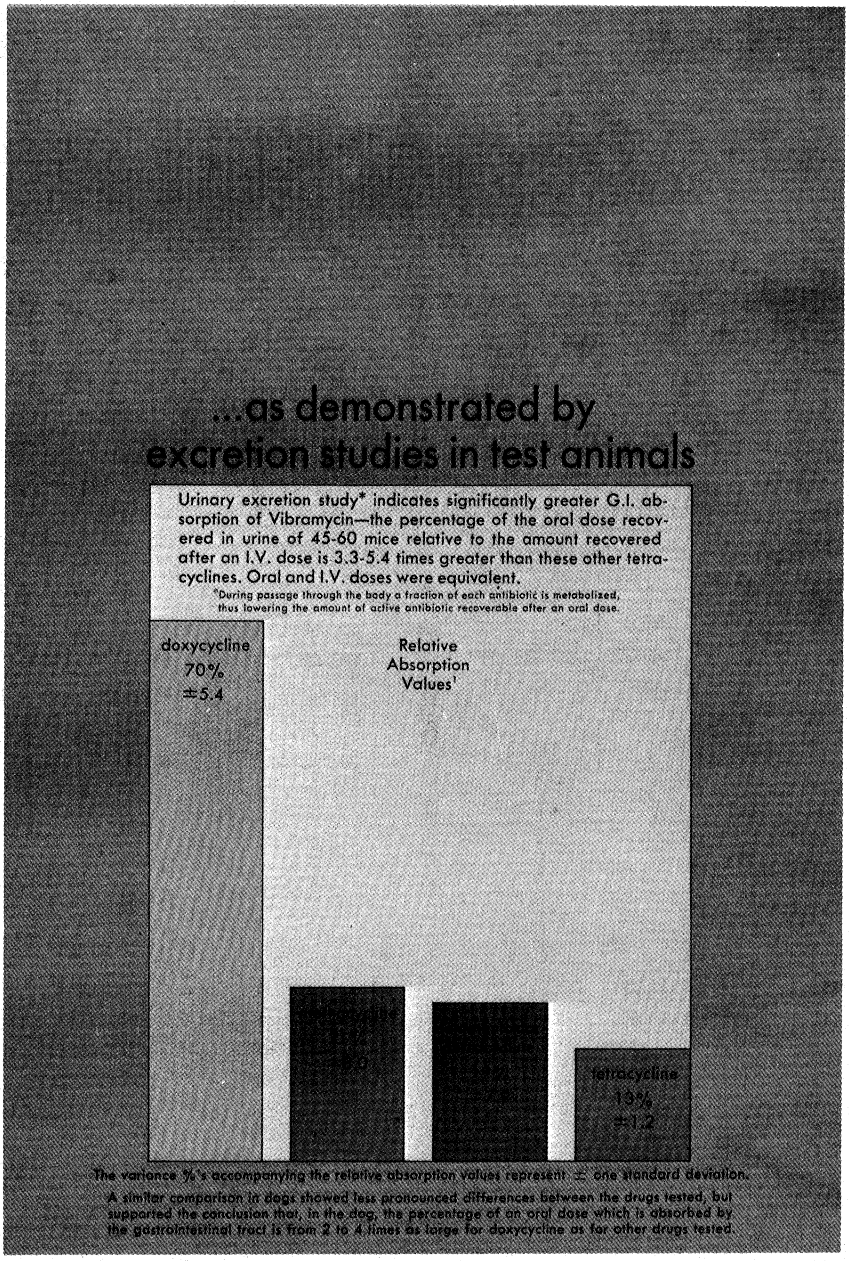
Vibramycin has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.*

Site of Infection	Indications	Pathogens (Susceptible Strains)
Ear, Nose and Throat	Pharyngitis, Tonsillitis, Otitis media, Sinusitis	Pneumococcus, Beta-hemolytic streptococcus, Staphylococcus, H. influenzae
Lower Respiratory Tract	Single-lobe pneumonia, Multilobe pneumonia, Bronchopneumonia, Bronchitis	Pneumococcus, Streptococcus, H. influenzae, Klebsiella pneumoniae
Soft Tissue	Impetigo, Furunculosis, Cellulitis, Abscess, Infected wounds, Paronychia	Staph. aureus, Staph. albus, Streptococcus, E. coli, Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis, Cystitis, Urethritis	Klebsiella-Aerobacter group, E. coli, Enterococcus, Staphylococcus, Streptococcus, Neisseria gonorrhoeae

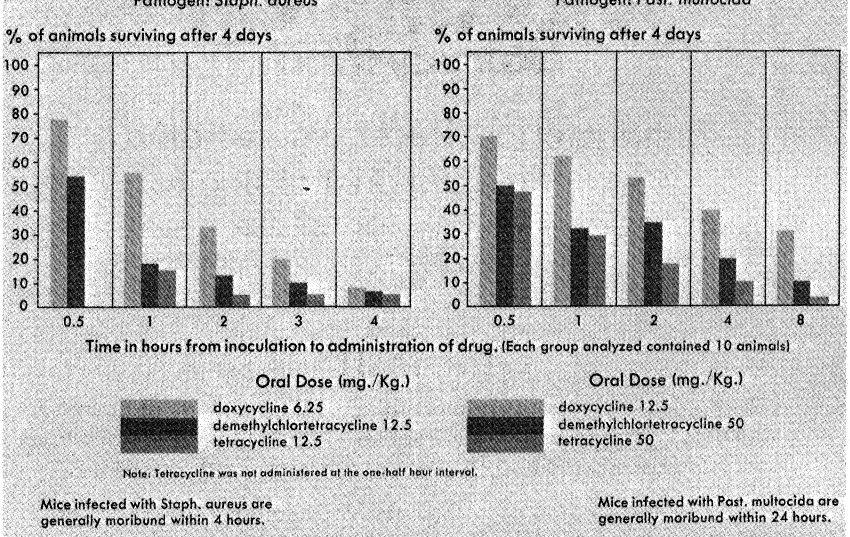
Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms:*

Site of Infection	Indications	Pathogens (Susceptible Strains)	
	Gastrointestinal infections	E. histolytica, Shigella	Salmonella, Pathogenic E. coli

*Because not all strains of the listed pathogens are susceptible, it is recommended that routine culture and susceptibility studies be performed.


...as demonstrated by
excretion studies in test animals
Urinary excretion study* indicates significantly greater G.I. absorption of Vibramycin—the percentage of the oral dose recovered in urine of 45-60 mice relative to the amount recovered after an I.V. dose is 3.3-5.4 times greater than these other tetracyclines. Oral and I.V. doses were equivalent.
*During passage through the body a fraction of each antibiotic is metabolized, thus lowering the amount of active antibiotic recoverable after an oral dose.
Relative Absorption Values¹
doxycycline
70%
±5.4
tetracycline
13%
±1.2
The variance %'s accompanying the relative absorption values represent ± one standard deviation.
A similar comparison in dogs showed less pronounced differences between the drugs tested, but supported the conclusion that, in the dog, the percentage of an oral dose which is absorbed by the gastrointestinal tract is from 2 to 4 times as large for doxycycline as for other drugs tested.

the results:

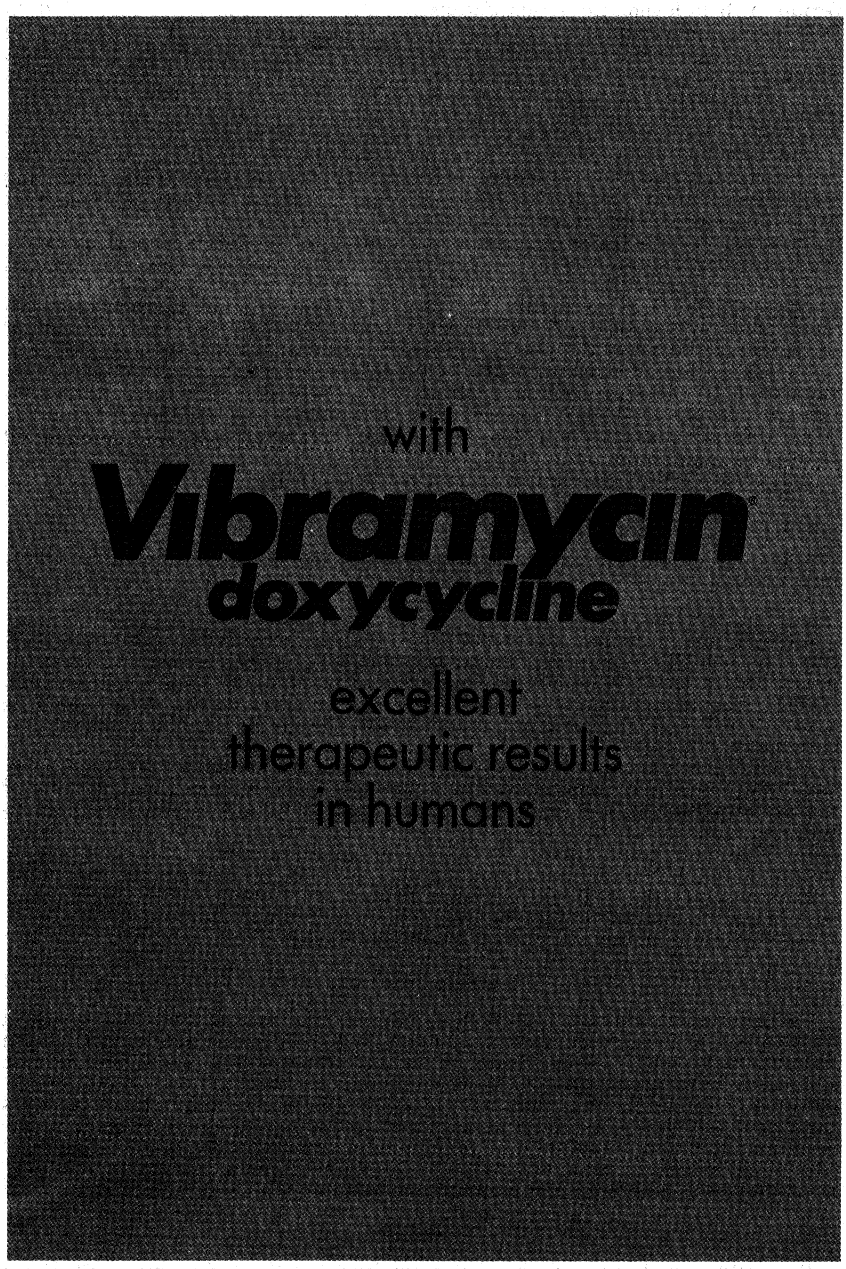


The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

the conclusion:

Even at a fraction of the dosage of other tetracycline antibiotics tested, Vibramycin provided a greater and more persistent chemotherapeutic effect.

The results obtained cannot be directly extrapolated to the clinical situation.


with
Vibramycin
doxycycline
excellent
therapeutic results
in humans

over 90% clinical success rate[3]

Of 1,250 patients treated with Vibramycin® (doxycycline), this analysis of the clinical success rate includes those cases in which the bacteriologic etiology was determined and sensitivity testing indicated organism susceptibility. Sensitivity testing is recognized to be important for the selection of the most appropriate antibiotic for a specific patient's infection.

Diagnosis Group	Clinical Response			Per Cent Success
	Favorable	Poor	Total	
Lower Respiratory Infections	77	6	83	93
Upper Respiratory Infections	123	4	127	97
Soft-Tissue Infections	104	4	108	96
Genitourinary Infections	39	16	55	71
Venereal (Gonococcal) Infections	66	2	68	97
Miscellaneous Infections	12	1	13	92
Totals	421	33	454	

For criteria used in evaluating results of therapy, see end of brochure.

Criteria for evaluating clinical results:

Upper and lower respiratory infections
Soft tissue infections
Miscellaneous infections

Favorable responses:
Includes those designated as "good" or "satisfactory."
Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.
Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses:
Cases in which it was felt that there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses:
Includes those designated as "good" or "satisfactory."

Good responses:
Those in which clinical symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

Satisfactory responses:
Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses:
Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

Vibramycin® (doxycycline)

Product Information

Description: Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from methacycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is α-6-deoxy-5-oxytetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD_{50}) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of Pneumococcus, Streptococcus, Staphylococcus, *H. influenzae*, and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β-hemolytic Streptococcus, Staphylococcus, Pneumococcus, and *H. influenzae*.

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the Klebsiella-Aerobacter group, *E. coli*, Enterococcus, Staphylococcus, Streptococcus, and *Neisseria gonorrhoeae*. Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus*, Streptococcus, *E. coli*, and the Klebsiella-Aerobacter group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of Gonococci, Staphylococci, and *H. influenzae*.

Gastrointestinal Infections: Due to susceptible strains of such organisms as E. histolytica, pathogenic *E. coli*, and species of Shigella and Salmonella.

Miscellaneous: Other infections due to susceptible strains of Bacteroides, Pasteurella, Brucella (in combination with streptomycin), Psittacosis, Listeria, Rickettsia, *Mycoplasma pneumoniae* (Eaton agent, PPLO), *H. pertussis*, *B. anthracis*, *C. welchii*, *N. meningitidis*, spirochetes (Treponema), *Donovania granulomatis*, and prostatitis and trigonitis due to Proteus or Pseudomonas.

Vibramycin (doxycycline) may be useful in the treatment of *acne vulgaris* and *acne conglobata*.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long-term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline: bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor: 2 oz. bottles.

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017

P169X67R1 PRINTED IN U.S.A.

Issued October, 1967

VIBRAMYCIN®

MONOHYDRATE AND HYCLATE (DOXYCYCLINE MONOHYDRATE AND HYCLATE)

Description

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Actions

Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD_{50}) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

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Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

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Pneumonia.—Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of Pneumococcus, Streptococcus, Staphylococcus, *H. Influenzae*, and *Klebsiella pneumoniae.*

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Ophthalmic Infections.—Due to susceptible strains of Gonococci, Staphylococci, and *H. Influenzae.*

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Vibramycin (doxycycline) may be useful in the treatment of *acne vulgaris* and *acne conglobata.*

Contraindications

This drug is contraindicated in individuals who have shown hypersensitivity to it.

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If renal impairment exist, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

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Adverse Reactions

Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not kown at this time.

Dosage

The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 or 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

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Supply

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PFIZER LABORATORIES,
Division of Chas. Pfizer & Co., Inc., New York, N.Y.

(Whereupon, at 11:25 a.m., the hearing adjourned until Thursday, September 19, 1968, at 9:30 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, SEPTEMBER 19, 1968

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

The subcommittee met, pursuant to recess, at 9:45 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Our witness this morning is Dr. Harvey Minchew, Acting Director, Bureau of Medicine, Food and Drug Administration. We appreciate having you here this morning, Dr. Minchew. You may present your statement in any way you see fit.

Did you wish to present some response to the statement made by the company yesterday?

STATEMENT OF DR. B. HARVEY MINCHEW, ET AL.—Resumed

Dr. MINCHEW. Yes, sir; with your permission I would like to do that.

Senator NELSON. Please go ahead.

Dr. MINCHEW. After my testimony yesterday on Vibramycin, Chas. Pfizer & Co., Inc., issued a press release and statement [1] taking exception to it. My testimony was based on the records and my own knowledge of the events in which I participated. We stand on the statement. We have the following comments on the eight points made in Pfizer's press release:

(1) Pfizer said that they were shocked and disappointed at my statement that the original submission for approval of Vibramycin was "inadequate and additional data were required."

This submission was inadequate and the details of the inadequacies were discussed with the company. This is not unusual at this stage of review of any new antibiotic.

(2) Pfizer said that it did not feature labeling claims that emphasize the safety and effectiveness of Vibramycin in comparison with established products. Our statement that they did seek to feature a "broader antibiotic spectrum" refers not only to the quoted paragraph in the Pfizer statement concerning the in vitro activity, which clearly claims

[1] See statement beginning at p. 3647, infra.

81-280 O—68—pt. 9— 8

"greater in vitro activity against a variety of Gram-positive organisms including Staphylococcus aureus * * *" but also the proposal of the company in their original package insert to claim efficacy for infections due to unspecified species of Proteus and Pseudomonas organisms.

(3) My statement regarding the efforts of the company to claim the advantage of not causing teeth discoloration is based on the facts. Labeling submitted but not approved, contained the following statement in conjunction with the description of the in vitro studies on calcium binding: "Less Vibramycin may be deposited in bones or teeth."

(4) My answer to the statement made by Pfizer of their reluctance to refer to thyroid darkening effects in certain animals in the package insert was adequately discussed yesterday.

(5) I have reviewed the series of meetings between January and July of 1967 and the original statement I gave is accurate. The file shows that final concurrence with all of the changes the Bureau believed necessary in the package insert was not obtained until July 31.

It is true, as Pfizer stated, that our meetings to discuss the package insert were conducted on a cordial and mutually respectful basis. We do not imply that it is somehow improper for industry to disagree with FDA on a medical matter.

(6) Pfizer has stated that at the time of their telephone call to Dr. Goddard on July 7, 1967, it was their understanding that "a decision on the generic name was all, to our knowledge, that was holding up the approval of the application." The file shows that as late as June 28, 1967, in a meeting with Pfizer they had not agreed to include the animal pharmacology section of the labeling and that other features of the final approval had not been resolved.

(7) Pfizer point No. 7 is to the effect that the Division of Anti-Infective Drugs approved their visual aid in August, and that Pfizer was justified in printing it on that approval.

Representatives of the company were told that the approval of the Division of Anti-Infective Drugs should only be tentative. They were advised of a recently established policy which required that initial advertising material would be studied elsewhere in the Bureau and formal approval would come from the Office of the Director of the Bureau of Medicine.

We will be glad to supply the committee with the memorandums of our conferences with Pfizer about this visual aid.

Taking into account all of the facts, including the fact that the four-color spread had been printed and that the detail force was en route to training sessions, Dr. Herbert L. Ley, Jr., then Director of the Bureau of Medicine, agreed to permit the use of that visual aid for a period of not more than 4 weeks from the date of the meeting on September 5, 1967. Four weeks was agreed upon because of the prolonged nature of the planned training period and the length of time required to print a new and corrected four-color visual aid. The company promised that it would expedite this.

The company asked that, if near the end of the 4-week period the new version had not been received, some of their detail men might use the old version on condition that they not direct the doctor's attention to the improper copy and not leave the detail aid with the

doctor. This last request was agreed to. Actually, that contingency is not involved here. Pfizer detail men made the misrepresentations on October 25, 1967, at the American Academy of Pediatrics meeting. This was long after the 4-week period agreed to on September 5, 1967. It was after the visual aid had been reproduced with corrections.

(8) Pfizer's contention that the statement concerning the deposition of tetracycline in bones and teeth was inserted at the request of a medical officer I cannot verify in our records. At any rate, the record is clear that this statement was strongly proffered by Pfizer and officially objected to by the Bureau of Medicine.

Senator NELSON. Thank you very much.

(The statement of Chas. Pfizer & Co. follows:)

STATEMENT BY CHAS PFIZER & CO., INC., REGARDING TESTIMONY PRESENTED BY DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION

We regret to say that Dr. Minchew's testimony is marked by serious distortions of fact, by omission of important fact, and in some cases by actual departures from the facts.

We object in the strongest possible terms to the adverse impression that Dr. Minchew's testimony creates. Our work with the FDA in seeking this approval was carried forward with thoroughness, with conscientiousness, and in a cooperative spirit. In fact, we were complimented by FDA on more than one occasion during the course of obtaining approval for Vibramycin for the thoroughness of our submission.

We are presenting herewith some examples of the grave inaccuracies and distortions contained in Dr. Minchew's tetsimony:

1. We were shocked and disappointed at Dr. Minchew's statement that the original submission of our application for approval of Vibramycin was "inadequate and additional data were required." This is not true. These are the facts. Representatives of the various divisions of FDA who reviewed this application were extremely complimentary about its content and organization. At no time did FDA ever tell us that more data were needed to prove the drug to be safe and efficacious. Nor did FDA ever tell us that the data we originally submitted were not an adequate basis for its approval.

Dr. Minchew's next sentence, referring to submission of additional clinical reports, carries the implication that this submission was made in order to fill a need that FDA had advised us existed. Any such implication is totally erroneous. Clinical studies on this drug, as is usual, were continued during the time of the review of the application by FDA, and periodically we submitted to FDA the results of those continuing studies. This is the type of clinical data to which Dr. Minchew refers in his statement.

2. Referring to Pfizer's original proposed package insert, Dr. Minchew commented that we tried to include features that would emphasize its safety and effectiveness in comparison with established products. As one illustration, he stated that we tried to claim "a broader antibiotic spectrum."

This is not so. Our proposed statement on the spectrum of action of Vibramycin was as follows:

"Vibramycin (doxycycline) is a broad spectrum antibiotic and has been shown to be active *in vitro* against both Gram-positive and Gram-negative organisms. It exhibits greater *in vitro* activity against a variety of Gram-positive organisms, including *Staphylococcus aureus* and less activity against some Gram-negative organisms than is seen with other tetracyclines."

This statement did not amount to a claim for a broader spectrum, but merely set forth its relative potency against Gram-negative and Gram-positive organisms. In other words, as we interpreted the scientific data, Vibramycin, as compared with certain other tetracyclines, appeared to have greater activity against a variety of Gram-positive organisms in test tubes, and less activity aaginst some Gram-negative organisms.

3. Dr. Minchew also indicated that in our original package insert proposal we attempted to claim "an advantage in not causing tooth discoloration." This is completely untrue. The following statement in our original proposed package

insert on this subject was approved verbatim by FDA and appears in our currently approved package insert:

"Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long term use of the drug, but has also been known to occur with treatment of short duration."

4. Dr. Minchew did not accurately state the reason for our reluctance to refer to thyroid darkening effects in certain animals in the package insert for Vibramycin. Our position simply was that such effects are observed with virtually all tetracyclines, and this had been known for several years, and yet FDA had not required any reference to this effect in earlier package inserts. We were completely willing to refer to these effects for Vibramycin if FDA required the package insert for the other tetracyclines to be revised to contain a similar reference. We felt somewhat strongly on this point since the degree of darkening observed with Vibramycin was somewhat less than with some of the other tetracyclines. Nevertheless, in the interest of moving the application along, we acquiesced.

5. Dr. Minchew's statement creates the impression that from January of 1967 through sometime in July of that year there was a whole series of meetings between Pfizer and FDA to discuss the content of our package insert, and that we were constantly unwilling to accept suggestions that the FDA representatives made. The facts are that there were only a very few meetings to discuss our proposed package insert, and at these meetings there was an honest exchange of views between our physicians and those of FDA. On some points, FDA conceded to our position and on others we conceded to theirs. We came away from at least two of these meetings with the understanding that agreement had been reached about package insert content only to learn subsequently that FDA officials had reversed themselves, or been reversed by others in FDA and additional changes were required. We felt that meetings with FDA to discuss our package insert were conducted on a cordial and mutually respectful basis. The tone of Dr. Minchew's statement belies this, and goes so far as to imply that it is somehow improper for industry to disagree with FDA on a medical matter.

6. Dr. Minchew did not accurately reflect the telephone conversation to which he referred which took place on July 7 between the representative of Pfizer and Commissioner Goddard concerning the delay in approval of this application. This telephone conversation dealt with one point only—the delay from February through the date of the call in resolving the different views among FDA personnel as to the appropriate generic name to be used for the drug. At that time, a decision on the generic name was all, to our knowledge, that was holding up approval of the application. When Dr. Goddard learned of this, he immediately made a decision as to the generic name for the drug and the final stages of approval proceeded thereafter at the expected rate.

On the subject of delay, however, it is pertinent to note that Dr. Minchew's testimony admits that on February 15, 1967 the review had been completed of the pharmacology, clinical data and chemical controls. It was not until *over six months later* that final approval of the application was granted.

7. Dr. Minchew testified at some length concerning the difficulties connected with approval of our original "visual aid" for Vibramycin, and we must take exception to the accuracy of much of his testimony on this subject.

The fact is that on August 16 we received approval from the Division of Anti-Infective Drugs of the copy for this visual aid. Based on past experience, approval by this Division, was final FDA approval for promotional materials. This approval was given by them with full understanding that it was our intention to print this material immediately. This was not a "tentative" approval of our copy, as Dr. Minchew stated, nor was he correct in stating that "it was pointed out to us that other approvals would be required."

Therefore, it came as a complete surprise to us to learn after we had printed the visual aid material on the basis of the approval received by the Division of Anti-Infective Drugs that a further review of the copy was to be made by the Bureau of Medicine.

We later learned that a change in procedure, to require such an additional review, had just been instituted by FDA without any knowledge of this change being transmitted to us.

We immediately telephoned Washington to ask for a meeting, explaining that we had in good faith printed our visual aid materials on the basis of the approval already received. And such a meeting was held.

Under these circumstances, we are at a loss to explain Dr. Minchew's reference that at this meeting we "unexpectedly" informed FDA that we had already printed the visual aid.

In view of the actual facts as stated above, we take strong exception to the statements by Dr. Minchew, which suggest that we printed the visual aid in order to create a "subtle kind of pressure to approve it, or at least to hold the required changes to an absolute minimum."

We are astonished by the further statements by Dr. Minchew that the FDA permitted us to use the visual aid that we had printed merely at the training sessions for our detail men, and that we had assured him that the revisions that FDA suggested would be made before that printed material could be used for detailing. The fact is that FDA specifically permitted us to utilize this printed material in detailing for a period of 30 days.

Dr. Ley himself acknowledged that the confusion about the earlier "approval" by the Division of Anti-Infective Drugs was largely contributed to by the Food and Drug Administration itself, and for the reason he permitted this use, though he required that certain changes be made in the detail material to be used after 30 days.

8. There is one comment which we feel compelled to make about Dr. Minchew's listing of two "major corrections" that Pfizer was required to make in the Vibramycin visual aid. One of those corrections related to the question of whether less Vibramycin will be deposited in the teeth and bones of children, than with other tetracyclines. That claim was placed in our visual aid at the suggestion of a physician in FDA's Bureau of Anti-Infective Drugs.

Senator NELSON. You may proceed and present your statement.

Dr. MINCHEW. Mr. Chairman, I am glad to respond to your request to discuss with your committee the background of Dynapen, especially the activities of the sponsor in advertising and promoting this antibiotic to physicians.

Dynapen is the trade name given to dicloxacillin by Bristol Laboratories, Syracuse, N.Y. Dicloxacillin is the newest member of the class of semisynthetic penicillin. Many of these penicillins have the property of being resistant to destruction by penicillinase, an enzyme produced by several bacteria, including some strains of staphylococci, which inactivate the original penicillin, penicillin G, and other similar penicillins. Thus, they are clinically useful in treating staphylococcus infections that would not respond to regular penicillin therapy. There are several penicillinase-resistant penicillins on the market, each with slightly different properties: methicillin, nafcillin, oxacillin, cloxacillin, and the drug under consideration, dicloxacillin.

Senator NELSON. You say, "Many of these penicillins have the property of being resistant to destruction by penicillinase." Is penicillinase the drug that is used in those cases where there is a dramatic reaction, allergic reaction to the penicillin?

Dr. MINCHEW. There is a marketed product of penicillinase, which is used on the grounds that it neutralizes the penicillin.

Senator NELSON. In this, as I recall, one of the problems with penicillin in the beginning, and I think it still is, that some people have a dramatic reaction to it and penicillinase was developed as a neutralizer of the penicillin itself; is that correct?

Dr. MINCHEW. It was not developed for that purpose. The penicillinase itself is actually an enzyme produced by the bacteria, so that it was not a synthetically developed chemical. It is an enzyme produced by the bacteria.

Senator NELSON. But is it used for the purpose of neutralizing allergic effects?

Dr. MINCHEW. Yes, sir.

Senator NELSON. And the semisynthetic ones do not react to the penicillinase?

Dr. MINCHEW. Well, the semisynthetic ones resist destruction by penicillinase. When the penicillinase acts on the penicillin, it breaks a particular bond in the penicillin molecule called the beta-lactam ring, and in doing so renders the penicillin inactive against the bacteria.

Senator NELSON. Does that mean that if a patient has an allergic, a seriously allergic reaction to some of the semisynthetics, that there is no neutralizer then available on the market?

Dr. MINCHEW. Penicillinase would not be an effective neutralizer.

Senator NELSON. Is there any other?

Dr. MINCHEW. Not in this sense, no, sir; not in this enzymatic sense. There are other drugs for the treatment of reaction to allergy but not penicillinase.

Senator NELSON. Are they effective drugs?

Dr. MINCHEW. Yes, sir, and also they would be in an emergency situation even with regular penicillin more effective than penicillinase in neutralizing the allergic reaction.

Senator NELSON. I see.

Dr. MINCHEW. Dicloxacillin was developed in the Beecham Research Laboratories, in England, and Bristol Laboratories' application form 5 to market the antibiotic in the United States was submitted to the Food and Drug Administration on November 10, 1965. Bristol's notice of claimed investigational exemption for a new drug had been submitted April 23, 1964. (Two other U.S. firms, Ayerst and Wyeth, also submitted NDA's for dicloxacillin to the FDA at approximately the same time Bristol did.)

It has been longstanding FDA position that all penicillinase-resistant penicillins should be primarily reserved for the treatment of infections caused by penicillinase-producing staphylococci, or for the initiation of therapy when there is strong reason to believe that this type of staphylococccus is responsible. The basis for this is that routine use of the semisynthetic penicillins carries the possibility of development of resistance of staphylococci to these penicillinase-resistant penicillins and destroying their effectiveness in treating penicillin-resistant staph infections. These are the strains of staphylococci that had been responsible for the serious outbreaks of so-called "hospital staph" epidemics throughout the country in the 1950's. It was the development by Bristol, in 1960, of methicillin, the first member of this family, that largely modified this grave situation.

FDA concern on this matter has been clear since early 1963. In May of that year Dr. Charles Lewis, then Chief of the Bureau of Medicine's Division of Antibiotic Drugs, wrote to Bristol Laboratories, concerning the labeling of their semisynthetic penicillin, Prostaphlin (oxacillin):

"At some appropriate place in bold type, you should point out that the administration of Prostaphlin (sodium oxacillin) for infections which will respond to penicillin G is inadvisable because uncritical use of the drug may increase the possible development of resistant organisms."

On July 12, 1966, FDA wrote Bristol advising that, in order to bring proposed labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face at the beginning of the "Indications" section. "Hypen"—which was their proposed name at that time "is particularly suitable against infections due to staphylococci resistant to penicillin G (or phenethicillin)," and that, in addition, the following should appear in the same section: "If it is determined that the infection is not due to a penicillin G-resistant staphylococcus, a change to penicillin G or phenethicillin may be considered." This statement referring to changing or "switching" antibiotics I will refer to hereafter as the "switch" statement.

On July 13, 1966, Bristol replied, in part: "We still feel that * * * such a statement (the switch statement) is not justified by the facts. We will continue to accumulate data and will bring this to your attention as more experience becomes available so that we may review it again." However, the labeling accompanying this letter incorporated the FDA recommendations.

On July 29, 1966, Bristol submitted revised draft labeling incorporating three minor changes requested by an FDA telephone conversation. Bristol also changed the trade name of the drug to "Dynapen."

About that same time in 1966, Bristol was promoting its semisynthetic Tegopen (sodium cloxacillin monohydrate) with an advertising theme that is was an "everyday penicillin," and depicting its use in routine office practice. In October, we publicly criticized this ad campaign as offering the drug for conditions for which it had not been approved. Bristol representatives visited with us, contending that the drug was indeed suitable for everyday use, and they were told that before such a range of usefulness could be approved the company would have to provide the medical justification for labeling changes to permit it.

On November 25, 1966, Bristol submitted proposed revised labeling for their already marketed antibiotic, Tegopen (sodium cloxacillin monohydrate). In this, they had deleted the statement advising that therapy be switched to penicillin G in the event that bacteriological studies show the infecting organism not to be a penicillinase-producing staphylococcus. They made it clear that they intended this change also to apply to dicloxacillin. This submission was followed in January 1967 by a marketing report for a number of penicillins, a report intended to support Bristol's contentions that the incidence of resistant staphylococci had not risen despite widespread use of the semisynthetics.

In an attempt to resolve the labeling of dicloxacillin, the FDA, more than a year ago, sent a questionnaire to 11 recognized experts in the field of microbiology and antimicrobial therapy. Among the questions asked, two dealt directly with the problem of so-called "restrictive" use.

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by Gram-positive cocci susceptible to their actions?" All 11 experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patent is showing excellent clinical response but the cultures now show the causative or-

ganism to be a Beta-hemolytic streptococcus or pneumococcus, would you change chemotherapy to penicillin G or V?" Eight answered, "Yes." Two answered, "No." One said "Probably would not change."

The results of this survey were made available to the company, and on May 31, 1967, another conference took place, at which Bristol reiterated the desire to recommend dicloxacillin for infections due to all sensitive Gram-positive cocci. They argued, among other things, that the early fear that staphylococci would develop widespread resistance to semisynthetic penicillins had not been borne out by many years usage of methicillin, another semisynthetic. FDA did not agree, and on June 14, 1967, wrote Bristol stating that the package insert should include a statement to the effect that "if it is determined that the infection is not due to a penicillin G-resistant staphylococcus, a change to penicillin G or phenethicillin may be considered." On June 19, 1967, a conference was held with Bristol to discuss again the "switch" statement; our position and that of Bristol remained different.

Subsequently, Bristol polled 16 physicians using a different set of questions than the FDA had formulated. Bristol concluded that the written responses tended to support the Bristol position, namely, that a penicillinase-resistant penicillin should not be reserved for the treatment of infections due to penicillinase-producing staphylococci because the drug had been shown to be highly effective both bacteriologically and clinically in infections due to other infections, such as streptococci and pneumococci, and resistance to it was more a fear than an actuality. Bristol submitted a tabulated summary of the results of their poll on July 18, 1967.

Mr. GORDON. Dr. Minchew, may I interrupt at this point? What proof is there that the use of a synthetic penicillin carries the possibility of development of resistant staphylococci to these penicillins and destroying their effectiveness in destroying infections?

Dr. MINCHEW. We come to some of this later in the statement. We will certainly discuss it in as much detail as you want.

Mr. GORDON. All right.

Dr. MINCHEW. On August 31, 1967, the Bureau of Medicine asked the FDA Medical Advisory Board to consider this problem and give their recommendations. The Board was presented with the Bureau of Medicine position, and the expert opinions as expressed in answers to all the questions in the FDA and Bristol questionnaires. After lengthy discussion, the view was expressed that the approved prescribing information for these semisynthetic penicillins should presently continue to limit indications to permit observation for aonther year or two to see whether staphylococcal resistance to these agents does become a significant problem. With this concern in mind the Board voted to adopt the recommendation:

That the labeling for dicloxacillin contain three general statements:

1. When the infecting organism is susceptable to penicillin G, the physician is advised to use penicillin G, V, or phenethicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

2. The principal indication is in treating infections due to penicillinase-producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcic infection.

3. This product is also effective in treating infections due to streptococci, pneumococci, and penicillin-sensitive staphylococci.

These recommendations were implemented by the Bureau of Medicine and used as the basis for developing the final labeling for all three dicloxacillin products manufactured by Wyeth, Ayerst, and Bristol.

At a September 12 conference, a statement seemingly agreeable to both Bristol and FDA was composed, and on September 19, Bristol submitted proposed package inserts. However, under indications two additional paragraphs were added by the company which pertained to the development of resistant strains. On October 19, 1967, FDA wrote Bristol that approval of these changes in the package inserts could not be given.

Further telephone conversations took place in November, December, and January; and on February 23, 1968, a conference was held between Bristol and FDA at which Bristol again presented its position on resistant staphylococci. The company presented additional data in which it was demonstrated that among Bristol's employees, exposure to semisynthetic penicillins had not been associated with any nasal carriage of methicillin-resistant staphylococci aureus. It was pointed out that the data did not seem pertinent to the past major issues. Further, they were informed that the other two producers of dicloxacillin had now submitted labeling conforming to all FDA requests, and that these would be acted upon.

On February 26, 1968, Bristol submitted revised labeling for dicloxacillin which conformed to the wording requested by FDA. They expressed disagreement with the switch statement wording, but agreed to accept it. They submitted corrected package inserts on March 5, 1968.

On March 8, 1968, Dr. Ley, the then Director of the Bureau of Medicine, was notified that the Division of Anti-Infective Drugs recommended approval of the application of Bristol for sodium dicloxacillin, and that the labeling submitted was acceptable. (Similar approvals were recommended for the sodium dicloxacillin applications of Ayerst and Wyeth on that date.)

However, the company's activity took a new direction. About a month later, on April 9, 1968, the Surgeon General of the Public Health Service, Dr. William H. Stewart, acting for Dr. Philip Lee, Assistant Secretary of Health, Education, and Welfare, received a position paper critical of our actions from Mr. Thomas Corcoran, an attorney for Bristol.

We were asked to comment on that position paper, a copy of which is enclosed for the record—exhibit A.

Senator NELSON. It will be printed in the record.

(The document referred to follows:)

EXHIBIT A

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, naficillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.

Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling. It is understood, however, that it is based on the possibility that some time in the future, there might appear in the environment organisms resistant to semi-synthetic penicillins if they are widely used now. Thus, semi-synthetic penicillins should be reserved for future use by implementing the reserve drug theory through labeling.

However, other antibiotics which have been marketed in the last few years have labeling which omits the elements of the reserve drug theory even though they are indicated also for use in the treatment of infections caused by pneumococci, streptococci and both resistant and non-resistant staphylococci. Such drugs include gentamycin, cephalothin, sephaloridine, methacycline, doxycyline and lincomycin. FDA approval of the omission is peculiar in view of the fact that resistant staphylococci strains have previously appeared shortly after market introduction of similar classes of antibiotics including many of the tetracyclines. Most recently, resistant staphylococci strains have appeared after lincomycin was marketed.

By comparison, although there are rare staphylococci in nature resistant to these penicillins, no significant increase in pathogenic strains which are resistant to the semi-synthetic penicillins have appeared even though methicillin has been in use over eight (8) years and oxacillin for over six (6) years. In contrast, strains resistant to penicillin and penicillin G appeared and increased shortly after those drugs were introduced. This omission, particularly with respect to the labeling for cephalothin and cephaloridine, is indefensible since these drugs are primarily used in hospitals where the problem of resistant infections developing is the most serious.

There are a number of explanations based on experience as to the reasons for the development of strains resistant to some antibiotics and not others. One turns on the distinction between bacteriostatic antibiotics (where resistant strains have usually developed) and bactericidal antibiotics (where resistant strains have not usually developed). It should be noted that such semi-synthetic penicillins as dicloxacillin are bactericidal rather than bacteriostatic, while many of the antibiotics not subject to the reserve drug theory are bacteriostatic.

These random applications of the FDA's policy become even less defensible when it is understood that the failure to apply the theory to the labeling of non-semi-synthetic-penicillin antibiotics would have a patient allergic to penicillin defenseless against some future epidemic of resistant staphylococci infection.

The scientific underpinnings of the reserve drug theory are extremely questionable. But unquestionably, its application has been discriminatory, arbitrary and scientifically unsound. Most recently, by applying the reserve drug theory to dicloxacillin, the FDA is in effect applying the test of relative efficacy in reverse despite the abundant legislative history that this factor cannot be considered by the FDA in approving new drugs. The FDA has refused to approve labeling allowing the marketing of dicloxacillin for streptococci, pneumococci and sensitive staphylococci because it has been shown to be better than penicillin G and penicillin V in the treatment of bacterial infections in that it is effective against penicillin G-resistant staphylococci.

It is urged, therefore, that the FDA either immediately discard the theory by deleting its elements from the labeling for semi-synthetic penicillinase-resistant penicillins or apply it even-handedly by requiring it in the labeling for all antibiotics which are indicated for use in the treatment of infections caused by pneumococci, streptococci and staphylococci. After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformally imposed or discarded.

MARCH 28, 1968.

Dr. MINCHEW. Our comments on this position paper are as follows, and I will be quoting for a few moments and will notify you at the end of the quote:

It is true, as Mr. Corcoran affirms, that the labeling advises the physician to use, or to change to, penicillin G when sensitivity studies indicate the pathogen is susceptible to it. It is not true, as Mr. Corcoran states, that "Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling."

The FDA did disagree with the desire of Bristol Laboratories, unique to it amongst the three companies involved, to insert into their package labeling a very extensive and discursive addition to the Medical Advisory Board's

in one sense (not changed in the nature of the agreement that we reached with the companies before they went on the market). We came to feel that it might well need an "Important Note," of the kind that you are suggesting, to offer more detailed information as to what experience had occurred around the world, and why it was very important for physicians to consider the recommendations in the indications section.

So, in effect, I think we are delving, as nearly as we can see, with the problem that you are suggesting. What the response will be to this tighter and more informative labeling when it is applied to the whole class of products, of which dicloxacillin is a member, would be something that would have to be observed in somewhat the way as the Chloromycetin problem was handled.

We all believe, after considering the views of the experts that we consulted and that the company consulted, and of our medical advisory board, that this labeling is consistent with good medicine, and as much help to physicians as we felt we could——

Senator NELSON. Have you sent communications with good documentary evidence and so forth to all the medical journals in the country asking them to editorialize on this matter?

Dr. MCCLEERY. No, sir.

Senator NELSON. Don't you think, if it is an important matter of public health and the practice of medicine, that you ought to use all the outlets available?

Dr. MCCLEERY. Yes, sir. There already have been editorials in this country. Those editorials have appeared in such journals as the New England Journal of Medicine in 1967. These opinions of experts, both in editorials and in articles, formed a part of the basis for the stand that we took in reference to the company's request. They are available. Those opinions have been given broadly to the medical profession, and I am sure, if the need arises, that we would further consider the suggestions you make.

Senator NELSON. You have the medical schools and a whole series of outlets. It just seems to me that this is an important matter of public health, that the FDA ought to be moving heaven and earth to be sure that the education is gotten out to the profession and to be sure that the labeling is really strong enough and tough enough, so that it makes the point clear.

I understand why the companies don't like it. They won't sell as much. But the public health certainly has to come first, and there will be a continuous push by the companies to expand the use of their products. So in my judgment they will end up winning that battle, just as they did with chloramphenicol. That one went over a period of 15 or 16 years, from 1952 until right up through now, and they won the battle hands down.

Dr. MCCLEERY. Well, it is certainly a logical possibility that it may occur again. We fervently hope it won't.

I might also say that one of the exhibits you will see is the remedial letter that went to 280,000-some physicians on the Dynapen problem. There was also a corrective journal ad, which we come to later, both of which were strong messages sent out by the company, in conjunction with us, that make all these points at this time. It may not be effective but we hope that it will. We will have to try to follow and see.

Senator NELSON. Well, I would understand why the companies would resist it, but it would seem to me that if it is important, there ought to be a special box in the package labeling and any place else where they advertise, and on the labeling. It seems to me you ought to single out this particular reason.

I can understand the doctor reading rapidly, the drug is good for all kinds of things, and there is a little cautionary statement to substitute other drugs when they are effective, but I don't expect it will be followed. It would seem to me you could make much tougher labeling both as to the package insert and as to the advertising in the journals, if you are going to make it work.

Now there is a big hullabaloo by the industry that the FDA is sticking its nose in our business, but, you know, they would be happy with no regulations at all. They would be happy to sell 10 times as much chloramphenicol or any of the rest of the stuff. That is their business, although I have been a little worried about their public conscience, but I am not going to trust my health and the health of the Nation to their public conscience when we have so many instances where they didn't have much of a conscience.

I think the FDA has just got to be tougher on this stuff.

Dr. MCCLEERY. May I just say one more word, Senator Nelson. We share your concern, although we may not always supply the response that you might wish us to. In this instance, the class revision of labeling is already underway, in order, hopefully, to do just what you are asking; that is, the inclusion of an "Important Note" to enlarge the understanding of the physician that uses the product, so that he will be informed in the ways which I think you are suggesting would be valuable.

Senator NELSON. I hope you are successful.

Dr. MCCLEERY. Thank you.

Senator NELSON. Please go ahead.

Dr. MINCHEW (reading): "On March 27, 1968, the Director of the Bureau of Medicine telephoned the vice president and medical director (Dr. Peltier) of Bristol Laboratories to explain again the basis for FDA's so-called 'restrictive' labeling for dicloxacillin. Dr. Peltier alleged that the labeling was discriminatory against this particular product.

"Dr. Ley informed him that this was so only because it was the first reflection of a new policy, and promised him that the labeling of other semisynthetic penicillins, as well as that of other appropriate antimicrobial agents, was already under study for comparable revision.

"Dr. Ley ended his telephone memo with this note, '* * * it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semisynthetic penicillins.' It is, therefore, worthy of serious note that on March 28, 1968, Bristol turned from the scientific to the legal-administrative approach, developed the copy of the argument of that date, retained attorney Thomas Corcoran to present this to the Office of the Secretary of April 9, 1968.

"Bristol, near the end of its March 28, 1968 position paper, suggests that the FDA apply the so-called 'reserve drug theory' evenhandedly or immediately discard it—this in spite of the assurance, on the day prior, of the Bureau Director that this was underway. Even more

improperly, they end their paper with this misleading suggestion: 'After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformly imposed or discarded.'

"It is misleading because it implies that the FDA reached its position in the absence of relying, in practical fact, on such an 'advisory panel,' which was known to Bristol not to be the case. It is misleading, also, because it was known to Bristol that the FDA, as part of its decision-making process in reaching the current position, already planned to reconvene the question after an appropriate interval allowed the collection of further evidence as to the potential danger represented by labeling these agents so that they might become in legal fact 'Everyday penicillins'."

Mr. Chairman, I thought that the background I have just related would assist you and your committee in evaluating what is to follow.

On May 7, 1968, Dr. Ley issued a letter to Bristol Laboratories advising the firm that the FDA had concluded that the drug was safe and effective for use as recommended in the labeling. A copy of the approved labeling of Dynapen is included for the record—exhibit B.

Senator NELSON. It will be printed in the record.

(The document referred to follows:)

EXHIBIT B—BRISTOL

DYNAPEN®—SODIUM DICLOXACILLIN MONOHYDRATE, CAPSULES—125 mg. and 250 mg.

DESCRIPTION

Dynapen (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2, 6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

PHARMACOLOGY

Dynapen (sodium diloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.[1,2,3] as measured at the two-hour level.

ACTIONS—(MICROBIOLOGY)

Dynapen (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s of Dynapen (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.15
Diplococcus pneumonial	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

INDICATIONS

The principal indications for Dynapen (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrated the drug is also effective in the dosages recommended in the treatment of repiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATION

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving Dynapen (sodium dicloxacillin monohydrate). Pruritus, uricaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilla, with or without overt allergic manisfestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q.6b.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q.6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q.6h or higher.
Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day or higher in divided doses q.6h.
Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.
Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.
N.B.: Infections caused by group A Beta-Hemolytic Streptococci should be treated for at least 10 days to help prevent the occurrence of acute Rheumatic fever or acute Glomerulonephritis.

SUPPLY

Dynapen (sodium dicloxacillin monohydrate) Capsules:
List 78923—125 mg./capsule, bottles of 24.
List 78925—125 mg./capsule, bottles of 100.
List 78933—250 mg./capsule, bottles of 24.
List 78935—250 mg./capsule, bottles of 100.
Also available:
List 78566—Dynapen sodium dicloxacillin monohydrate). For Oral Suspension, 62.5 mg./5 ml., 80-ml. bottle.

REFERENCES

1. Data on file at Bristol Laboratories.
2. Bennett, J. V. Gravenkemper, C. F. Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262.
3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139-145, 1965.

BRISTOL

DYNAPEN®—SODIUM DICLOXACILLIN MONOHYDRATE, POWDER FOR ORAL SUSPENSION

DESCRIPTION

Dynapen (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl Penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

PHARMACOLOGY

Dynapen (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of pencillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.[1 2 3] as measured at the two-hour level.

ACTIONS—(MICROBIOLOGY)

Dynapen (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

NOTE.—Numbered footnotes at end of article, p. 3663.

The average Minimal Inhibitory Concentration (M.I.C.'s) of Dynapen (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A bete-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

INDICATIONS

The principal indications for Dynapen (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinanase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteriods, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving Dynapen (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of heptatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q.6h.
Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in equally-divided doses q.6h.
For more severe infections such as those of the lower respiratory tract or disseminated infections:
Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q.6h. or higher.
Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day or higher in equally-divided doses q.6h.
Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.
Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.
N.B.: Infections caused by group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

DIRECTIONS FOR DISPENSING

Prepare suspension at the time of dispensing. Add a total of 45 ml. water to the bottle. For ease in preparation, first shake the bottle to loosen powder and then add the water in two portions—shake well after each addition. This will provide 80 ml. of suspension. Each 5 ml. teaspoonful) will contain Dynapen (sodium dicloxacillin monohydrate) equivalent to 62.5 mg. of dicloxacillin. The reconstituted suspension is stable for 14 days under refrigeration.

SUPPLY

List 78566—Dynapen (sodium dicloxacillin monohydrate) For Oral Suspension, 62.5 mg./5 ml., 80-ml. bottle.
Also Available:
DYNAPEN (sodium dicloxacillin monohydrate) Capsules
List 78923—125 mg./capsule, bottles of 24.
List 78925—125 mg./capsule, bottles of 100.
List 78933—250 mg./capsule, bottles of 24.
List 78935—250 mg./capsule, bottles of 100.

REFERENCES

1. Data on file at Bristol Laboratories.
2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Gloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257–262.
3. Naumann, P. and Kempf. E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139–145, 1965.

Dr. MINCHEW. Ten days later, on May 17, 1968, an airmail letter, signed by Bristol's vice president and medical director, was sent to practicing physicians throughout the United States. This letter announced that Dynapen would be available within a week and that it "is a new specific useful in a broad range of skin and soft tissue infections." The airmail envelope also emphasized "A New High Potency Penicillin Specific for Skin and Soft Tissue Infections." Copies of the letter and envelope are included for the record—exhibits C and D.

Senator NELSON. They will be printed in the record.

(The information referred to follows:)

EXHIBIT C

BRISTOL LABORATORIES,
Syracuse, N.Y.

Re New high potency penicillin, specific for skin and soft tissue infections.

DEAR DOCTOR: Within the next week, a new high potency penicillin—sodium dicloxacillin monohydrate—will be available for use in your practice. Dynapen® (as the product is called) is a new specific useful in a broad range of skin and soft tissue infections. Its outstanding bactericidal action, its excellent oral absorption (superior to all other penicillins), and its low incidence of side effects offer a persuasive rationale for prescribing Dynapen in infections of the skin and underlying tissue where resistant staph are so often known or suspected. For example, furunculosis, carbuncles, impetigo, cellulitis, pyoderma, abscess, pustular acne, ecthyma, infected skin ulcer, lymphangitis and lymphadenitis; in postoperative infections; and in infected wounds, burns and lacerations—caused by these organisms—all are exceptionally responsive to treatment with Dynapen.

A number of facts account for the superiority of Dynapen. First of all, Dynapen is bactericidal—killing sensitive pathogens outright, rather than merely inhibiting their growth. Resistance has not developed during therapy. Yet, as you know, therapy with bacteriostatic agents such as the tetracyclines and erythromycins is frequently complicated by the development of resistance.

Not only is Dynapen bactericidal but it is so well absorbed an oral dose of 125 mg. provides averages blood levels far in excess of the concentrations necessary to kill susceptible organisms *in vitro*. The exceptionally high blood levels attained with Dynapen on oral administration make this new agent *superior in absorption to all other penicillins*. Oral doses of 125 mg. yield peak blood levels 5 times higher than 250 mg. (400,000 units) of penicillin G 2 to 4 times higher than 250 mg. of potassium penicillin V. In fact, this penicillin is so well absorbed that blood levels achieved are equal whether the drug is administered orally or intramuscularly.

During more than four years of clinical trails, Dynapen has been evaluated in thousands of patients. For example, it was prescribed at various dosage levels in the treatment of 589 patients with a variety of pathogenic staphylococcal infections. In 204 cases of sensitive staph infections, 99% were cured or improved. In 385 cases of penicillin G-resistant staph infections, 96% were cured or improved. Results obtained at the recommended dose of 125 mg. q. 6 h. in adults and 12.5 mg./kg./day in children were excellent; doubling this dose did not increase clinical effectiveness in such infections.

On the basis of reports to date, side effects with Dynapen (sodium dicloxacillin monohydrate) are exceptionally rare—approximately 1% in patients receiving the recommended dose for mild to moderate infections. The evidence to date clearly suports the contention that the lower dosage does mean a lower incidence of side effects. Of course, as with any penicillin, the possibility of allergic reactions must always be considered.

With all of these advantages, Dynapen is also comparable in cost to other antibiotics, and incidentally, it costs significantly less than most of the "cyclines" and "mycins."

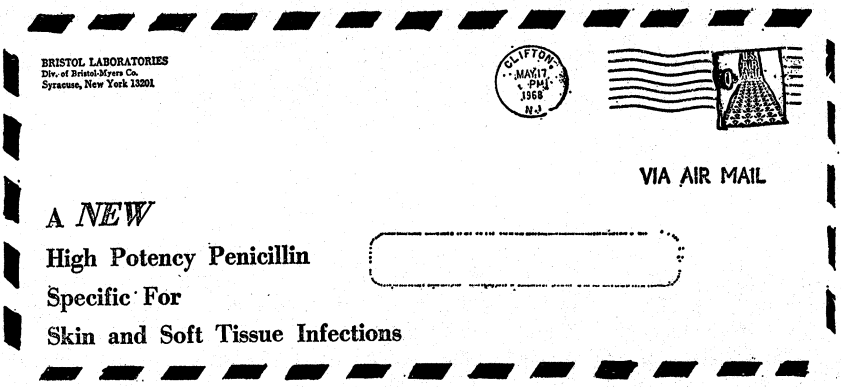
In sum: bactericidal action, the highest blood levels of any oral penicillin, no direct toxicity, an excellent clinical record, a notable lack of side effects, and patient economy, are truly decisive reasons for considering Dynapen whenever you treat resistant staphylococci skin, soft tissue, postoperative and wound infections.

Please see enclosed Official Package Circulars which provide the necessary prescribing information. However, to get a real feel for the drug, may we suggest you return the Business Reply Card for clinical trial supply.

Sincerely yours,

H. C. PELTIER, M. D.,
Vice President, Medical Director.

EXHIBIT D



Dr. MINCHEW. When we received a copy of the Dynapen promotional letter, on May 20, 1968, it was seen immediately that the letter was naming the drug for uses beyond the intent of the labeling. I asked that our Division of Medical Advertising evaluate the letter and other features of Bristol's initial advertising campaign in medical journals on the basis of the approved labeling. About the same time, an Arlington, Va., physician was given a detail piece which will be discussed.

We regarded the promotional letter announcing Dynapen as seriously misleading in a number of respects. For example:

1. The too-general main theme, "* * * penicillin for Skin and Soft Tissue Infections," invited uncritical use of Dynapen as an "everyday" penicillin when, in fact, the approved labeling restricts use of this drug to treating infections that are due to penicillin G-resistant staph.

2. The letter stated that Dynapen is a "specific useful in a broad range of skin and soft tissue infections." The implication given by "broad range" in the promotional letter was that Dynapen is indicated for infections caused by a wide variety of bacterial organisms. This is inconsistent with the limitations of use in the approved labeling.

Senator NELSON. Does Dynapen have the effectiveness on various bacteria that no other drug does? Is there any such case?

Dr. MINCHEW. Only in the area of penicillin G resistant staphylococci is it particularly valuable, but even here there are other drugs which may well work against the penicillinase producing staph. There are no bacteria for which no other drugs are effective and these are.

Senator NELSON. Is it more effective, these other drugs, than any other drugs available on the market?

Dr. MINCHEW. For the penicillinase producing staph or the others?

Senator NELSON. For the others, not the penicillinase?

Dr. MINCHEW. No, sir.

Senator NELSON. So that to implement the position of FDA on this, it ought to be solely limited to the use of penicillinase-resistant staph?

Dr. MINCHEW. Our position is that it should be limited to the treatment of penicillin-resistant staph infections or in initiating therapy when such an infection is suspected. You don't often know the resistance pattern of the staphylococcus when you first start therapy.

Senator NELSON. And if it turns out that it is not a penicillinase-resistance staph infection, it is your position that they ought to switch to penicillin G or some other, is that correct?

Dr. MINCHEW. Yes.

Senator NELSON. Do you think in your labeling, in your approved promotional ads, that this is made sufficiently clear?

Dr. MINCHEW. We believe so.

Senator NELSON. Please go ahead.

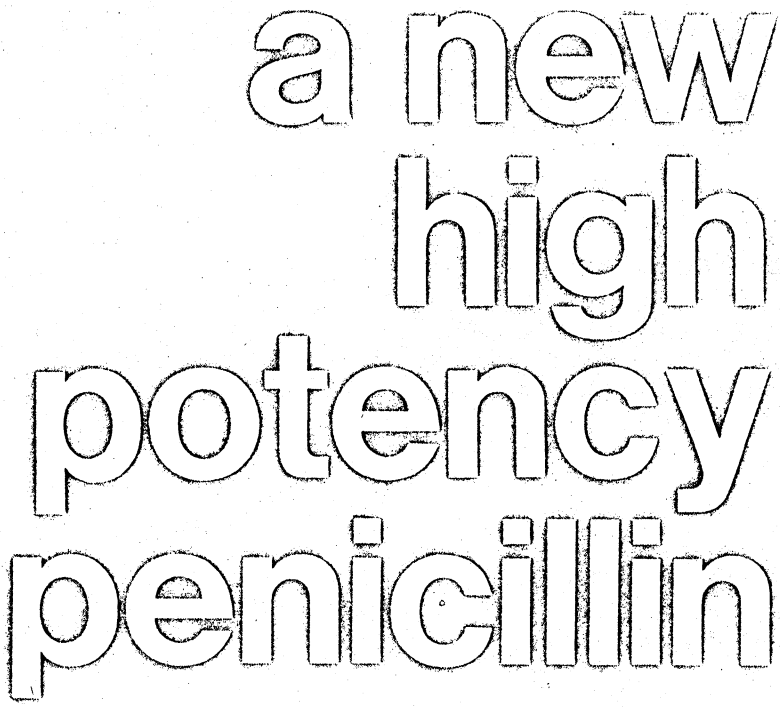
Dr. MINCHEW. 3. The promotional letter was silent both as to the need for culture and sensitivity testing, and to the need to switch therapy if a penicillin G-sensitive organism is later found to be the causative agent. We regarded these omissions as particularly misleading because it acted to encourage unapproved use of Dynapen as an "everyday" penicillin.

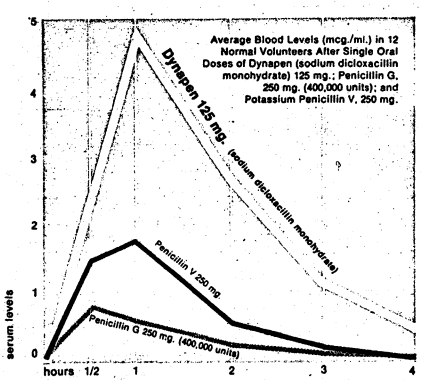
Mr. Chairman, the initial Dynapen letter sent to physicians was not a long letter but, in our opinion, it was misleading almost in its entirety.

The initial ad campaign in Medical World News—exhibit E—and the Medical Tribune carried the same misleading promotional impact as the promotional letter in several respects.

(The exhibit follows:)

EXHIBIT E





Unexcelled absorption.

In oral doses of 125 mg., Dynapen (sodium dicloxacillin monohydrate) yields peak blood levels 5 times higher than 250 mg. (400,000 units) of penicillin G, 2 to 4 times higher than 250 mg. of potassium penicillin V. In fact, this new high potency penicillin is so well absorbed that blood levels achieved are equal whether the drug is administered orally or intramuscularly.

Low cost therapy.

With all of its advantages, Dynapen is comparable in cost to other leading brands of penicillin, and costs significantly less than brand-name broad or medium spectrum "cyclines" and "mycins."

*The principal indications for Dynapen are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment in those infections where a penicillinase-producing staphylococci is suspected.

The clinical record

Outstanding cured-improved record. Excellent results were obtained at the doses recommended for mild-to-moderate infections (125 mg. q. 6h. for adults; 12.5 mg./Kg./day for children under 40 Kg.).

Dynapen in Coagulase Positive Staphylococcal Infections

125 mg. Capsules	131 Patients
Clinical Response	
Cured	99 } 98%
Improved	30 } 98%
Unimproved or Worse	2
Bacteriological Response	
Normal Flora/No Growth	113
Superinfection	1
Resistance	5
Carrier or Residual Infection	12

250 mg. Capsules	288 Patients
Clinical Response	
Cured	224 } 99%
Improved	61 } 99%
Unimproved or Worse	3
Bacteriological Response	
Normal Flora/No Growth	265
Superinfection	2
Resistance	3
Carrier or Residual Infection	18

62.5 mg./5 ml. or 125 mg./5 ml. Suspension	227 Patients
Clinical Response	
Cured	194 } 99%
Improved	31 } 99%
Unimproved or Worse	2
Bacteriological Response	
Normal Flora/No Growth	214
Superinfection	3
Resistance	—
Carrier or Residual Infection	10

1% side effects in recommended doses for mild to moderate infections. On the basis of *all* reports to date, side effects (limited primarily to mild GI upsets) are exceptionally rare — *less than* 1% in patients receiving the 125 mg. and the 62.5 mg./5 ml. formulations.

Adverse Reactions to Dynapen

Formulations	Dosage Schedule	Number of Patients	Number of Side Effects
Total		1510*	35* (2.3%)
125 mg. capsules	q. 6h.	379	5 (1.3%)
62.5 mg./5 ml. oral suspension	q. 6h.	133	0 (0%)
250 mg. capsules	q. 6h.	479	21 (4.4%)
125 mg./5 ml. oral suspension	q. 6h.	422	7 (1.6%)

*Side effects occurred in 2 of 97 patients treated at other dosages.

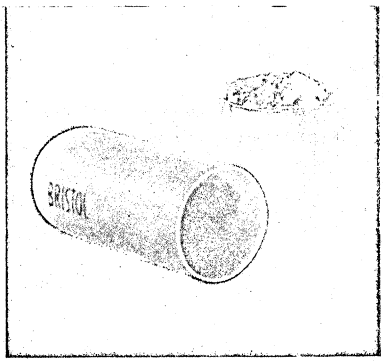
These data clearly support the contention that *the lower dosage means a lower incidence of side effects.*

for prescribing information see next two pages

a new high potency penicillin

outstanding bactericidal performance in skin and soft tissue infections:

cellulitis, pyodermas, boils, abscesses, infected wounds and lacerations



TEXT OF OFFICIAL PACKAGE CIRCULAR-DI-7891-2-1 March, 1968

Description: DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

Pharmacology: DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.[1,2,3] as measured at the two-hour level.

Actions (Microbiology): DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

Indications: The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

Contraindications: A history of allergic reactions to penicillins should be considered a contraindication.

Precautions: As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

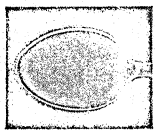
Guide to principal indications

Skin and soft tissue infections such as:

Furunculosis	Abscess
Carbuncles	Pustular acne
Impetigo	Infected skin ulcer
Ecthyma	Lymphangitis
Cellulitis	Lymphadenitis
Pyoderma	

as well as infected wounds, burns and lacerations

125 mg. capsules



highly palatable Oral Suspension, 62.5 mg./5 ml., that eliminates the penicillin taste.

Dosage guide

Usual adult dose for mild to moderate infections: 125 mg. q. 6h.*

Usual children's dose for mild to moderate infections: 12.5 mg./Kg./day in four equally divided doses*

*Higher and/or more frequent doses should be used for more severe infections.

NEW

DYNAPEN®

new and specific for skin and soft tissue infections

SODIUM DICLOXACILLIN MONOHYDRATE

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

Adverse Reactions: Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Dosage: For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q. 6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q. 6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q. 6h. or higher.

Children weighing less than 40 Kg. (88. lbs.): 25 mg./Kg./day, or higher, in divided doses q. 6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by Group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

Supply:

List 78923—DYNAPEN (sodium dicloxacillin monohydrate) Capsules, 125 mg., bottles of 24.

Also available:

List 78566—Oral Suspension, 62.5 mg./5 ml., 80 ml. bottle.

References: 1. Data on file at Bristol Laboratories. 2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262. 3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139-145, 1965.

[illegible] Telephone Service: (315) [illegible]. If you have any question relating to the use of DYNAPEN (sodium dicloxacillin monohydrate) or any other Bristol product, please call this number collect. A physician in the Medical Department of Bristol Laboratories will be available to answer your question.

BRISTOL

Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. On Friday, May 24, 1968, the then Commissioner Goddard telephoned Mr. Morris Weeden, president of Bristol Laboratories, informed him that the certificates for marketing the drug had been withdrawn, and offered to meet with him at 9 a.m., Monday, May 27, to discuss Bristol's Dynapen promotional campaign.

Senator NELSON. What do you mean, certificates for marketing the drug? Are you saying you wouldn't do it?

Dr. MINCHEW. All antibiotics go through the certification procedure, and when they meet the standards of identity, strength, quality, and purity, there is issued a certificate which legally allows them to enter interstate commerce. Commissioner Goddard withdrew those certificates.

Senator NELSON. Which meant you withdrew the drug from the market?

Dr. MINCHEW. Which meant that the drug in interstate commerce was then illegal.

Senator NELSON. And was that amount of the drug which was already in the marketplace withdrawn?

Dr. MINCHEW. We will come to that subsequently. During that weekend, action was taken to determine the extent of the distribution of Dynapen, including all lots initially certified. All shipments were ordered embargoed at the wholesale level.

The meeting took place as requested. Mr. Weeden was accompanied by Dr. Peltier and his house counsel, Mr. Simonton, and by Messrs. Corcoran, Foley, Meers, and Lane of counsel.

Dr. Goddard and members of his staff presented the FDA's complaints against the promotional campaign in detail. The record of this meeting reflects that remedial action was accepted by the firm and the following pattern was established:

1. The Commissioner requested full reports as to what Bristol was saying to its detail men about Dynapen.

2. A remedial letter was to be sent airmail to some 280,000 practicing physicians, correcting the faults contained in the Bristol promotional letter.

3. A remedial ad; in this case, a correct ad bearing a legend stating it was to replace a previous ad which the FDA regarded as misleading. It was to be run in the journals where the defective ad appeared.

4. Each remedial form was to include a straightforward scientific statement of the place of Dynapen in therapy.

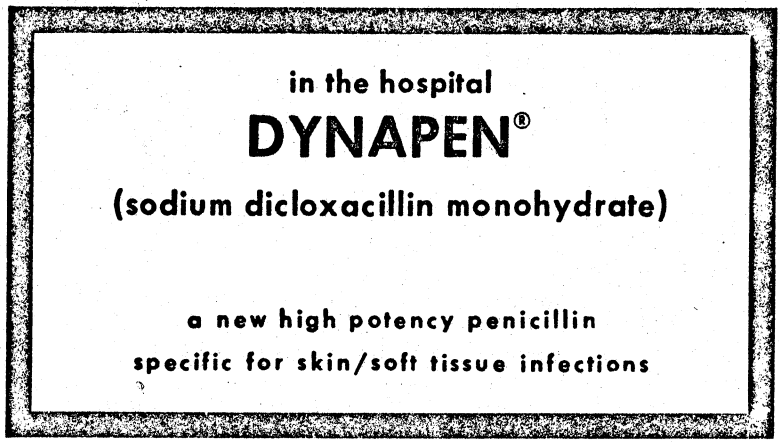
5. Bristol was to send drafts of proposed remedial actions to FDA by May 29, 1968, for consideration at a meeting with FDA on May 31.

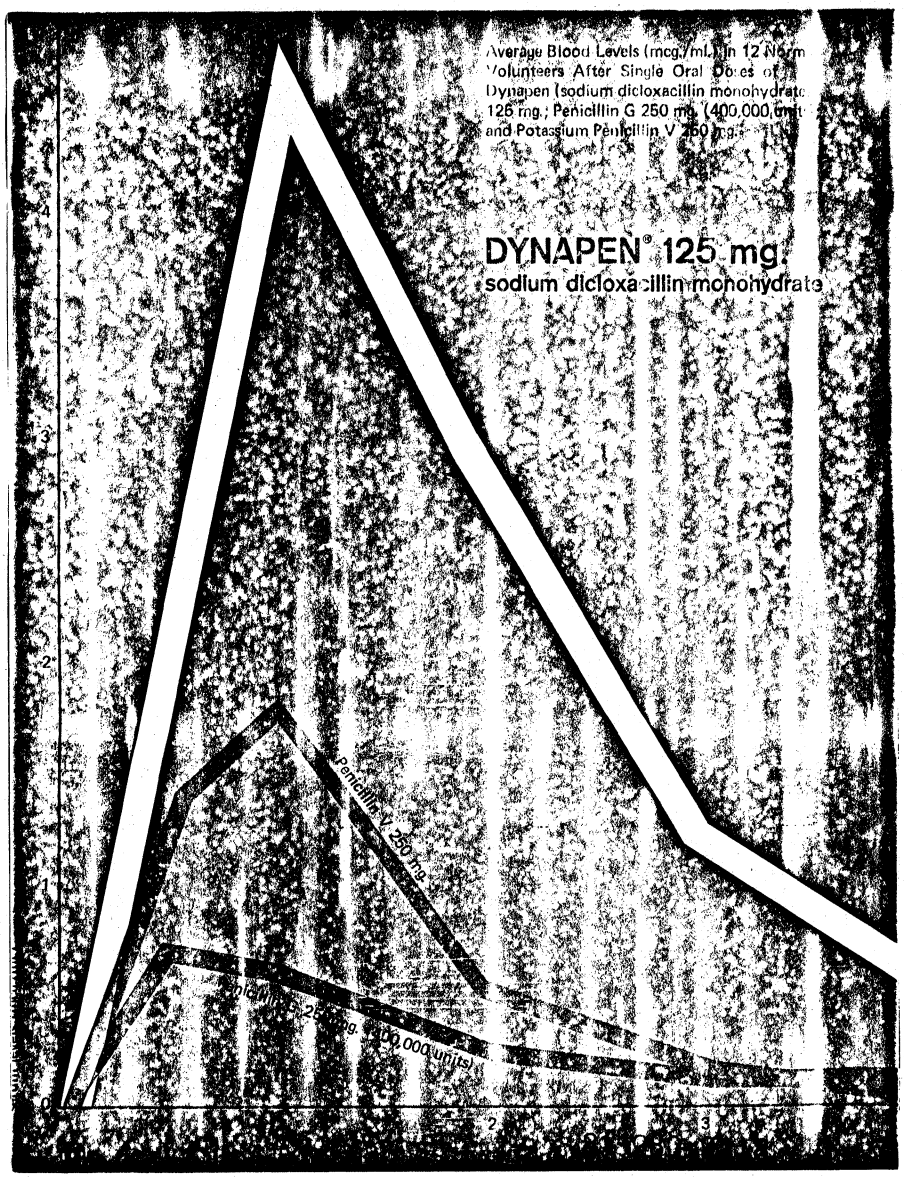
Collateral action was taken to determine how far Bristol's initial campaign had been carried by their detail men. Our inspections of Bristol's plant showed that some 90,000 promotional folders for detail men had been produced. About 30,000 of these had been mailed to the approximately 300 Bristol representatives who were located west of the Mississippi and in Florida. Copies of these folders are being made available for the record—exhibits F and G.

Senator NELSON. They will be printed in the record.

(The information referred to follows:)

EXHIBIT F


in the hospital
DYNAPEN®
(sodium dicloxacillin monohydrate)
a new high potency penicillin
specific for skin/soft tissue infections


Average Blood Levels (mcg./mL.) in 12 Norm
Volunteers After Single Oral Doses of
Dynapen (sodium dicloxacillin monohydrate
125 mg.; Penicillin G 250 mg. (400,000 unit
and Potassium Penicillin V 250 mg.
DYNAPEN® 125 mg.
sodium dicloxacillin monohydrate
Penicillin V 250 mg.
Penicillin G 250 mg. (400,000 units)
3
2
1
0
2
3

ANTIBIOTIC RESISTANCE OF STAPHYLOCOCCI

"For the past decade more and more strains of staphylococci isolated from the community at large have been noted to produce penicillinase. Therefore the distinction as to whether a patient's infection arises in the community or is hospital-acquired no longer serves as a useful guide to choosing antimicrobials with which to initiate treatment."

"During 1967, 76% of staphylococci isolated from in-patients and 53% of strains isolated from out-patients were resistant to penicillin G."

-- Koenig, M. Glenn, "Staphylococcal Infections - Treatment and Control", Diseases of the Month, April 1968, Year Book Medical Publishers Pages 9-10.

"However, the original concept that the penicillinase resistant penicillins should be restricted only to the treatment of proved resistant staphylococcal infections is no longer tenable; delay in the administration of these agents contributes to the high mortality rate in serious infections caused by staphylococci that proved to be resistant."

--New Drugs, 1967 Edition, Page 12.

DYNAPEN®

(sodium dicloxacillin monohydrate)

A new high potency penicillin
with outstanding bactericidal performance
in the oral treatment
of hospital infections
due to staphylococci:

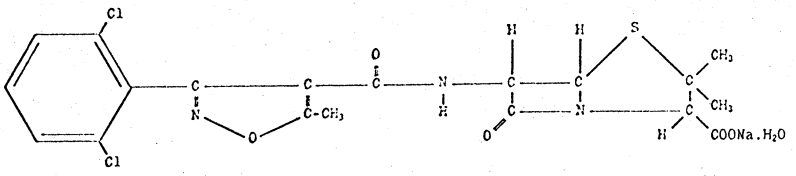
- post-operative infections
- trauma complicated by infection
- burns
- wounds
- fractures
- any skin or soft tissue infection

DYNAPEN(R)

sodium dicloxacillin monohydrate

DESCRIPTION

DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4 isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococ-col infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.



SOURCE

Obtained by acylation of 6-aminopenicillanic acid (6-APA) with 2,6 dichlorophenyl and isolated as the sodium salt monohydrate.[3]

Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S$

CHEMICAL PROPERTIES

Colorless, crystalline solid[2]

Molecular Weight: 510.3[2]

Solubility: Greater than 100mg./ml. of water at room temperature.[3]

Stability: Highly resistant (13 times more so than penicillin G) to inactivation by acid. Also resistant to inactivation by staphylococcal beta-lactamase.[1,4,5]

Activity Remaining in Per Cent Under Varying Conditions[2]

Time (days)	Temperature 24°C	4°C
2	100	
9	30	
14		90.9

1 mg. of pure sodium salt monohydrate equals 1164 penicillin units; 0.8591 mcg. equals one unit.[3]

EXCRETION

Renal clearance, about 200 ml. per minute, is considerably less than that of penicillin G which approximates total renal blood flow (500ml. per minute). No detectable accumulation occurs though, even at doses of 250 mg. or 500 mg. every six hours.

TOXICITY

Acute: No deaths in rats, rabbits, or dogs given single oral doses of 8000, 5000, 3000 mg./kg. respectively. LD_{50} for mice, 8700 mg./kg.

Chronic: No adverse effects in dogs given oral doses as high as 500 mg./kg./day or rats given 1000 mg./kg./day for three months. No deaths occurred in dogs and the same number occurred in treated as in control rats.

PHARMACOLOGY

DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500 and 1000 mg.[1,2,3] as measured at the two hour level.

ACTIONS (microbiology)

DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci. The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms is as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

INDICATIONS

The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should super infection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time. Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs) or more;

125 mg. q6h

Children weighing less than 40 Kg. (88 lbs);

12.5 mg./Kg./day in divided doses q.6h

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs) or more;

250 mg. q6h or higher

Children weighing less than 40 Kg. (88 lbs);

25 mg./Kg./day or higher, in divided doses q.6h

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLY

List 78923-DYNAPEN (sodium dicloxacillin monohydrate)

Capsules, 125 mg., bottles of 24

Also available:

List 78566-DYNAPEN (sodium dicloxacillin monohydrate)

For Oral Suspension, 62.5 mg./5ml., 80-ml. bottle

REFERENCES

1. Data on file at Bristol Laboratories.
2. Bennett, J.V., Gravenkemper, C.F., Brodie, J.L., and Kirby, W.M.M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparison with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262.
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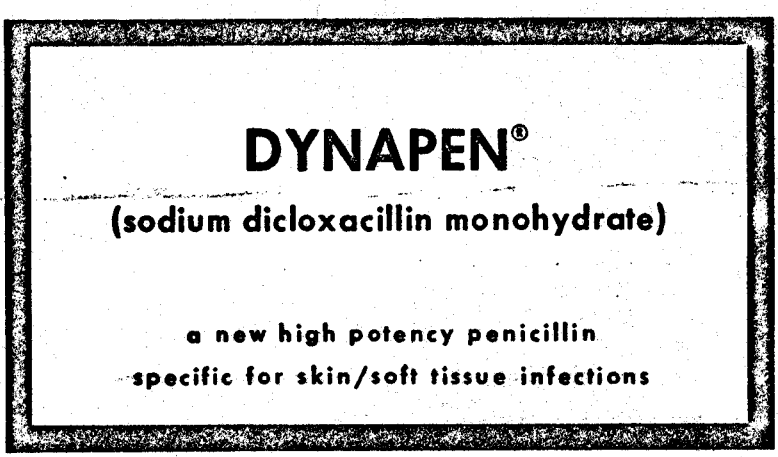
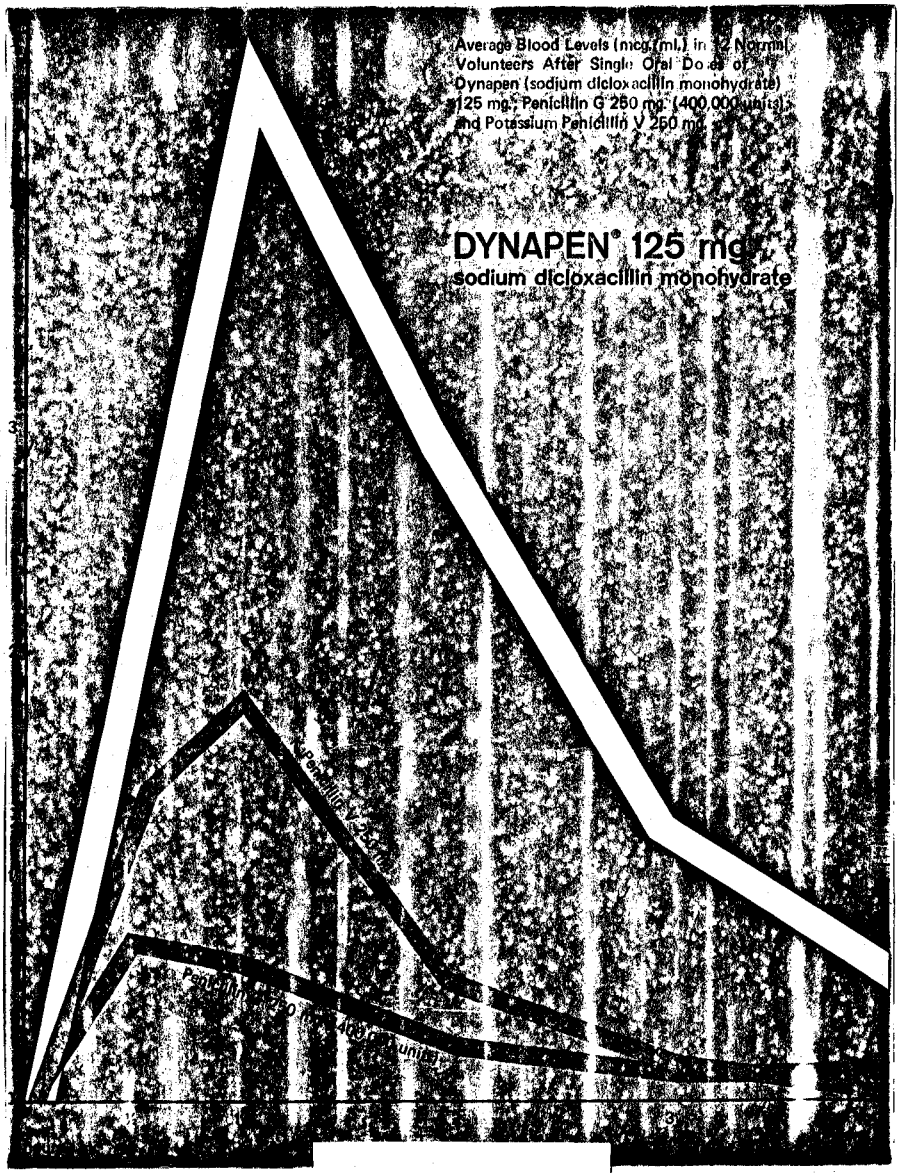
/BRISTOL/ Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

EXHIBIT G


DYNAPEN®
(sodium dicloxacillin monohydrate)
a new high potency penicillin
specific for skin/soft tissue infections


Average Blood Levels (mcg./ml.) in 12 Normal Volunteers After Single Oral Doses of Dynapen (sodium dicloxacillin monohydrate) 125 mg., Penicillin G 250 mg. (400,000 units) and Potassium Penicillin V 250 mg.
DYNAPEN® 125 mg.
sodium dicloxacillin monohydrate

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"For the past decade more and more strains of staphylococci isolated from the community at large have been noted to produce penicillinase. Therefore the distinction as to whether a patient's infection arises in the community or is hospital-acquired no longer serves as a useful guide to choosing antimicrobials with which to initiate treatment."

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DYNAPEN(R)

(sodium dicloxacillin monohydrate)

A new high potency penicillin
with outstanding
bactericidal performance in
skin and soft tissue infections
due to staphylococci:

- pyoderma
- wounds
- boils
- cellulitis
- lacerations
- post-operative

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sodium dicloxacillin monohydrate

DESCRIPTION

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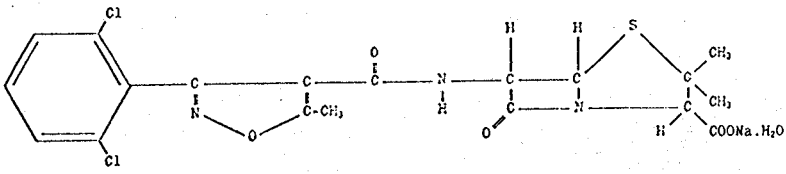

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Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S$

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Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time. Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

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DOSAGE

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125 mg. q6h

Children weighing less than 40 Kg. (88 lbs);

12.5 mg./Kg./day in divided doses q.6h

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs) or more;

250 mg. q6h or higher

Children weighing less than 40 Kg. (88 lbs);

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SUPPLY

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Capsules, 125 mg., bottles of 24

Also available:

List 78566-DYNAPEN (sodium dicloxacillin monohydrate)

For Oral Suspension, 62.5 mg./5ml., 80-ml. bottle

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/BRISTOL/ Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. Mr. Chairman, I am sure that your committee will see quickly that the detail men's message to physicians was similar to that in the company's promotional letter and journal ads.

It was found that about 64,000 packages of 24 capsules of Dynapen had been distributed, about 42,000 units to retail pharmacies and about 3,500 units to hospitals.

Because of the large amount of material shipped, it was decided to request recall of the goods to a level of control of the firm.

Senator NELSON. What did that mean, physically?

Mr. GOODRICH. That meant getting it back either in their own warehouse or in the case of materials that was in drugstores the company was required to send a telegram to all the druggists to the effect it would be illegal to fill a prescription with that product until the matter was clarified.

Senator NELSON. And how long did it take for clarification to occur?

Mr. GOODRICH. Clarification took until June 21, when the corrective ad ran in the Medical World News.

Senator NELSON. And how long was it withheld from the market then?

Mr. GOODRICH. From May the 24th, when Dr. Goddard sent them a telegram canceling the certificates, until June 21, when the corrective ad appeared in Medical World News.

Senator NELSON. I want to commend the FDA for this action. I think it is strong and dramatic and the proper thing to do, and I am confident if you continue with this kind of action each time they intentionally violate the regulations that have been established, that it will have some impact, because I think it would appear that the only effective way is to do something dramatic enough to not only protect the public but to make it expensive for them to engage in this kind of activity.

It seems to me in the past frequently it wasn't sufficient penalty to their violation of the FDA regulations. If the penalty is made tough enough every single time, it may very well work. So I think the FDA is to be commended for this very strong action.

Dr. MINCHEW. Prior to meeting with the firm on May 31, 1968, the FDA prepared guidelines for the remedial letter. At this meeting Bristol was told that their proposed remedial letter was promotional, not adequately corrective, and unsatisfactory. Composition of the remedial ad was settled.

Bristol agreed at this meeting to notify its detail men not to use the promotional folder and to use only the approved package labeling for detailing Dynapen. The firm agreed to "freeze" stocks of Dynapen through a letter addressed to wholesalers and a letter to all retail accounts. The letters were to state the reason for the "freeze." Copies of these communications are being included for the record—exhibits H, I, and J.

Senator NELSON. They will be included in the record.

(The information referred to follows:)

EXHIBIT H

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

REQUEST FOR EMBARGO OF DYNAPEN®

DEAR PHARMACISTS: The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

EXHIBIT I

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

Important Notice to all Bristol Wholesalers:

REQUEST FOR EMBARGO OF DYNAPEN®

The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

EXHIBIT J

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

REQUEST FOR EMBARGO OF DYNAPEN®

DEAR HOSPITAL PHARMACIST: The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

Dr. MINCHEW. Another meeting was set for Monday, June 3, 1968, to finalize remedial actions previously discussed. At this meeting, the contents of the remedial letter and correct ad were agreed upon. Bris-

tol was advised that recertification could be effected only after the remedial ad had appeared in the same journals as the original ad.

The events following these decisions are reflected in the remedial letter and the correct ads, copies of which are included for the record—exhibits K and L.

Senator NELSON. They will be included in the record.

(The information referred to follows:)

EXHIBIT K

BRISTOL LABORATORIES,
Syracuse, N.Y.

DEAR DOCTOR: The Food and Drug Administration has asked that we call your attention to our letter of May 17, 1968 which announced the coming availability of Dynapen (sodium dicloxacillin monohydrate). The Food and Drug Administration has expressed concern that our discussion of this drug in terms of treating skin and soft tissue infections created misleading impressions concerning the proper use of Dynapen in its limited appropriate indications.

Therefore, we wish to specify the indications and limitations for use of this drug in detail as follows:

1. The prinicpal indication for Dynapen is in the treatment of infections known to be due to penicillinase-producing staphylococci which have been shown to be sensitive to it.

2. If antibiotic therapy is considered necessary in potentially serious infections while awaiting reports of cultures and sensitivity studies, Dynapen may be used to initiate therapy in such patients in whom a penicillinase-producing staphylococcus is suspected. (See Important Note below.)

Important Note

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When it is judged important that treatment be initiated before definitive culture and sensitivity results are known the choice of Dynapen should take into consideration the knowledge that its has also been shown to be effective only in the treatment of infections caused by pneumococci, Group A betahemolytic streptococci and penicillin G-sensitive staphylococci. In serious, life threatening infections oral preparations of the penicillinase-resisant penicillins should not be relied on for initial therapy.

Methicillin, a compound working through a similar mechanism against penicillin G-resistant staphylococci, has been available for nine years. It is a fact that strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. It has been demonstrated that such strains are almost always resistant to other penicillinase-resistant penicillins, such as the isoxazole group of which Dynapen is a member. When such a strain is isolated, use of routine antibiotic discs cannot be relied on to differentiate relative sensitivity. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, the Food and Drug Administration is concerned that widespread use of the penicillinase-resistant penicillins in infections other than those due to penicillin G-resistant staphylococci may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Therefore, if the bacteriology report indicates the infection is not due to a penicillin G-resistant staphylococcus, the physician is advised to continue therapy with a drug other than Dynapen or any other penicillinase-resistant semi-synthetic penicillin.

Indicated surgical procedures should be performed.

Contraindications

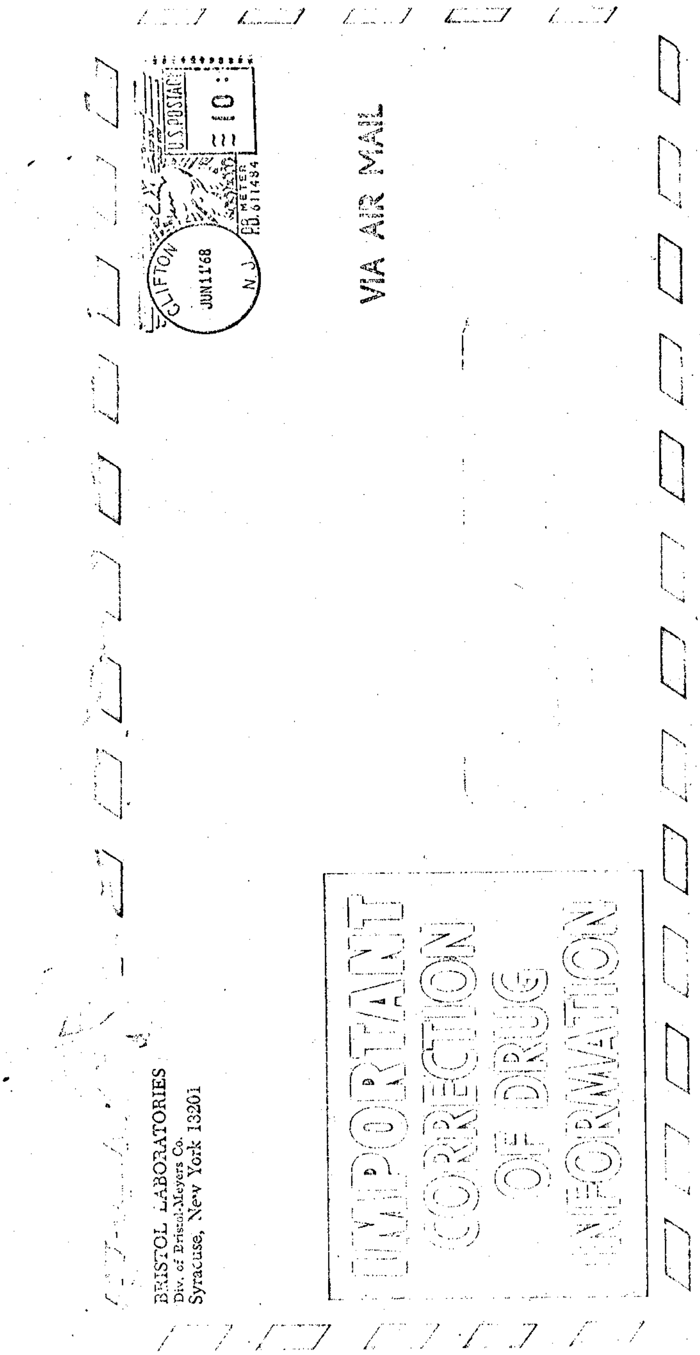
A history of allergic reactions to penicillin should be considered a contraindication.

Information in our announcement letter, or that you may have received from one of our sales representatives, should be carefully considered in light of the preceding clarification.

We have discontinued the advertising in question. Future advertising will be appropriately modified. The drug is not available for prescription at this time. We will notify you when it becomes available.

Sincerely,

H. C. PELTIER, M.D.,
Vice President, Medical Director.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VIA AIR MAIL
BRISTOL LABORATORIES
Div. of Bristol-Meyers Co.
Syracuse, New York 13201
IMPORTANT
CORRECTION
OF DRUG
INFORMATION

EXHIBIT L

new high potency penicillin
for treatment of known
pen. G resistant staph or for
initiating treatment
whenever this organism is
suspected

Dynapen is bactericidal
Dynapen is exceptionally well absorbed
Dynapen is highly effective against pen. G resistant staph
Dynapen is low cost therapy

Now available

Dynapen

Published to replace a previous ad in this space which the Food and Dr Administration considered to creat misleading impressions concernin proper use of Dynapen.

TEXT OF OFFICIAL PACKAGE CIRCULAR-DI-7891-2-1 March, 1968

Description: DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

Pharmacology: DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.[1,2,3] as measured at the two-hour level.

Actions (Microbiology): DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

Indications: The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin or other appropriate antibiotic therapy because of the greater clinical experience in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

Contraindications: A history of allergic reactions to penicillins should be considered a contraindication.

Precautions: As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

Adverse Reactions: Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Dosage: For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q. 6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q. 6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q. 6h. or higher.

Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day, or higher, in divided doses q. 6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by Group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

Supply:
List 78923—DYNAPEN (sodium dicloxacillin monohydrate) Capsules, 125 mg., bottles of 24.
Also available:
List 78566—Oral Suspension, 62.5 mg./5 ml., 80 ml. bottle.

References: 1. Data on file at Bristol Laboratories. 2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262. 3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139-145, 1965.

Bristol Telephone Service: (315) 437-6060. If you have any question relating to the use of DYNAPEN (sodium dicloxacillin monohydrate) or any other Bristol product, please call this number *collect*. A physician in the Medical Department of Bristol Laboratories will be available to answer your question.

BRISTOL
Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. We instituted recertification of Dynapen as of June 21, 1968.

Mr. Chairman, if you have any questions, my associates and I will attempt to answer them.

Mr. GORDON. Mr. Chairman, may I interrupt here? The subcommittee has secured documents taken from the files of the Food and Drug Administration that pertain to this matter, and I ask that they be included in the record at the appropriate place.

Senator NELSON. Without objection.

Could you comment—and I commend the FDA for its prompt action on Dynapen—is there any explanation why some 6 weeks elapsed between the faulty promotion of Vibramycin detailing at a medical meeting, and your contact with the manufacturer to request corrective steps?

Dr. MINCHEW. It certainly takes an additional amount of time to obtain the proper type of documentation when we are dealing with action over oral detailing. In the case of the Vibramycin, the problem was in obtaining affidavits and having the adequate legal documentation to support our action.

The situation with the Dynapen was that the errors were written errors in promotional labeling and journal advertising over which we felt that immediate action could be supported.

Senator NELSON. So you acted as expeditiously as you could in the Vibramycin case. You simply didn't have the documents in hand to support action until you secured affidavits and so forth, is that correct?

Dr. MINCHEW. I believe we did, unless Mr. Goodrich has——

Senator NELSON. Excuse me, did you have some questions?

Mr. GROSSMAN. A couple of questions. First, in looking over the various cases in the last several days, I wondered if you feel that there is some type of consistency in policing activities of advertising? In other words, do you feel that the action you are taking in these cases is consistent with the degree of risk, or how is it decided what action you are going to take? Perhaps Mr. Goodrich would wish to respond as to the legal point of view.

Mr. GOODRICH. We have decided in each case on the basis of an examination of the ad and the company's performance on whether or not a remedial letter would be required. This has been taken up in each instance at the Commissioner level. Dr. Goddard initiated it. Dr. Ley has continued it.

The practice has been for the Division of Medical Advertising and the Director of the Bureau of Medicine, when they encounter an advertisement that they regard as particularly offensive, to call that to the Commissioner's attention.

Part of our program has been to pay special attention to the initial campaign for the launching of a new product. We advised this committee of that some time ago, and we followed through on it.

This has been important to make sure that the drugs are initially introduced to the profession on the basis on which they were approved. That is what led us into the Vibramycin, Dynapen episodes.

Now in the case of Dynapen, we felt that because we had a long and protracted discussion with the company, because we felt we had a clear understanding with them about the conditions of appropriate use, and because of the initial launching of the product completely at

variance with what we thought we had agreed upon, we concluded, Dr. Goddard and the others, that these steps, certification cancellation, withdrawing the drug and remedial letters were the most appropriate. This was the first instance for a remedial ad.

Mr. GROSSMAN. In this same area on page 4 of Dr. Minchew's prepared statement, he is talking about Tegopen. He said, "In October, we publicly criticized this ad campaign as offering the drug for conditions which it had not been approved."

What does he mean by "publicly criticized"?

Mr. GOODRICH. We met on October 20, 1966, before the Pharmaceutical Advertising Club in New York to discuss on a broad basis the FDA's requirements and the industry's performance in complying with advertising regulations.

I personally took up the eight products that had been introduced in the previous year, and that had achieved rank among the 200 most prescribed.

Tegopen was one of those drugs. We presented to the group, including Bristol and its people who were there, photographs of the advertising campaign and our criticism of it. Essentially, it was that the Tegopen was characterized as an everyday penicillin. The visuals on the ads showed physicians using it at, as I remember it, 10:01, 10:08, 10:14 a.m., and so forth, in patients, which would mean routine practice.

We then said that our understanding was that the product had been approved for a special purpose and not as an "everyday" penicillin. Bristol came to see us within a very few days, as our statement indicates, saying: "We think that Tegopen is indeed an everyday penicillin," and that is when we told them that they would have to get approval for such a purpose.

Mr. GROSSMAN. May I ask you, do you think this is the normal procedure? In other words, would you consider this a normal procedure to criticize, to make a statement publicly without contacting the firm first and/or trying to stop the promotion by the firm?

Mr. GOODRICH. We considered it an invitation by the pharmaceutical advertising group, as a whole, and the companies, to meet with us and discuss on a broad basis what it was we expected in advertising, and what we thought of the existing practices.

Now we haven't had another meeting of that kind. I didn't initiate the invitation. It was initiated by someone else. We simply participated.

In other words, to get this matter of prescription drug advertising corrected, this offered us an opportunity to talk both with the companies, with advertising agencies, and with their creative people. We thought we talked with them on a level that was fully understood.

Mr. GROSSMAN. It just seems to me if there is improper advertising in any case like this, by one particular firm, that the option of FDA would not be to go to a forum and publicly discuss it, but would rather be to go to Bristol and tell them, "You do this or you do this or we are going to stop the distribution of the drug."

Mr. GOODRICH. As the facts show, this has been our practice since that time. It became important in October 1966 to communicate with the entire industry and with their advertisers and the others concerned.

Mr. GROSSMAN. One other point.

Senator NELSON. May I interrupt? Was that a public meeting?

Mr. GOODRICH. Yes, sir.

Mr. GROSSMAN. One other point. On page 3, and this is involved a little bit with a different problem, I wonder how effective your warnings are to the doctor. We have talked about the other aspects of advertising. I don't know, maybe a doctor looks at words differently than I do as a lawyer. But I notice that it says on page 3, one of the warnings recommended would be, "If it is determined that the infection is not due to a pencillin G resistant staphylococcus, a change to penicillin G or phenethicillin may be considered."

Now as a doctor, do I react very violently when I see, "May be considered"?

Mr. GOODRICH. I think you react properly. We have, in the Dynapen letters, and in the promotional revisions that are now underway, expressed that more positively.

Mr. GROSSMAN. One final point, if I may. Senator Hatfield can't be here this morning. He has another hearing. Yesterday I think he and Dr. McCleery were discussing this point of how long and what action was taken with Vibramycin on the visual aids. I would like to ask that two letters be included in the record.

One is a letter from Chas. A. Pfizer to Dr. McCleery, dated October 6, and one is dated October 23, signed by Dr. Minchew, relating to the fact that the FDA did in fact say that the visual aids could be used for 1 month's time. I think you agreed to that. Thank you.

(The letters follow:)

CHAS. PFIZER & CO., INC.
October 6, 1967.

Re Vibramycin.

R. S. MCCLEERY, M.D.,
Director, Division of Medical Advertising, Bureau of Medicine, Food and Drug Administration, Washington, D.C.

DEAR DR. MCCLEERY: We refer you to your meetings with Mr. Alterno and Dr. Trout on September 5 and September 6, 1967 in regard to Vibramycin.

As a result of these meetings Dr. Ley gave us permission to use the existing Vibramycin visual aid and compendium for a period of one month from the date of approval (September 14, 1967) and we were then to replace that visual with the new revised visual aid.

During the coming week of October 9, 1967 the new visual aids will be sent to our sales force. Upon receipt of the revised visual aid the detailman will return his copy to his District Manager and will sign a return sheet. The visual aid, along with the compendum, will then be returned to the company where they will be destroyed.

Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., October 23, 1967.

"Vibramycin Suspension"—NDA 50-006
"Vibramycin Capsules"—NDA 50-007

Re Vibramycin—148z.3 and 148z.4.

CHAS. PFIZER & CO., INC.,
New York, N.Y.
(Attention: Mr. M. G. Adair)

GENTLEMEN: We have no objection to the Vibramycin visual aid (P159x67R1—Issued October 1967) submitted with your letter of October 6, 1967, nor to the manner in which you propose to dispose of copies of the previous visual aid and compendium.

The draft of the compendium submitted with your letter of October 2, 1967 is satisfactory.

Sincerely yours,

B. H. MINCHEW,
HERBERT L. LEY, Jr., M.D.,
Director, Bureau of Medicine.

Senator NELSON. I want to thank you very much for your presentation this morning. Our next hearing will be on Wednesday at 10 a.m. The witness will be Dr. Philip Lee, Assistant Secretary of HEW, and staff, to discuss the HEW Task Force Report on Prescription Drugs.

Thank you very much.

(Whereupon, at 10:45 a.m., the committee adjourned until Wednesday, September 25, 1968, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, SEPTEMBER 25, 1968

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

The subcommittee met, pursuant to recess, at 10:15 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The witness this morning is Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs of the U.S. Department of Health, Education, and Welfare.

Dr. Lee, we appreciate your taking the time to come over here and testify this morning. Your testimony will be on the Report of the Task Force on Prescription Drugs. You may present your statement in any way you wish. If you wish to elaborate on it you may, or you may depart from it.

STATEMENT OF DR. PHILIP R. LEE, ASSISTANT SECRETARY, OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY DR. MARK NOVITCH, OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, HEW; MILTON SILVERMAN, PH. D., OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, HEW; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, FOOD AND DRUG ADMINISTRATION, HEW

Dr. LEE. Thank you, Mr. Chairman.

I am accompanied by Mr. William Goodrich on my right, Assistant General Counsel; on my immediate left by Dr. Milton Silverman and on his left, Dr. Mark Novitch, both members of my staff in the Office of Health and Scientific Affairs. Dr. Silverman and Dr. Novitch have been two of the key staff members on the Task Force on Prescription Drugs.

Just over a year ago, former Secretary Gardner established a special Task Force on Prescription Drugs, asking that we thoroughly examine the problems of covering the costs of out-of-hospital prescription drugs under medicare. We were not bound to recommend for or against any specific program or approach. Rather, our directive was first to investigate and then to make whatever recommendations we found to be appropriate.

The Secretary—like many others—recognized the enormous complexity of this assignment. Some answers, he felt, might be found speedily, and this has turned out to be true. Others, he predicted, might take many months or even years of work, and this, too, was an accurate forecast.

The task force still has not completed the detailed studies on program financing, administrative procedures, reimbursement methods, and utilization review, all of which are essential to a final determination. When this material has been analyzed, we shall be in a position to submit our final report, which we expect to be completed before the end of 1968.

We have made two interim reports, however. The first was submitted to the Secretary in March of this year. In it, we recommended legislation to establish reasonable cost and charge ranges for drugs supplied in federally supported health programs. We also recommended legislation to authorize publication of a Federal drug compendium.

A second interim report, much broader in scope, was released earlier this month. Today, Mr. Chairman, I am pleased to submit a copy of the report for the record and to have this opportunity to discuss portions of it in somewhat more detail.

Senator NELSON. You are referring to the task force's second interim report on August 30, 1968?

Dr. LEE. Yes.

Senator NELSON. That report will be printed in full in the record.[1]

Dr. LEE. Thank you very much, Mr. Chairman.

In fulfilling its mission, the task force has been confronted with many of the same problems which have been considered in the exhaustive and informative hearings conducted during the past year or more by your distinguished subcommittee.

You have demonstrated a keen interest in drug research, drug patents, drug promotion, and drug prices. The task force has also examined these problems.

You have demonstrated interest in the prescribing habits of physicians. The task force has reviewed this as well.

You have been interested in drug quality, and in the confused problems of chemical equivalents and clinical equivalents. So has the task force.

And—of most importance—we share the conviction, I am sure, that the major goal of our efforts must be to improve the quality of health care provided to all Americans.

This was stressed last year by Secretary Gardner, when he established the task force upon a directive from the President. The Secretary said:

> In all of its work, I have asked the task force to measure the value of possible solutions not only in terms of dollars to be saved, but in the quality of health care to be delivered.

Before discussing our recent report, Mr. Chairman, I feel it is important to note that even before the task force embarked on its mission, it was evident that we would need a tremendous amount of basic, objective information on drugs—on their development, production,

[1] See report beginning at p. 3737, infra.

distribution, prescription, costs and uses. And at the start, we found that much of the information we urgently needed simply was not available.

This lack of scientific data was clearly responsible for much of the controversy which has characterized this entire area. For example, on the warmly disputed matter of "generic equivalents," it was all too obvious that much of the controversy was due to the fact that we didn't have the facts. We had to go out and get them—to go into the laboratories and clinics, and carry out the necessary scientific research.

Senator NELSON. I might say, Dr. Lee, as I have read over the past year and a half the publications issued by the Pharmaceutical Manufacturers Association, I have noted that they made assertions that would make it appear to the physician that they had the facts, which they obviously did not have, on this issue. Please continue.

Dr. LEE. In this and other phases of the task force's operations, I feel it is also important to emphasize the invaluable assistance we have received from virtually all of the groups and associations and scientific communities involved. More than 200 of the Nation's experts in this area have given freely of their time to provide us with the benefit of their advice and counsel. Leaders of the drug industry have offered us a wealth of previously unavailable information.

The task force has assembled a great deal of material which should be made widely available to Congress, to Government agencies, to the drug industry, to the medical profession, to health insurance groups, to consumer groups, and others. This information will be made available in a series of background papers. The first, about the health needs and resources of the elderly, and their actual use of prescription drugs, will be published very shortly. Others will follow quickly thereafter.

Time will not permit even a brief discussion of all the findings and recommendations we have presented to date. Three areas may be of particular interest to your subcommittee—first, the prescribing patterns of physicians and the sources of information on which these patterns are based; second, the promotional activities of drug manufacturers; and third, drug quality and the equivalency of generic name products.

Clearly, Mr. Chairman, the key figure in establishing patterns of drug use is the prescribing physician. Because these patterns are so central to the success of a medicare drug insurance program, the task force has looked carefully at the process of decisionmaking in drug therapy.

It is not a simple process. Each time a course of therapy is selected, the well-trained and conscientious physician must try to answer such questions as:

Which is the best drug for the problem at hand?

Which is the most appropriate dosage form?

What are the optimal amounts and duration of therapy?

What side effects, if any, must be anticipated?

Is some condition present which would rule out the use of this drug?

Is the patient taking another drug with which this one is incompatible?

Under the best of circumstances, judgments on these and similar questions are difficult, and their difficulty as well as their importance, Mr. Chairman, cannot be overstated.

This is why we are devoting a major effort to the review of claims for all drugs approved through the new drug procedures of FDA between 1938 and 1962. If the labeling claims are not supported by substantial evidence, the prescriber is misled as to the effectiveness that may be expected.

This is also why we are trying to improve the adverse reaction experience reporting systems available to the FDA.

Senator NELSON. You are saying you are reviewing the labeling claims made on the new drugs between 1938 and 1962; is that right?

Dr. LEE. Yes, sir.

Senator NELSON. And you have the authority under the 1962 law, I understand, to control the labeling on those drugs?

Dr. LEE. Right.

Senator NELSON. Can you advise the committee how far along you are in a review of the claims made for these drugs?

Dr. LEE. As you know, this study was initiated with the National Academy of Sciences—National Research Council, to review the efficacy of approximately 3,000 drugs. About half of these have been completed and submitted to the Food and Drug Administration.

Based on the review by panels of scientists in each of the drug areas, the Food and Drug Administration is now determining what actions it is appropriate to take under individual circumstances .There are several different categories. And these are being evaluated, of course, in terms of their effectiveness. Safety is not at issue, because that was a requirement prior to 1962.

Senator NELSON. How many have been reviewed of the 3,000?

Dr. LEE. About how many? About half. Mr. Goodrich can give us more detail.

Mr. GOODRICH. About half of the reports have been received by the Food and Drug Administration from the Academy. Dr. Lee establish a task force to deal with those reports. About 10 percent of what we have received have been processed through that task group.

Announcements have been made in the Federal Register of the status of about half of those drugs. In short, we are just starting the announcements of the results of the Academy review and our implementation steps which Dr. Lee was about to discuss in terms of the various categorizations of these drugs.

Dr. LEE. The drugs have been categorized, Mr. Chairman, as ineffective, possibly effective, probably effective, effective but—in other words, requiring some change in the labeling—and those that are effective and require really no change in labeling.

Senator NELSON. Have you released any information on the 1,500 as to those which are ineffective, those which are probably ineffective, and so forth?

Dr. LEE. On a limited number. Mr. Goodrich can give you that information.

Mr. GOODRICH. Yes, we have. This has been done on a product basis as we receive the reports back. The first announcement was on a citrus bioflavinoid product on which the announcement was that the product was ineffective.

We gave notice of a proposal to withdraw the product from the market. The companies are resisting both at the administrative level and by suing us in the court in Alexandria for a declaratory judg-

ment to the effect that we haven't any right to examine the effectiveness of this class of drugs.

Senator NELSON. This is a prescription drug?

Mr. GOODRICH. No.

Senator NELSON. And they are contesting the legal authority of the FDA to act in this?

Mr. GOODRICH. Yes.

Let me go back. It is an over-the-counter drug for so-called capillary fragility, for bleeding states. The contention is that since the product became generally recognized as safe some years ago—it is essentially innocuous—that it is not subject to have the effectiveness review that is now going on. We, of course, are contesting that issue in the district court in Alexandria.

Senator NELSON. Under the law, if the drug is one of that class of drugs involved here and is found to be ineffective, does FDA have the authority to require its removal from the marketplace?

Mr. GOODRICH. We think so. The drug industry is contending in a suit that has been pending in Wilmington, Del., since soon after the enactment of the 1962 amendments that they have certain protections under the grandfather clause of the 1962 amendments. That case has never been pressed on to trial because of the pendency of the NAS–NRC review, and the plaintiff has been reporting to the court that it wishes to await further process in that review before deciding what to do about that pending action in Wilmington.

Senator NELSON. The National Academy is doing the review?

Mr. GOODRICH. Yes.

Senator NELSON. And they, I assume, are using consulting clinicians around the country?

Dr. LEE. Yes, sir, the Academy set up a number of panels with a chairman of each panel. They review all the data that is available, evaluate it and make their recommendations.

Senator NELSON. And on this drug they came to the conclusion it was ineffective?

Mr. GOODRICH. Yes.

Senator NELSON. Is the company contesting that conclusion?

Mr. GOODRICH. No, they are contesting our right to subject the article to administrative procedures of requiring proof of effectiveness. They would, of course, I think contend that they have some evidence that the product is effective. They have submitted that evidence to the Food and Drug Administration, and it has been reviewed and found to be wholly inadequate.

Senator NELSON. So what they would like is a chance to sell placebos at high prices?

Mr. GOODRICH. Right.

Senator NELSON. Please go ahead.

Dr. LEE. To return to my statement, Mr. Chairman, and to focus on the adverse drug reaction reporting system available to the Food and Drug Administration, we are trying to improve this system. And I would just like to cite a recent example in an article which revealed that among a group of patients hospitalized for chronic illness, 35 percent had at least one reported adverse drug reaction. Eighty percent of these reactions were either moderate or major in their severity. Only 20 percent were described as minor.

Some drug reactions are unpredictable and often have more to do with an unusual patient response than with any common side effect of the drug. Others, while predictable, are quite probably regarded as an acceptable risk in obtaining an important therapeutic effect. But many adverse reactions are needless, especially when an agent of serious potential toxicity is used in the treatment of a relatively minor illness.

The lesson of this and similar studies is clear, Mr. Chairman. The rational use of today's increasingly potent drugs requires not only continuous access to current, objective, and accurate drug information during the years of practice, but also a thorough medical school grounding in the principles of drug therapy. The task force strongly supports improvement in both of these areas.

Senator NELSON. You state that the rational use of today's increasingly potent drugs requires continuous access to current, objective and accurate drug information. Is there wide access on the part of the medical community now to objective, accurate drug information on all drugs?

Dr. LEE. No, I don't believe it is adequate, Mr. Chairman. If a physician wishes to seek out the information, he can obtain it. But there are a variety of sources that he must use, beginning with a textbook of pharmacology. There are textbooks on current drug therapy which usually are published every year or two, or brought up to date every year or two. The articles, of course, are prepared many months in advance of publication, so that it may mean that for a particular disease area the description is 1 or 2 or more years old.

He requires current information like the Medical Letter, which relatively few physicians subscribe to. The physician also requires information which we think can best be made available in a drug compendium. In other words, information on all the drugs that are available—factual, accurate information.

And this simply isn't available to the physician today, as Mr. Goodrich pointed out, except in the package insert provided with the individual drug. When a physician wishes to compare the effectiveness and side effects of one drug with other drugs he must go to the individual package inserts to get that kind of detailed information.

Senator NELSON. But does the doctor always have the package inserts?

Dr. LEE. No, sir, he rarely has them.

Senator NELSON. If he is just writing a prescription, the package insert is in the drugstore?

Dr. LEE. That is correct.

To return again to my statement, Mr. Chairman, we must begin with the medical schools. Pharmacology, it seems, is the stepchild of medical education. It is both a clinical and a laboratory science. But historically, it has been placed in the preclinical curriculum, far removed from the actual therapeutic situation. The clinical aspects of drug therapy appear to receive scant and insufficient attention and, as a consequence, many students emerge without the thoughtful and critical attitudes that are necessary to make wise therapeutic judgments.

Some forward-looking schools have added a second course in pharmacology, taught during the latter part of the curriculum, in which

stress is placed not only on the use of drugs in actual therapeutic situations but also on the evaluation of drug promotional claims. The task force believes that a clinically oriented course in drug therapy should be made a part of the curriculum in all medical schools, and it has recommended Federal support for this purpose.

We have also been concerned, Mr. Chairman, about the kinds of drug information and continuing education opportunities available to prescribing physicians.

A small number of publications and periodicals do contain the comparative, objective data that are needed. But the existence of these publications, which are highly regarded by expert clinicians, are largely ignored or unknown to the majority of practicing physicians.

Likewise, a small number of medical schools and other health organizations provide regular opportunities through postgraduate courses for prescribers to renew and expand their store of drug information. But these opportunities are relatively scarce and they, too, fail to reach the majority of physicians.

Most of the drug information received by practicing physicians comes from the advertising and promotional activities of drug companies—from printed and graphic advertisements and from drug salesmen known as detail men.

Senator NELSON. Your task force concludes that most of the drug information received by practicing physicians comes from advertising and promotional activities of drug companies and is printed in graphic advertisements and from drug salesmen known as detail men?

Dr. LEE. Yes, sir.

Senator NELSON. That is a fine commentary on the source of information that the great, distinguished medical profession uses in prescribing drugs for its patients. I think it raises a very serious question, and one which it seems to me the American Medical Association ought to be addressing itself to. In all the hearings I have had thus far they seem to be standing on the sidelines unconcerned about the continuing education of the medical profession. That is a disturbing matter to me.

Dr. LEE. We share your grave concern about this, Mr. Chairman. We think this is one of the more important observations made by the task force out of this wealth of material that was accumulated and evaluated. I think it is a matter of grave concern to the profession; it is a matter of grave concern to the medical schools that have the responsibility for providing the basic education for physicians; and, it is of concern to the public. The public should be aware of the fact that their doctors are obtaining their information about the drugs which they prescribe from the advertising provided by drug companies.

From the testimony presented before the subcommittee and from independent studies conducted by the task force staff, it is apparent that drug advertising is steadily being improved by the control of false or misleading claims, and those unsupported by adequate scientific data. Through the enforcement of new FDA regulations and cooperation of leaders in the drug industry, drug advertising is becoming more factual, informative, and accurate than ever before.

Senator NELSON. It is true, however, cases continually appear before the FDA in which the company is making claims for drugs which are not approved by the FDA, is it not?

Dr. LEE. That is correct.

Senator NELSON. We had that testimony last week on precisely that question. So you haven't solved the problem of getting the companies to comply with FDA standards, approved standards and guidelines in advertising of products either in the promotional advertising or in the promotion done by the detail man himself; is that not correct?

Dr. LEE. That is correct. And, of course, this is true not only for the drugs introduced between 1938 and 1962, which are currently under review by the National Academy of Sciences, but also in the drugs more recently introduced. In some of your recent hearings you focused on those problems very specifically.

It concerns me that many, if not most, physicians rely primarily on the companies' promotional material and on the detail men for drug information. The prime function of advertising is to sell drugs, and therefore, one cannot and should not expect such advertising to be fully objective.

Senator NELSON. Let me say at this point, Doctor, it seems to me that one of the serious problems is that the medical profession has had a misplaced confidence in the integrity of the manufacturers of the drugs. And if the manufacturers of the drugs were honestly presenting the case in an objective fashion, the medical profession would be justified in relying upon them.

But when they spend $600 million a year and develop over a period of years the confidence of the profession, the profession has then been led to believe that they can believe what the manufacturers say. And I think that is the tragedy here. And one of the sad parts of that is that the one group that has the qualifications to intervene and notify the physician that the manufacturers have been overdrawing their claims and making misleading claims is the profession itself, the American Medical Association.

I don't blame a physician if he has great confidence in the integrity of the company and then accepts the claims they make for it. The problem is, his confidence is misplaced and he does not know it. And the FDA has been unable to get through to make clear, apparently, to the profession, and the American Medical Association, their own professional organization has been grossly derelict in their responsibility toward notifying the profession about the improper claims being made by the manufacturers even in their own advertising, in my judgment. It is not wholly the fault of the physician in the sense that he has a misplaced confidence in a great and distinguished American industry.

Dr. LEE. I want to cite a few examples, Mr. Chairman, of some of our concerns. For example, with respect to the selling of drugs and the objectivity of advertising:

> That a drug is merely the minor molecular modification of an existing, well-proven product is seldom made known in advertising.
>
> Relative costs are seldom discussed in advertising.
>
> The relative advantages of other drugs in the same therapeutic class are likewise seldom mentioned in advertising.

The task force is concerned not merely with the content of drug promotion, but also its volume. Currently, the drug industry is spending nearly $500 million per year on drug research and an estimated $600 million on drug advertising, drug detailing, and other forms of

promotion. The sheer amount of this material has reached supersaturation proportions, and contributes, I am certain, to increasing confusion among doctors.

The task force has made three recommendations which, if implemented, Mr. Chairman, would help restore some balance to the provision of drug information.

First, we reaffirmed our earlier proposal, and yours, for the establishment of a Federal drug compendium, which would list and accurately describe not only the most popular drug products, but all of them, and which would also provide prescribers with some indication of relative costs.

Senator NELSON. Dr. Lee, as you know, I have introduced a compendium bill. The PMA did some kind of a survey which brought out the fact that the majority of the physicians were negative to the idea of a need for a compendium. I assume that is because the majority of them are confident that they are getting accurate, objective information from the drug company, which they are not. If they were, a compendium might not be necessary, although I think there are some other points in favor of such a publication.

You have to be able to compare the products, one product versus another, and one dosage form, and so forth. What about the question raised that it would be such a massive document that it would be unmanageable?

Dr. LEE. We don't agree with that at all. We think it is a perfectly manageable document, and not only that, but it is essential to achieving the objective of having available in the physician's office adequate information about all drugs. The complaints about the size of the volume are misplaced and not correct in our view.

Senator NELSON. Some suggestion has been made by those who oppose a compendium of all drugs that there be a compendium of the 600 most widely prescribed, which according to them, would cover 90 percent of the drugs.

Wouldn't it be correct, if you are talking about massive volume size, that you might very well divide your compendium into two parts: One, a compendium of the 600 more widely used drugs, and put it in one volume, covering 90 percent of the drugs; and in volume II of the compendium, put the balance. Would that be feasible?

Dr. LEE. Mr. Chairman, we don't think that is at all necessary. We don't think it would be a massive tome the size of a complete Webster's Dictionary. Part of the problem is the way in which the information is made available in the compendium.

I might just ask Dr. Silverman to say a word about this, because he has looked into this matter very carefully for the task force.

Dr. SILVERMAN. I think, Mr. Chairman, that producing a compendium consisting of a limited number of drugs based on current frequency with which they are prescribed would bring up this situation. If you so limit this to the 600 or 400, or whatever number you like, sir, most widely prescribed drugs, this—possibly, by coincidence—would omit most of the generic-name drugs on the market.

Dr. LEE. It would put them at a significant disadvantage.

Senator NELSON. I don't exactly follow that. I assume when they say "widely prescribed drugs" they meant prednisone, not Meticorten, Paracort, or other trade name.

Dr. SILVERMAN. Specifically, the low-cost generic-named drug is not in fact widely prescribed.

Senator NELSON. I wasn't thinking of it in those terms. I hadn't thought they were. I thought if you were going to list the drug, prednisone, you would list prednisone and you would list all those who produced prednisone whether it is generic or brand name, not just the company that is selling most of it.

Dr. LEE. That would be the approach that we think would be essential for the compendium. And, of course, really the crux of the resistance to the compendium is that it would be based on the generic name and not on the brand name of the product. The compendium would list drugs primarily by generic name, but also would list manufacturers and the trade name of the product. The organization of the volume would be on the generic rather than on the trade name.

Senator NELSON. I had assumed that there wasn't any dispute about that. Maybe I was in error. Obviously, in the case one was examining in some detail here, prednisone, the range, according to the Medical Letter, 59 cents to $17.90 a hundred, and their panels of physicians and consultants on the chemical evaluation of the drugs reached the conclusion that they are all equivalents.

So, if you only listed the brand which sold the most, you would be listing Meticorten and you wouldn't be listing Merck or Lannett or American Pharmacal that were running at prices of 80 cents, a dollar, $2.20. But I have been amazed at the number of doctors I have talked to, when I discussed the price in the article in the Medical Letter, who had been prescribing Meticorten for patients that it was in the marketplace not at $17.90 a hundred but in the marketplace at 59 cents a hundred. And they have no way of getting the information.

So if you had a compendium, you would know that these others are available in the market.

Dr. LEE. It is essential that adequate price information be available. In most cases this would be relative price information. This is part of the effort to provide physicians with accurate and adequate information.

Senator NELSON. And you are satisfied that you could list them all in the compendium, and obviously supply adequate, objective, detailed, scientific information about the drug?

Dr. LEE. Absolutely; yes.

Senator NELSON. How many drugs would that involve in the compendium?

Dr. LEE. How many drugs would be in the compendium?

Senator NELSON. I don't mean how many brands or generic names, I mean how many different compounds?

Dr. SILVERMAN. About 1,200 distinct drug entities, but the number of products would be perhaps in the tens of thousands.

Dr. LEE. Because of the different companies.

Mr. GORDON. Dr. Lee, you have talked about the most widely prescribed drugs. Are these necessarily the most useful drugs?

Dr. LEE. That is a very difficult question, because you have to consider that in relation to the individual patient receiving a drug prescribed by the individual physician. It is difficult to make a generalization. They were obviously prescribed by individual doctors because they were thought in circumstances and for the particular patient to be valuable for that particular situation or condition.

Based on our evaluation of the most commonly prescribed drugs, the fact that many are available generically, and yet they are prescribed by their brand name, we believe that the cost to the patient is higher than it need be. The cost of drugs is an important area of concern. But to say that they weren't the best drugs for the particular patient is impossible to say. It is very hard to generalize, Mr. Gordon, on that kind of question.

Mr. GORDON. Yet in discussing the role of the physician, you talk about rational prescribing. I question the rationality——

Dr. LEE. The task force also questioned it. Under existing conditions it is difficult, if not virtually impossible, considering the range of patients and the range of medical conditions that the physician has to deal with, and considering the lack of the kind of information that he needs, for the physician to make what we would consider to be rational prescribing decisions. I don't know that this is really possible or is in fact taking place.

Part of rational prescribing includes consideration of price. As you well know, this simply isn't available, or is very difficult to obtain. Most physicians simply don't have it.

Senator NELSON. For instance, you could have what is a very valuable drug, but a drug that was not valuable for the purpose it was prescribed. For example, chloramphenicol is very valuable as a drug, but it is irrationally prescribed when prescribed for acne, hangnails, sore throat, and so forth, as the testimony indicated before the committee. So in that case it certainly isn't a very valuable drug.

Dr. LEE. That is right. All those people for whom it was prescribed who did not have the conditions for which it is almost exclusively needed or for which it is the drug of choice, were the victims of irrational prescribing. You have mentioned a number of conditions for which chloramphenicol is not only not the drug of choice, but is not indicated. In years past it was unfortunately prescribed for a number of other conditions—the common cold, virus upper respiratory infection. In those cases, it was not rational prescribing.

Having been in practice, I know it can be very difficult prescribing correctly for a patient. The decisions are often very difficult, weighing the benefit of a particular drug in a particular patient with the possible side effects of that drug. Then you must add to these considerations the price of the drugs. You have to consider that as one of the elements in rational prescribing.

Second, in terms of the recommendations, we have proposed that the Federal Government either publish or support publication of a journal which would provide up-to-date guidelines on drug therapy. Although the Government might provide the funds, the actual content would represent the independent judgments of experts in drug therapy.

Third, we have urged Federal support for the efforts of local medical societies, medical schools, hospitals, and foundations to provide

continuing education courses for practicing physicians, emphasizing current applications of drug therapy.

Finally, Mr. Chairman, there is the subject of generic equivalence, which has been considered at great length by your subcommittee.

Here it is important to define a few terms. We have used the term "chemical equivalents" to indicate those multiple-source drugs which contain essentially identical amounts of the same active ingredient, in the same dosage form, and which meet all official standards.

Biological equivalents are those chemical equivalents which, when administered in the same amounts, will provide essentially the same biological availability, as measured by such parameters as blood levels or urinary excretion.

Finally, clinical equivalents are those which, when administered in the same amounts, will produce the same therapeutic effect as measured by control of a symptom or a disease.

Using these terms, I believe we can define the central issue quite simply:

Given two drug products which are chemically equivalent, will they give essentially the same clinical effects in human beings?

The task force has given serious study to this matter. In reaching our conclusions, we have reviewed the existing literature. We have had access to the results of new biological availability studies conducted as part of our operations by the Food and Drug Administration, and by Public Health Service hospitals. We have had the advice of workshop participants from the clinics and research laboratories of hospitals, universities, and industry. We have had the counsel of an advisory group on clinical trials, composed of distinguished experts representing clinical medicine, pharmacology, and biostatistics, as well as representatives of the official compendia with their responsibility for the maintenance of drug standards.

We have reached the conclusion that—except in rare instances—drugs which are chemically equivalent, and which meet all official standards, can be expected to produce essentially the same biological or clinical effects.

There are, as I have just mentioned, a few instances on record in which this has not been the case. One of these concerns chloramphenicol, and in this case the nonequivalent products have been promptly removed from the market.

Senator NELSON. All the chloramphenicols were batch tested prior to marketing, correct?

Dr. LEE. Yes, sir.

Senator NELSON. So there was not a USP standard established for that drug, was there?

Mr. GOODRICH. There was a standard established for it. The standard was found to be inadequate in assuring the biological availability.

Senator NELSON. Now, have certain changes in the standard been made?

Mr. GOODRICH. Additional proof of biological availability, using human volunteers, has been required as a prerequisite to certification. In addition to the chemical standard, we have found that it is necessary to test the formulation to make sure it gives a reliable blood level response.

Senator NELSON. Does this happen to be one of those rare drugs where the only test of equivalency is in fact a clinical test, or a biologic test, at least?

Dr. LEE. That is correct. In the case of chloramphenicol we have found that a biological test is required. We believe, however, that it is not necessary to have an additional clinical test in the treatment of disease when equivalent blood levels have been produced.

Senator NELSON. What I am getting at is whether the companies have now been admitted back to the market?

Mr. GOODRICH. By presenting evidence showing an adequate blood level response to the formulations. Now, this is not a situation such as we had some years ago with intrinsic factor in which you required a biological test for each batch. To the contrary, this is a formulation examination, some sharpening of the chemical standards, and on top of that, a requirement of the study of biological availability to make sure the drug was getting into a proper blood-level situation.

Senator NELSON. But those chloramphenicols were removed from the market and in order to come back on the market, they had to present a test of biological equivalency, and they have done that?

Mr. GOODRICH. Yes, sir.

Senator NELSON. Have you been able to establish an objective test out of all this? What have the firms done to their production methods that made the drug more quickly available physiologically, and if they have done something specific, could that be put into the standard?

Mr. GOODRICH. We should have our scientific people answer that in detail. I would be afraid to try to give you the exact details. I do know that some formulation changes were made, and that the tests of biological availability were required.

Dr. LEE. I think it is important also, Senator Nelson, to add that the FDA also requires good manufacturing practices and quality controls, so that we can assure the public that the steady flow of the drugs into the marketplace continues to meet the standards. To assure compliance the FDA carries out plant inspection and also test drugs obtained in the marketplace.

It isn't just meeting the standard. If we didn't have these other factors built in through the Food and Drug Administration I think it would be difficult to give the kind of assurance that is necessary.

Senator NELSON. Doctor, I will have to leave for 10 minutes. The Interior Committee has some important measures to dispose of, and they need me to constitute a quorum. So we will recess for 10 minutes, and I will be back.

(Recess.)

Senator NELSON. Please go ahead, Doctor.

Dr. LEE. Mr. Chairman, before returning to my statement, in your absence I reflected a little bit on the question that you and Mr. Gordon raised earlier with respect to the compendium. There is a point that requires more clarification. This has to do with the most commonly prescribed drugs and why we shouldn't list and describe them in a single volume and then list and describe the rest of the drugs in a second volume. The assumption behind this proposal is that this first volume would be the most frequently used by the physicians, and would be less bulky and more easily used.

Based on our studies and our conclusions regarding rationality and irrationality of prescribing, it could well be that if we put 400 or 600 drugs in this volume I, that we would be including a large number of drugs that were being prescribed not in a rational fashion. At the same time we might be describing the best drugs, the most appropriate drugs in the other, little used volume. This was a point that I really didn't make clear in my earlier statement as to why we believe that all drugs should be listed generically and not in relation to frequency of use. I think it was implicit in what you were saying and it is a point that needs to be emphasized.

Senator NELSON. On the problem of volume size, I guess in any event you could resolve it if it were too bulky, you could still have two or three volumes.

Dr. LEE. Surely you could, but it shouldn't be on the basis of frequency of prescribing.

Senator NELSON. Yes.

Dr. LEE. There was one other point while we are on this subject. In discussing the guidelines for physicians on drug therapy, I would just like to make a little clarifying point on that. One of the examples in the United States of such material is the Medical Letter. In Great Britain the Government publishes a Prescribers Journal.

I don't know if you have seen this. But it is a Government publication. The authors of these articles are totally independent of the Government. The journal includes excellent summary information on drugs for particular disease conditions. It is the sort of thing that I had in mind in my testimony, but in going over it quickly I did not emphasize this point.

Senator NELSON. This publication, as I understand it, is circulated in Great Britain, New Zealand, and Australia; did you say that in your testimony?

Dr. LEE. No; I didn't say that in the testimony. That is why I wanted to make the point. It is in the report, but it is not in my statement.

Senator NELSON. I saw it in the report.

Dr. LEE. That is right.

Senator NELSON. Has this publication received some public funds for support?

Dr. LEE. This is a Government publication.

Senator NELSON. It is a Government publication?

Dr. LEE. Yes, sir. It goes to the physicians without charge. In this country, a physician can subscribe to Medical Letter, but the number is rather small, perhaps 10,000 to 20,000 physicians.

Senator NELSON. We had testimony on that. I thought it was 10 out of some 200,000.

Dr. LEE. Yes.

Senator NELSON. Is this also in the nature of a compendium?

Dr. LEE. No. The Medical Letter and Prescribers Journal are quite different. They are what I call a guide to rational prescribing.

Senator NELSON. This is just a continuous flow of current information to the physicians; is that right?

Dr. LEE. Correct; by people who are expert in their particular field. It is very useful, but it is not readily available in this country.

On the question of drug prices, Dr. Novitch has brought to my atttention a very simple chart which the Ministry of Health makes available periodically to the physicians.

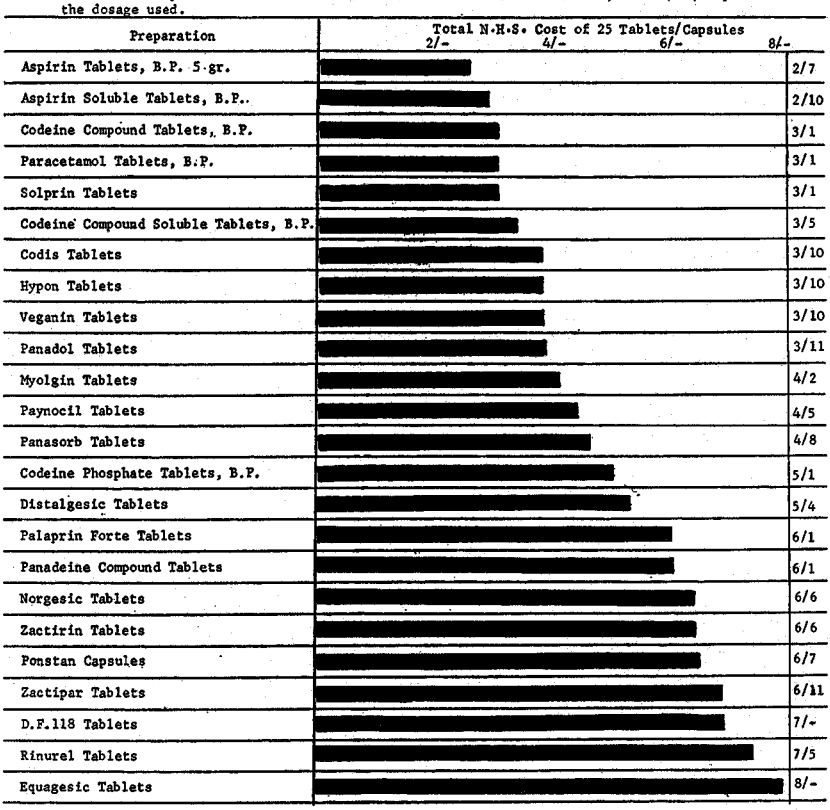
Senator NELSON. We will put that in the record at this stage in your testimony.

(The document referred to follows:)

Comparative Costs of

ANTIPYRETICS AND ANALGESICS

NOTE This list of preparations has been compiled from those commonly prescribed on Form E.C.10. The cost includes professional fee etc. The actual cost of treatment will, of course, depend on the dosage used.



Issued by the Ministry of Health
(E.C.L.43/66)

October, 1966
D76109/1/551v 75m 10/66 CL

Dr. LEE. It is just a simple, graphic statement, and very helpful to the physician. It is just a reminder. That could be issued in addition to the periodic updating of the compendium, which would include the information on prices. This sort of thing could be issued monthly or more often than that, if necessary.

Senator NELSON. I don't quite understand the graph at the first glance at it. Can you explain it?

Dr. NOVITCH. Mr. Chairman, this chart, published, I believed, in 1967, compares the prices of various analgesics and antipyretics—drugs for pain and fever. At the top is simple aspirin. It shows the cost of 25 tablets to National Health Service to be about 30 cents in U.S. currency.

Others are listed in the ascending order of cost. At the bottom, the most expensive is a combination product containing aspirin and meprobamate. And it sells for about 96 cents in U.S. currency. Others are single active agents selling for almost the maximum price listed.

The impression which the Ministry seeks to convey to practitioners is that—this comes along with the Prescribers Journal—some of the standard preparations are quite effective and available at less cost than some of the more expensive products on the market.

Senator NELSON. Thank you.

Dr. LEE. It it a matter of communicating really relative costs in a very simple direct fashion, and I think quite an effective fashion.

To return to my statement——

Mr. GORDON. May I ask a question, Dr. Lee?

Since that seems to be a rather simple type of publication, and it probably wouldn't be too expensive to publish it, why can't the Department of HEW publish it under its existing authority? Specifically, I have in mind section 705 of United States Code 21, where the Secretary may cause to be disseminated information regarding food, drugs, devices, and so on and so forth, dealing with the health and welfare of the people.

Dr. LEE. Several things. One is, I think that such a publication by a Government agency might be less acceptable to the medical profession than a non-Government publication even though the same people wrote the articles.

Second, if we were to undertake such a publication—it is an important part of our recommendation—and if the decision was made to do so, we would certainly want it thoroughly discussed before Congress as to whether it should be a Government or non-Government publication. I think that kind of issue should be thoroughly aired before the Congress because I think you would want to hear the alternatives, the costs of alternatives, and their likely acceptance before a final judgment was made.

Mr. GROSSMAN. Doctor, may I ask you a question with regard to equivalency? Could you tell me how many drugs you tested to date in making a determination?

Dr. LEE. How many drugs we have tested in the Food and Drug Administration and the Public Health hospitals?

Mr. GROSSMAN. Yes.

Dr. LEE. Dr. Novitch.

Dr. NOVITCH. The present Food and Drug Administration tests are concerned mainly with antibiotics. A total of 44 products—that is, representing all manufacturers—are under test now. The exact number of drug entities involved is less than a dozen. Two drugs are under study in Public Health Service hospitals.

Mr. GROSSMAN. Do you anticipate that more drugs will be tested?

Dr. NOVITCH. Yes. We have not only recommended that the tests continue, but that Federal funds be expanded.

Mr. GROSSMAN. Let me ask you this for information. You say you reached the conclusion that except in rare instances drugs which are chemical equivalent, et cetera. Is this conclusion based on what you have done in the past, or what you surmise will continue in the future, or how does this work?

Dr. NOVITCH. It is based largely on past experience. But also, the goal of FDA's present efforts is to seek new standards which could make it possible eventually to use laboratory tests in place of the biologic availability studies that are now required with chloramphenicol. The major goal is to achieve some sort of correlation between prospective new standards and the clinical studies that are now underway.

Dr. LEE. Of course, this also involved a review of the available information and the literature on various studies that had been done.

Mr. GROSSMAN. My problem is, you say this is your conclusion, and I assume based on a thorough, complete, final study.

Dr. LEE. As new drugs emerge, new studies will be required. Thus it has to be a continuing study. This has now been established as a continuing activity within the Department.

Mr. GROSSMAN. Am I correct in saying that as far as all drugs that are presently on the market are concerned, you would make this conclusion or statement?

Dr. LEE. Yes, you can draw that conclusion from our statement.

Mr. GROSSMAN. And have all drugs in fact been tested for this purpose?

Dr. LEE. For clinical equivalency, no. But you think that, based on the evidence that we examined, both from the literature and from the clinical studies and from the biological studies, from the standards that have been developed over a number of years, our conclusion was that there are relatively few where there will not be clinical equivalency when you have chemical equivalence.

Senator NELSON. Meeting USP——

Dr. LEE. Meeting the standards. And, of course, we are updating the standards. Efforts are currently underway to update those standards.

Mr. GROSSMAN. Dr. Lee, I think it was in the New York Times of Tuesday, July 16—I remember when this came out, because there was a big furor about it—and since that time I have heard different reports as to what the truth was of the article which appeared, I think, in the Washington Post, implying that the FDA had found that there were differences in drugs in equivalency.

I know it mentions chloramphenicol specifically, but it also mentioned other drugs. There was a lot of confusion, and I heard this was a false report, and somebody let this out when it shouldn't have come out. Can you clear this up for us?

Dr. LEE. I am not exactly certain of the study to which you referred, but I believe it was the study that was conducted at Georgetown University. And if I recall correctly—we can provide you a more detailed statement for the record—there were three drugs. One was chloramphenicol, and one was a sulfa drug, and the other was diphenylhydantoin, which is used for the treatment of epilepsy.

In the drugs that were tested the requirements differed. The sulfa drugs, which are used primarily to treat urinary tract infections, required the careful analysis of the urinary excretion rates and the

availability of the drug in the urinary tract on an around-the-clock basis.

In the testing of drugs used for the treatment of seizures, one of the generically equivalent drugs was absorbed more rapidly and had a higher blood level than the brand name drug. In this case it might be necessary to do clinical studies to determine if that is clinically equivalent, clinically effective when you find these biological differences.

There are some statistically significant biological differences that we did not consider clinically important and which Dr. Ley, in commenting on this report, did not consider significant. At the time of the publication of the report the implication was made that you could generalize from the study of these three drugs.

Mr. GROSSMAN. It says, "Already the statistics have shown that two grams of the drug may have the same chemistry and behave differently in the human body." And the whole emphasis of the article is to show that, with a big picture of Dr. Ley setting next to you right here.

Dr. LEE. We can provide you with Dr. Ley's statement made at the time, because I think that clarifies it. It is difficult recalling from memory the content of an article published 2 months ago. But I would be glad to supply more detailed information on those three particular drugs.

Mr. GROSSMAN. I would appreciate that. Thank you.

Mr. GORDON. As I understand it, as far as the sulfa drugs are concerned, the differences were not clinically significant; is that correct?

Dr. LEE. That is my impression, Mr. Gordon. I believe that the differences were not statistically significant. To be certain, however, we will provide that for the record. I don't want to try to recall this from memory when we do have and can provide you with specific information.

(The subsequent supplemental information submitted by Dr. Lee follows:)

In late 1967, Parke Davis and Company presented data to the Food and Drug Administration indicating that several brands of chloramphenicol on the market gave lower blood levels than those produced by the preparation for which the Parke Davis' new drug application had been previously approved. Under its contract with Georgetown University, the FDA arranged for blood level studies on chloramphenicol, and a number of other drugs, including sulfisoxazole, and sodium diphenylhydantoin.

Dr. Christopher M. Martin and associates at Georgetown administered chloramphenicol capsules to healthy volunteers in a group of studies comparing the blood levels of Parke Davis' Chloromycetin with those of two generics. Georgetown concluded that the generic chloramphenicol capsules gave significantly lower blood levels than Chloromycetin and the drugs could not be considered therapeutically equivalent to the Parke Davis product. FDA then conducted further experiments on chloramphenicol capsules from other manufacturers, and its conclusions were similar to those of Georgetown.

Similar experiments, also on healthy volunteers, were conducted at Georgetown with three different manufacturers' sulfisoxazole tablets and three manufacturers' sodium diphenylhydantoin capsules. The FDA's review of these data led to the conclusion that there were no significant clinical differences between the three sulfisoxazole products. The data developed from the diphenylhydantoin experiment, are indefinite, and do not permit a conclusion of any clinical significance with respect to these drugs at this time.

Data from the Georgetown work have been useful to the FDA, but these studies provide no basis for concluding that generic products "work less well" than the brand-name product.

Dr. Christopher Martin later presented a paper on the studies on the three drugs which had been conducted for the FDA at Georgetown University before the American Society for Pharmacology and Experimental Therapeutics at the University of Minnesota. In announcing his results, Dr. Martin implied that all of these drugs showed a lack of equivalency. Since his conclusions were without proper justification, the Commissioner of FDA issued the attached press release on August 20, 1968, setting forth FDA's position with respect to the Georgetown study on clinical equivalency.

[For release, p.m.'s, Tuesday, Aug. 20, 1968]

"The Food and Drug Administration has in no sense concluded that 'generic' drugs are less effective as a class than 'brand-name' products," FDA Commissioner Herbert L. Ley, Jr., M.D., declared today.

"In my opinion, there are fewer than two dozen drugs where therapeutic differences among competing products may be a problem," he said.

Dr. Ley's comments were made in response to a report today on the results of studies on three drugs conducted for the FDA at Georgetown University. Dr. Christopher M. Martin presented the paper at the fall meeting of the American Society for Pharmacology and Experimental Therapeutics at the University of Minnesota.

"Data from the Georgetown work have been useful to the FDA, but it is completely unwarranted to reach any general conclusions about drug equivalency on the basis of these exploratory studies," Dr. Ley said.

Only one of the three drugs tested showed a clinically significant difference in blood levels produced by the various products administered to volunteers, the FDA Commissioner pointed out.

"Jumping beyond that to the conclusion that there are serious doubts generally about the effectiveness of 'generic' versions of drugs simply isn't valid," Dr. Ley said.

The FDA now is sponsoring comparative studies on more than a dozen drugs, but Dr. Ley said the Agency will not announce its conclusions until it has accumulated definitive data.

Senator NELSON. Just on the point of your conclusion that when drugs are chemical equivalent and meet all the chemical standards they are therapeutically equivalent except in rare instances, as you are aware, we have had distinguished pharmacologists and clinicians appear before the committee and give the same testimony. And I assume that when you refer to the fact that you have relied upon the literature, and clinicians, and past experience, and so forth, that that also involves the rather vast experience of the Defense Supply Agency, the VA, and general hospitals and others who buy on competitive bidding. And on one occasion they get one brand of prednisone or one brand of chloramphenicol—that isn't an example—one brand of another drug.

Dr. LEE. Tetracycline.

Senator NELSON. And their experience over the years has been that if they meet the same standard and have the same chemical composition, that they are therapeutically equivalent; is that correct?

Dr. LEE. That is correct. Because this is a highly charged and controversial area, the task force made a very extensive study. The task force study has been going on for well over a year. We consulted with the leading experts in the field; our staff reviewed the literature; we had the special studies carried out; we reviewed the experience of the Defense Supply Agency and other agencies who have had just the kind of experience that you have described. Our conclusions really are based on a detailed examination of the information that is available today.

Senator NELSON. Thank you.

Dr. LEE. To return to my statement, and the comment that Dr. Goddard, former Commissioner of Food and Drug made, he expressed the view that such nonequivalency might be found among perhaps two dozen drugs. Nothing which has been discovered during the past year has caused the task force to dispute Dr. Goddard's prediction.

Nevertheless, Mr. Chairman, it is evident that the issue of chemical equivalency and clinical equivalency has been clouded by articles, publications, press statements, and promotional claims which seem designed to make the issue appear much larger.

One example is a recent publication entitled "Bibliography on Biopharmaceutics," which contains 501 documented references dealing with the influence of pharmaceutical formulation on the therapeutic activity of drugs. According to its publisher, this volume supposedly refutes what is termed the "myth of therapeutic equivalency."

We have had this book reviewed by the professional staff of the task force, by the Food and Drug Administration, and by our consultant experts. They are in agreement on the following points:

1. The publication is a useful compilation of references on the subject of biopharmaceutics.

2. Of the 501 references, only 221 were actually conducted in human subjects.

3. Of the 221, only 76 were—by the authors' own evaluation—adequately designed or controlled experiments.

4. Of the 76, only 12 represented comparisons between what might seem to be different brands of the same chemical equivalents.

5. Of these final 12, most compared different dosage forms—such as tablets versus effervescent solutions—or different salts—such as sodium derivatives versus potassium derivatives or different coatings—such as delayed release products versus rapid release products. Some of the products studied failed to meet existing USP or NF standards, and thus would be illegally on the U.S. market.

And just to make the point, Mr. Chairman, 12 out of 501 references.

Accordingly, it appears that there were only two or three which demonstrated statistically significant lack of clinical equivalency, and in one case, the differences were described as being without any practical clinical importance.

The finding that only two or three of the 501 citations in this book represent significant lack of clinical equivalency would therefore seem to be consistent with the statement in the task force report that "lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."

Senator NELSON. I might say that I read the Pharmaceutical Manufacturers Association release on this, and I was quite astonished. And then I wrote to the Secretary of HEW, Mr. Cohen, and called this to his attention, and then received a memorandum analysis back from Dr. Silverman, who analyzed this.

I think this is one of the problems—I think this is just another example of the association itself again making a terribly misleading claim which just doesn't hold water at all—and this has happened time after time after time—a distorted picture which may stand now totally refuted by the analysis of the Department of Health, Education, and Welfare.

And I am just curious to know when the Pharmaceutical Manufacturers Association is going to stop this nonsense, and, as Mr. Stevenson said one time, talk some sense to the American people. It gets a little worrisome spending time checking on the accuracy of PMA's statements. But this kind of statement gets circulated widely over the country, and the doctors read it, and the doctors say, it is true again, there is no generic equivalency, we have got another piece of proof. And probably by the expenditure of millions and millions of dollars they just brainwash the country with falsehoods.

And every time I catch them we are going to have a public hearing and expose them. If nobody else is going to do it, I am going to do it, because they are doing a disservice to the public health and the medical profession, and they are doing a disservice to the drug companies they represent, and they ought to be pulled up short on the halter when they do it.

And I am pleased to have this documentary evidence placed in the record. And I will insert the letter of Mr. Cohen as well as the response of Dr. Silverman.

(The information referred to follow:)

SEPTEMBER 9, 1968.

Hon. WILBUR COHEN,
Secretary, Health, Education, and Welfare,
Washington, D.C.

DEAR MR. SECRETARY: On August 5, 1968 the Pharmaceutical Manufacturers Association distributed a "Bibliography on Biopharmaceutics" accompanied by a press release, both of which are attached.[1]

Since your Department's Task Force on Prescription Drugs has been concerned with the matter of therapeutic equivalency, I would appreciate your comments on the attached documents.

Kindest personal regards,

Sincerely,

GAYLORD NELSON,
Chairman, Subcommittee on Monopoly.

NEWS RELEASE OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

WASHINGTON, D.C., August 5, 1968.—The scope and importance of the science of "biopharmaceutics" are detailed in an extensive bibliography just pubilshed by the Pharmaceutical Manufacturers Association.

"This unique publication refutes the astonishing myth that there are no significant differences among dosage forms of the same drug," C. Joseph Stetler, president of the association, said.

The bibliography contains abstracts and journal references on the influence of pharmaceutical formulation on the therapeutic activity of drugs. Listed are 501 citations. They establish a literature base in a field where, in a broad sense, some ten thousand articles are published annually.

The compilation is an outgrowth of testimony presented before the Monopoly Subcommittee of the Senate Small Business Committee. In these hearings some witnesses suggested that differences in formulation of drug products were negligible or of minor significance in their effect on patients.

"The bibliography lists well-designed clinical studies to show the opposite is true," Mr. Stetler said. "They describe clinically measurable differences among widely varying and widely used classes of drugs beyond those already documented in the hearings."

"Since different formulations of the same drug made by the same manufacturer may produce different results in patients, it is hardly surprising that the same drug made by more than one company may differ even more markedly," Mr. Stetler explained. "No two companies make a drug in exactly the same way.

[1] The "Bibliography on Biopharmaceutics" has been retained in committee files.

Thus the variations denoted in the articles of this bibliography, whether subtle or pronounced, can have significant effects in patients."

"It is interesting to note," the PMA executive added, "that the extensive research required for this study failed to turn up a single reference establishing that all formulations of the same drug from a variety of sources are equivalent—or even probably equivalent. Yet this invalid assumption has been made repeatedly in proposed legislation at both state and federal levels."

Studies in the compilation indicate that drug uniformity cannot be established simply by testing the end product.

"Thus compliance with such standards as the United States Pharmacopoeia and the National Formulary is no guarantee of product effectiveness in actual patients," Mr. Stetler asserted. "This is not to imply any criticism of the USP and the NF, both of which have done outstanding work in developing drug standards. But it is to say that therapeutic equivalence can only be shown in the clinic or by well-designed *in vivo* or *in vitro* presumptive testing, complex and exceedingly costly as this may be."

"In the final analysis, the excellence of a product must depend upon the excellence of the manufacturer. There are no substitutes for quality control of a high order and consistently good manufacturing practices," Mr. Stetler said.

The PMA president pointed out that because of budget and manpower the FDA concentrates its inspections in major company plants, being unable to give much attention to the smaller firms that have the greatest number of product recalls.

"Yet member firms of the PMA, producing 95 percent of the nation's prescription drug supply, have only 20 percent of the recalls. Companies making only five percent of available drugs are identified with 80 percent of the recalls despite little regulatory attention. Such a record should be a warning to those who blandly assume the equivalency of drugs produced under a variety of conditions," he stated.

"To deny that formulation is important is to deny the very basis of the profession of pharmacy," Mr. Stetler said.

Of the 501 citations in the bibliography, 221 cover *in vivo* human studies, with the remainder concerned with studies in animals as well as *in vitro*. About 20 percent appeared originally in the *Journal of Pharmaceutical Sciences* of the American Pharmaceutical Association.

"It should be borne in mind," the preface to the bibliography states, "that there is a massive body of information concerned with such subjects as: the stability of an active ingredient in a pharmaceutical formulation and the stability of the formulation itself as well as with preservatives, sterility, flavors, and other significant pharmaceutical factors which ultimately affect the therapeutic activity of a drug. Articles on these topics, however, were generally excluded..."

(Definition of biopharmaceutics: a field encompassing the study of the relations between the nature and intensity of the biological effects observed in animals and man and the following factors—the nature of the form of a drug, such as ester or salt; the physical state, particle size and surface area; the presence or absence of adjuvants; the type of dosage form; and the pharmaceutical process used in manufacturing).

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., September 24, 1968.

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

DEAR SENATOR NELSON: I have asked the professional staff of the Department's Task Force on Prescription Drugs to review the Pharmaceutical Manufacturers Association publication, *Bibliography on Biopharmaceutics*, as requested in your letter of September 9.

I am enclosing for your information a report prepared by the Task Force staff director, Dr. Milton Silverman.

Sincerely,

WILBUR COHEN, *Secretary.*

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
September 13, 1968.

To: Philip R. Lee, M.D.
From: Milton Silverman, Ph. D.
Subject: Bibliography on Biopharmaceutics.

On August 5, 1968, the Pharmaceutical Manufacturers Association released a publication entitled *Bibliography on Biopharmaceutics*, citing 501 references on the influence of pharmaceutical formulation upon the therapeutic activity of drugs.

In an accompanying news release, a PMA spokesman stated: "This unique publication refutes the astonishing myth that there are not significant differences among dosage forms of the same drug."

This statement in itself is somewhat astonishing. Among responsible scientists and clinicians, we are not aware of any doubt that there may be significant differences. The important question is how often these differences occur, and what threat they pose to the welfare of patients.

Here it is important to agree on the groundrules for the analysis—obviously, there will usually be substantial cilnical differences between two products in different dosage forms, such as one in solution and one in tablets, or one in a coated tablet and one in an uncoated tablet.

But that is not the issue. The important question is whether or not there will be clinically important differences when two different products, containing essentially the same amounts of the identical active ingredients, in the same dosage form, both meeting USP, NF or other official standards, are administrated in the same way—and whether this can be demonstrated in human subjects through properly designed, valid experiments.

With this in mind, it seemed desirable for the Task Force, its consultants, and the Food and Drug Administration, to review the new publication, with its 501 references. The following points were obvious:

Of the 501 references, only 221 were actually conducted in human subjects.

Of the 221, only 76 were—by PMA's own evaluaton—"adequately designed or controlled" experiments.

Of these 76, only 12 represented comparisons between what might seem to be different brands of the same chemical equivalents.

And of these final 12, most compared different dosage forms (such as tablets versus effervescent solutions), or different salts (such as sodium derivatives versus potassium derivatives), or different coatings (such as delayed release products versus rapid release products). Some of these final products failed to meet existing USP or NF standards, and thus would be illegally on the U.S. market.

At the most, Task Force staff and our consultants agree, there were only two or three which demonstrated statistically-significant lack of biological equivalency, and in one case, the differences were described as being without any practical clinical importance.

In summary, it seems evident that the new publication represents a useful compilation of the literature on this subject.

The finding that only two or three of the 501 citations in this book indicate significant lack of clinical equivalency would seem to be consistent with the Task Force statement that "lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."

Dr. LEE. Mr. Chairman, I have tried to suggest several of the major issues pertaining to the use of prescription drugs which both your subcommittee and the Secretary's task force have examined in very considerable detail. As you know, the work of the task force—like that of the subcommittee—has been much more extensive than is reflected in my presentation. And our work is continuing, leading, as I have indicated, toward recommendations on the vitally important—indeed central—question of including under medicare coverage of the cost of out-of-hospital prescription drug costs. This

issue alone is of tremendous importance to the task force, your subcommittee, and the American people.

My colleagues and I will be pleased to answer any questions you may have.

Senator NELSON. I would like at this moment to just read into the record a paragraph from a letter I received from Dr. Robert E. Howard, of Cincinnati, Ohio, president of Ohio State Medical Association, a letter dated October 18, 1967.[1] The reason I read this paragraph is because it is, I think, a rather dramatic example of how successfully the manufacturers with their advertising have brainwashed distinguished medical people in this country. Listen to what he says in the paragraph:

> We have not even produced any scientific data or substantive expert testimony which has been offered the subcommittee to support the claim of generic equivalence of drugs. Indeed, we are certain that such evidence has not been placed before you because we know it does not exist.

I don't know how he knows it does not exist but he knows it somehow.

> A comprehensive study of this question, so basic to your entire inquiry, is now being made with the Department of Health, Education, and Welfare at the direction of the President. When it is completed, we feel confident it will illuminate the fallacy of so-called "generic equivalent." We urge you to withhold until then judgment on the testimony, the sweeping claims, the unsupported generalizations you have heard over the past several months, for without incontrovertible scientific evidence, this controversy cannot be resolved by the public or the Members of Congress.

Dr. LEE. I would just comment, Mr. Chairman, that we believe now that we have made that scientific evidence available to the committee. Certainly we have reviewed it, and it forms the basis of our recommendations.

Senator NELSON. I just want to commend the HEW for what I think is an exceptionally fine start on the evaluation of a rather comprehensive problem, and I think it is a great public service.

Dr. LEE. We hope that the background documents, Mr. Chairman, which we will be making available, and of which initial publication is to start fairly soon, will be very useful far beyond their value to our task force. We believe they will be very useful to your subcommittee, and to many other committees of the Congress, to the scientific community, to physicians, and to consumer groups for further analysis and evaluation. There is really a wealth of material available in these background documents, and we think that it will add to public understanding of the problem, as well as a better understanding by the scientific community and the medical profession of these complex problems.

Senator NELSON. As these various task force reports become available, it will probably be valuable and helpful if we could have hearings on them and explore the implications of what your findings are for our own hearing record, if you are willing to appear on them.

Dr. LEE. We would be delighted to do so.

Senator NELSON. Mr. Gordon.

Mr. GORDON. Dr. Lee, in the release issued by the Pharmaceutical Manufacturers Association is the following statement: "In these hearings"—referring to the hearings held by this subcommittee—"some

[1] See app. I, p. 3861, infra.

witnesses suggest that differences in formulation of drug products were negligible or of minor significance in the effect on patients."

As far as I know, none of the witnesses before our subcommittee discussed differences in formulation of drug products. The subject we discussed was clinical equivalency. Would you explain for the record the difference in the meaning of these two terms?

Dr. LEE. The formulation of drug products—there are a variety of factors that go into that in their different dosage forms. A single drug may be prepared as a capsule, tablet or in liquid form. There are also different kinds of liquid preparations. These are different dosage forms. In the formulation of a tablet changes can also be made, for example, different degrees of compression of a tablet may produce different effects biologically or clinically.

There are a number of factors that go into formulation. In certain cases the different formulations will affect either the biologic equivalence or the clinical equivalence of a particular chemically equivalent drug. But what we are talking about when we are talking about clinical equivalence or biological equivalence, we are talking about the identical dosage forms, and we are not talking about different formulations. I think that should be made clear.

Mr. GORDON. This really tends to confuse rather than illuminate.

Dr. LEE. I would agree with your statement.

Mr. GORDON. Doctor, on page 61 of your task force report you say that one of the prerequisites for rational prescribing is knowledge by the physician of "the advantages or disadvantages of alternative forms of therapy."

As I understand it, the physician must know the relative safety and efficacy of drugs to determine which one is most suitable for his patients. Am I correct in that?

Dr. LEE. Yes.

Mr. GORDON. How can the average practicing physician make such determination, even if he had the labeling?

Dr. LEE. He bases it, of course, on various sources of information that he has. His interpretation of this information, and the particular circumstance under which he is prescribing the drug for an individual patient.

We don't have, as I indicated, in a form readily available to physicians the kind of information that is available to the British physicians through the simple, regular Prescribers Journal furnished by the Government. The Medical Letter fills that need for those physicians who utilize it. It is an excellent publication. But unfortunately most physicians don't receive it and don't read it. As a result there isn't available to most physicians an up-to-date comparative evaluations of drugs with respect to given conditions.

There are a number of textbooks that have been published and are available to physicians, but I am sure that they are not in every physician's office. Usually, when faced with a question about a drug, the physician will turn to a book that consists of paid advertising, the Physicians' Desk Reference. The material in there, of course, includes information on post-1962 drugs, and it also included information on drugs from 1938 to 1962, and even before. Because it may include data on these earlier drugs we can't always have assurance that that includes the best information available on effectiveness.

There is not included in PDR the kind of objective comparison that I think would be most beneficial to the physician. Even the specialist physician—that is, one who deals with people with a limited number of conditions, let's say a rheumatologist—for considerable difficulty in making judgments as to one drug versus another in an individual case. It is a tough proposition, even if you are well informed about a narrow area, to keep up to date. It is difficult to make the judgments, I would say, under the best of circumstances.

Mr. GORDON. Do you think that the compendium will eventually carry this type of information?

Dr. LEE. No, that is not the intention of the compendium. I think we need, as I indicated in my testimony, information to the physicians on an up-to-date basis on the alteratives. Again, I cite the Medical Letter and the Prescribers Journal which is available to British physicians, that is the kind of information the physician needs on a regular basis. These prescribing guides, if you wish to call them that, are quite different from the proposed compendium, which would be a compendium of all the drugs. The compendium would be a reference for the physicians, and would include price information.

I see those as two different, but complementary, sources of information that are essential for the physician today as drugs get more potent and as problems get more complex. Just as the potential for good is much greater, the potential for harm is very much greater because of these advances in drug therapy. In the reference I cited in my testimony, of a group of patients in a chronic disease hospital, 35 percent of them had adverse reactions of one sort or another to drugs which had been prescribed by physicians in an institutional setting where they were obviously very concerned about the problem.

Senator NELSON. In your testimony you state that the promotional activities of the drug manufacturer to advertising displays and detail men were, in the judgment of the task force, the most influential factor on the prescribing habits of the physician.

Last week we had 3 days of hearings, and three cases were presented by the FDA showing three different drug firms that had gone beyond the approved and agreed limits in making claims for their drugs, especially the detail men. Do you have any ideas—since this is such an important factor in the prescribing practices of the physician—do you have any ideas on how we could better control this activity, particularly by the detail men?

Dr. LEE. Of course, you put your finger on an area that we are just beginning to really look into in great detail. The Food and Drug Administration has, since the 1962 amendment, taken on certain priority areas, and has dealt with these, I think, with vigor and effectiveness. I would like to ask Mr. Goodrich to say just a little bit about the present efforts to understand more of the activities of the detail men, and to see what in fact can and should be done to deal with the problem, because there is no question about it, it is a problem.

Mr. GOODRICH. Simply as we noted last week, Senator, when we were testifying here, after we received the sales bulletins which you were good enough to send us, it became obvious to us that we needed a good deal more information about detailing practices.

And so we organized an investigation which has been started to get together information both on the printed materials that are used by

detail man in showing—in explaining his product to the prescriber, and the sales material, if we can get ahold of it, that is used within the company in educating the detail man, the bulletins, the training bulletins, and training things of that kind.

This investigation has just started and will be pursued until we get enough information on this important aspect of drug promotion to have some judgments on it. And this is where we are at the moment.

Dr. LEE. We really don't know enough at the moment, Mr. Chairman—and I think that you have really highlighted this area as a singularly important one. It is one where we will be attempting to get the kind of information that is necessary to make wise and sound judgments.

Senator NELSON. You don't have any notion of when that aspect of your task force study will be completed?

Dr. LEE. This is not a task force function, this is a responsibility of the Food and Drug Administration, and it is an ongoing responsibility.

Senator NELSON. And the remaining investigation of this specific point now?

Dr. LEE. Yes, sir.

Senator NELSON. I had just one more question. The minority counsel raised the question about the testing of drugs by the FDA. It occurred to me that you might have been thinking of the program launched by Dr. Goddard to take a certain number of commonly prescribed drugs and work up a comparison of equivalency among the various compounds—the various makes of the same drug. Is that program proceeding now? What is the status of it?

Dr. LEE. Dr. Silverman, do you want to describe the current status?

Dr. SILVERMAN. I think, Senator, that it might clarify the situation if I could throw a few dimensions of this ball game into the testimony.

There has been a good deal of discussion, sir, about the magnitude of this problem, with the possibility that many hundreds or thousands of drugs would have to be tested, and that this would be beyond the present or possibly the future potentialities of the Government. The actual situation is far from this, sir. I think I can illustrate this best by indicating the actual number of drugs that might require testing. We have looked at this very carefully in terms of the drugs which are now used by the elderly. We have studied the top 400-odd, and with very minor exceptions, these would probably apply to the population at large.

Senator NELSON. When you say hundreds, are you talking about 400 different——

Dr. SILVERMAN. Drug entities, which may represent many times this number of products.

Of these, approximately 70 percent or more are still under patent. There are no generic equivalents legally on the market. Of the other 30 percent, a number have chemical or physical characteristics which would make them seem less essential for testing.

Here we have set up our own series of priorities. We have taken those drugs which in the first place are, in our terminology, critical drugs, involved at least potentially in lifesaving situations or in the control of seriously diseased conditions.

Among those, we have taken those which are in solid form, tablets and capsules, and the general feelings based on the state of the art is

that these drugs which are already in solution will be absorbed very rapidly.

Among those which are in solid form, we have given top priority to those which are of relative low solubility, with relative insoluble active ingredients. Those which are highly soluble, those which it has been demonstrated by some of the FDA and Public Health hospitals, are quickly dissolved.

Of the drugs which we feel demand top priority, there are only two or three dozen drugs which will require testing at the outset. This is not an inhuman job by any means, and we are on our way to doing it.

But this job, Senator, will never be completed. Because as soon as a drug comes out from under patent, and it becomes legally possible to make new generics, these will probably have to be looked at in the same way.

I recognize that there is one school of thought which says that we cannot make any statement about generic equivalency or lack of equivalency until we have tested all generics. In a way, this is true. Thus, we cannot say that all the tablets of a particular product meeting USP requirements will meet those requirements, because we have tested only a certain sample—and the only way we could test them all would be to destroy them all—but I think this kind of sampling although it is not 100 percent sure, gives us the practical protection that we require.

Senator NELSON. As I remember it, Dr. Goddard was intending to select x number and complete some kind of a study within the limits of some particular period of time; isn't that correct?

Dr. SILVERMAN. It is our expectation, sir, that the top priority drugs will be completely assayed by 1970.

Senator NELSON. 1970?

Dr. SILVERMAN. Yes, sir.

Dr. LEE. There is one other aspect of this, Mr. Chairman. One is this continuing study which Dr. Silverman has described. And the other is the sampling of drugs in the marketplace to make sure that they do in fact meet the standards, as an additional protection for the consumer of the drugs. The drugs tested will be taken out of pharmacies, drugstores, and sampled and tested in the FDA laboratory in St. Louis. This will be a continuing surveillance operation to make sure that even with the good manufacturing practices and even with meeting the official standards, that, in fact, in the marketplace the drugs continue to meet the requirement standards.

Mr. GORDON. I have one nitpicking question. You say there are only two or three which demonstrate an initial lack of equivalency and one of them has no practical clinical importance. Are there two or three? Which is it?

Dr. LEE. Dr. Silverman.

Dr. SILVERMAN. There are two. One of them, as you have probably surmised, is chloramphenicol.

Mr. GORDON. There are two, but one has no practical——

Dr. SILVERMAN. The second one is tetracycline. And in the article cited in this publication, the scientists who wrote the article pointed out quite clearly that although differences were detected these were not of any clinical importance.

Mr. GORDON. So we actually come down from the 501 to one?

Dr. SILVERMAN. No, there are two. There are differences which are statistically obvious.

Mr. GORDON. But therapeutically, clinically——

Dr. SILVERMAN. There is one. There was a third which is in a kind of gray zone, and I wouldn't care to state whether this does or does not belong in this category.

Mr. GROSSMAN. One last question: I take it that you have not come to any conclusions yet as to what type—or whether there is a need for a drug formulary, and the relative cost. You talk about costs here sometimes when we were talking about the compendium. I take it that that is separate.

Dr. LEE. That is a separate matter that is still under study and evaluation. When we make the final report to the Secretary as it relates to coverage of prescription drugs under medicare out of the hospital, we will make our final recommendations, as it relates to the formulary.

Mr. GROSSMAN. Do you anticipate that you will make a decision as to a recommendation between the approach taken by Senator Long for a national formulary and that taken in another bill introduced by the minority members of this committee on regional and State formularies?

Dr. LEE. I think we are examining the alternatives with respect to formularies, and the results of ongoing programs using formularies, trying to get as much data as we can on this issue, and the potential cost savings. We will make specific recommendations that will deal with this.

Mr. GROSSMAN. But you weren't implying that the costs would be included in the compendium?

Dr. LEE. The costs, yes, sir; relative costs should be either in the compendium or as a companion publication brought up to date on a regular basis, so that the physician has that information available.

Mr. GROSSMAN. But that is not what you mean by a formulary?

Dr. LEE. No; definitely not.

Mr. GROSSMAN. Thank you.

Senator NELSON. Thank you very much, gentlemen, for your appearance this morning.

Dr. LEE. Thank you very much, Mr. Chairman.

(The Task Force on Prescription Drugs Report previously referred to follows:)

TASK FORCE ON PRESCRIPTION DRUGS

Second Interim Report

and

Recommendations

August 30, 1968

Office of the Secretary
U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Washington, D.C.

(3737)

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UNITED STATES GOVERNMENT

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY

TO : The Secretary

DATE: August 30, 1968

FROM : Philip R. Lee, M.D., Assistant Secretary for Health and Scientific Affairs

SUBJECT : Task Force on Prescription Drugs - Progress Report

Prescription Drugs in Medicare

The Task Force has not yet developed definitive recommendations on the possible inclusion of out-of-hospital prescription drugs under Medicare.

We are referring to the Social Security Administration for detailed cost analysis such subjects as program financing, reimbursement methods, and administrative approaches. When this analysis is complete, it will be reviewed by the Task Force and appropriate recommendations prepared for your consideration.

Background Reports

As a result of the work of the Task Force staff and its consultants during the past year, a very large amount of information has been obtained on various aspects of the use, production, and distribution of prescription drug products. Much of this has previously been unavailable, and it is urgently needed by the drug industry, pharmacy, the health professions, consumer groups, Congressional committees, and many Federal and State agencies.

We propose to publish these as a series of background volumes which will serve as the objective basis for many of our recommendations, as well as source material for discussion and further research. It is our plan to publish these volumes on the following subjects:

1. Use of Prescription Drugs by the Elderly
2. The Drug Industry
3. Drug Distribution
4. Drug Prescribing
5. Drug Quality
6. Current Domestic and Foreign Drug Insurance Programs
7. Drug Classification and Coding

Interim Report

I am forwarding with this memorandum the second Interim Report of the Task Force with our findings to date and recommendations.