FOOD AND DRUG ADMINISTRATION PRACTICE AND PROCEDURE, 1976

JOINT HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON LABOR AND PUBLIC WELFARE

AND THE

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

NINETY-FOURTH CONGRESS

SECOND SESSION

ON

EXAMINATION OF THE HISTORY OF FOOD AN DRUG ADMINISTRATION'S REGULATORY EFFORTS AND THE PROCEDURES THEY USE IN CONSIDERING VARIOUS DRUGS GIVEN TO ANIMALS THAT MAY BE CONSUMED BY THE AMERICAN PEOPLE

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CONTENTS

CHRONOLOGICAL LIST OF WITNESSES

TUESDAY, JULY 20, 1976

STATEMENTS

ADDITIONAL INFORMATION

FOOD AND DRUG ADMINISTRATION PRACTICE AND PROCEDURE, 1976

TUESDAY, JULY 20, 1976

U.S. SENATE,
SUBCOMMITTEE ON HEALTH, COMMITTEE ON
LABOR AND PUBLIC WELFARE, AND THE SUBCOMMITTEE
ON ADMINISTRATIVE PRACTICES AND PROCEDURES,
OF THE COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The subcommittees met, pursuant to notice, at 10:20 a.m., in room 4232, Dirksen Senate Office Building, Senator Richard S. Schweiker presiding pro tempore.

Present: Senators Kennedy, Schweiker, and Hathaway.

Senator SCHWEIKER. The joint hearing of the Senate Health Subcommittee and the Administrative Practice and Procedure Subcommittee will please come to order.

We apologize to the witnesses for the delay. The problem is that Senator Kennedy, our chairman, has been testifying before the Senate Finance Committee on some matters pertaining to amendments to the tax bill which Senator Kennedy had taken a strong stand on. He was leaving the hearing, hopefully to come here, but he has been called back to the hearing, so we do not feel it is fair to keep the witnesses waiting any longer.

I have been asked by his staff to go ahead with the meeting.

I would like first to read an opening statement. This is a statement by Senator Kennedy that I am reading for him [reading:]

OPENING STATEMENT OF SENATOR KENNEDY

Two years ago, when we began this investigation of FDA, we began with you—the employees of the agency, who must carry out the daily activities of the most important health regulatory agency in the country. Although we had subpeaned you to testify, we realized the difficult position we were placing you in within your agency.

You testified candidly and convincingly, with obvious deep feeling for the importance of your work and frustration at the difficulties you were encountering. You recounted very disturbing stories—stories of inappropriate industry influence, undue pressure to approve drugs, alteration of files, pressure to change opinions, misuse of advisory committees, retaliatory transfers, et cetera.

Now, as we near the end of this phase of our inquiry into the drug industry, we return to you, the employees of FDA.

Yesterday, an important accord was reached between these committees, Secretary Mathews, and the New Drug Review Panel. We will have an independent review of your previous testimony and its implications. We will be able to move forward with efforts to restructure and reform your agency in a constructive

way. I believe, for the first time, we have a chance to cooperatively begin to set things straight.

We return to you today to help us start on that path.

Those of you who have been before will have the chance to reaffirm what you have said and to offer suggestions to improve both the review process and your agency.

Those of you here for the first time will add relevant testimony—will show that the problems remain current today.

I have always believed that a full understanding of what went wrong is a prerequisite to setting it right. That is our dual goal today—to understand and to begin to move to set things right.

Senator SCHWEIKER. Our first panel of witnesses is made up of employees of both the Bureau of Drugs and the Bureau of Veterinary Medicine of the FDA. These witnesses will give testimony about recent events in both of these Bureaus of FDA. The witnesses include Mr. Philip Sheeler, Mr. John Evans, Mr. Rodney Zenk, Dr. Marvin Seife, Dr. Vincent Karusaitis, Dr. Merle Gibson, Mrs. Mary Bruch. Dr. Richard Dunham, Mr. Frank Pipari, and Dr. William Gyarfas.

At this point, since I know you do not have prepared statements, I would like to go through some of your individual experiences. We will begin with a case of turkeys contaminated with potentially dangerous residue.

I would like to call on Mr. Sheeler to answer a few questions.

Mr. Sheeler, can you tell us what this residue was, why was it dangerous, and when the first contaminated batch of turkeys was sent out of North Carolina?

STATEMENTS OF PHILIP SHEELER, JOHN EVANS, RODNEY ZENK, DR. MARVIN SEIFE, DR. VINCENT KARUSAITIS, DR. MERLE GIBSON, MRS. MARY BRUCH, DR. RICHARD DUNHAM, FRANK PIPARI, AND DR. WILLIAM GYARFAS, FOOD AND DRUG ADMINISTRATION, A PANEL

Mr. SHEELER. Sometime around April or March 1975 we received some tissue residue reports from the U.S. Department of Agriculture reporting the presence of ipronidazole, a carcinogenic agent, in the tissue of turkeys. It is within the province of my particular branch of the Bureau of Veterinary Medicine to issue assignments to the appropriate district offices to make an investigation as to the cause.

And it was at that time that we investigated the tissue residue.

Senator SCHWEIKER. Why was the wrong group embargoed?

Mr. SHEELER. Ipronidazole is a carcinogenic agent and, as such, it is not approved for its presence in the tissue of turkeys.

Section 409 of the Food, Drug and Cosmetic Act does not permit the presence of carcinogenic agents in edible tissue at the time of slaughter. Consequently, the USDA decided to embargo those turkeys.

Senator SCHWEIKER. Now, was the right group or the wrong group embargoed?

Mr. SHEELER. Subsequent to the embargo of the turkeys, we had rumors from the fields to the effect that it was possible that the U.S. Department of Agriculture had improperly embargoed the wrong lot of turkeys and had accidentally released a lot which did contain the ipronidazole.

We requested the field office to check out whether these rumors had any evidence, in fact, as to what had happened. We subsequently

found out from a supervisory investigator that he had verified the fact that USDA had, in fact, embargoed the improper lot and had released the lot contaminated with ipronidazole.

Senator SCHWEIKER. So the contaminated group was not embargoed, is that what you are telling us?

Mr. SHEELER. That is correct, yes.

Senator SCHWEIKER. What action did you take when you found that out?

Mr. SHEELER. When the supervisory investigator called us, we told him that in view of the fact that the USDA had apparently lost control over the lot, that this was now in interstate commerce, and that we would inform the Bureau of Foods, who has jurisdiction over human foods, to contact them, to give them guidance as to how to proceed in this area.

We also stated that we would contact the USDA to get further information about the situation.

Subsequently, we did call the Bureau of Foods and we did inform them about a situation as far as we knew of it at that time.

Senator SCHWEIKER. You attended a meeting, as I understand it, where this action was discussed, and you were criticized at that meeting. Is that correct?

Mr. SHEELER. Yes.

Subsequent to our issuing the information to the Bureau of Foods, Mr. Rod Zenk, who is employed in my branch, wrote a memorandum of the situation, and a copy of it was sent to Dr. Cazier, who was Deputy Director, Division of Veterinary Review.

The day after, at approximately 11 o'clock, after the issuance of that memo, Mr. Zenk, Mr. John Evans who was the Program Director for my branch, and myself, were notified that a meeting had been set up that afternoon in Dr. Van Houweling's office.

Senator SCHWEIKER. Would you identify the doctors?

Mr. SHEELER. Dr. Philip Cazier at that time was the Deputy Director of the Division of Veterinary Review. Dr. Van Houweling is the Bureau Director, Bureau of Veterinary Medicine.

We attempted to find out the contents of that particular meeting so that we could prepare ourselves, but we were not told except that it did deal with tissue residue reports.

Senator SCHWEIKER. What happened at the meeting?

Mr. WHEELER. Well, at the meeting we were asked several questions by Dr. Van Houweling. Actually, two questions were asked of me by him. Namely, if I had called up the Bureau of Foods, and I said I had, and he then asked me why I had called up the Bureau of Foods.

Senator SCHWEIKER. Why you had called?

Mr. SHEELER. That is correct.

Senator SCHWEIKER. Why did he ask you that?

Mr. SHEELER. I do not know why he asked me that question.

Senator SCHWEIKER Wouldn't calling the Bureau of Foods be a normal thing to do in view of what you found?

Mr. SHEELER. Well, I explained to him that this was a normal thing to do in view of the fact that the USDA had lost control over the product, and this was a human food subject to jurisdiction of the Food and Drug Administration. We were dealing with a carcinogenic agent within the tissues, and that, in the spirit of consumer pro-

tection, if nothing else, that we would be obligated to inform the Bureau of Foods for appropriate action on their part.

After that, he asked the question whether I was aware or not or, for that matter, anyone that was present at the meeting, was aware of the fact that USDA did, in fact, have jurisdiction over these things under the Meat Inspection Act.

Several people attending the meeting informed him that there was joint jurisdiction——

Senator SCHWEIKER. Joint jurisdiction between whom now?

Mr. SHEELER. U.S. Department of Agriculture and the Food and Drug Administration.

Nothing much more was said by me during the remainder of the meeting.

Dr. Van Houweling did state that if the USDA wanted us to hold their coat while they were fighting the battle, so to speak, that would be fine, but we would not take the initial steps in that area.

Senator SCHWEIKER. Did you get the feeling or the impression that it was wrong for you to notify the Bureau of Foods?

Mr. SHEELER. I got the impression that I was being thoroughly chastised for informing the Bureau of Foods in relation to this entire episode.

Senator SCHWEIKER. Is the Bureau of Foods part of FDA?

Mr. SHEELER. Bureau of Foods is part of FDA.

Senator SCHWEIKER. Why on earth would you not inform a peer group which had similar responsibilities of information that was detrimental to the interests of consumers, whether here or abroad?

Mr. SHEELER. As far as I am concerned, my action was consistent with the policy as set forth in various policy guides within the agency, which specifically stated what we had done was totally within agency policy.

The only reason that was represented to us during the meeting was that probably we would be placing the USDA in an embarrassing position if we pressed this too much.

Senator SCHWEIKER. All right.

Now, I would like to go to Mr. Evans.

Mr. Evans, were you at that meeting?

Mr. EVANS. Yes, sir.

Senator SCHWEIKER. You basically agree with Mr. Sheeler's account of the meeting, or is there some other information you would like to add that might be relevant?

Mr. EVANS. His recollection is correct.

Senator SCHWEIKER. Did you write a memo summarizing the meeting?

Mr. EVANS. Yes, I did.

Senator SCHWEIKER. As I understand it, the memo went through a number of drafts, is that correct?

Mr. EVANS. That is correct.

Senator SCHWEIKER. What was the problem?

I assume that basically the memo was a kind of minute of the meeting or record of action taken, is that correct?

Mr. EVANS. That is correct.

Senator SCHWEIKER. Why did you have so much trouble drafting the memo?

What was the hang-up? Why did the memo have to be rewritten a number of times?

Mr. EVANS. There were certain items in the memorandum that had been deleted or changed around to other thoughts.

Senator SCHWEIKER. What parts were they?

What specifically was the problem that necessitated redrafting of the memo?

Mr. EVANS. When the memorandum was initially drafted, Mr. Sheeler wanted it specifically in the memorandum to show that Dr. Van Houweling had given him instructions not to contact the Bureau of Foods. There were a couple of other items in there dealing with the fact that——

Senator SCHWEIKER. The initial draft said you should contact the Bureau of Foods?

Mr. EVANS. Should not.

Senator SCHWEIKER. Should not?

Mr. EVANS. Should not contact the Bureau of Foods.

Senator SCHWEIKER. Some people did not want to sign that, is that correct?

Mr. EVANS. Right.

After Mr. Sheeler, Mr. Zenk, and I had initialed off on the original draft, it was sent up to other participants at the meeting for their review. A third draft came down to us with those items deleted.

At that time, Mr. Zenk and I refused to sign it.

Senator SCHWEIKER. Did that not seem strange to you, this matter of whether or not to put the subject of whether it was appropriate to contact the Bureau of Foods in a memorandum describing a situation in which a known carcinogenic contaminant was present in a product that somebody was going to consume?

Let me put it this way.

If you were on the receiving end—eating this product—how would you feel about it?

Mr. EVANS. I would want all the facts stated.

The thing that was strange was that there were certain items being deleted for no reason that I could see at the time.

Senator SCHWEIKER. Finally, after the memo was drafted, I understand that an addendum was added to it.

What did that addendum say?

Mr. EVANS. That addendum was added, I assume, by Dr. Van Houweling. I do not know for a fact that he himself added it, but I assume that he did. It stated, in fact, that he had contacted—been in contact with the Bureau of Foods and that the Bureau of Foods concurred with his thought on it, but we would in the future contact the Bureau of Foods.

Mr. SHEELER. I would like to add one thing to what Mr. Evans said. It may not come across too directly, but very specifically, during the meeting, Dr. Van Houweling gave specific orders not to contact either the Bureau of Foods or the USDA to solicit additional information.

When the first memo was written by Mr. Evans, this paragraph was present in the draft. Subsequent revisions removed those instructions on the draft.

I would not sign off on the memo unless that paragraph was in the draft, which instructed us specifically not to contact the Bureau of

Foods because the Bureau of Foods subsequently did contact us for additional information. And in accordance with the instructions that had been given to us, I could not give them additional information.

Upon receiving that draft with this deletion, I spoke to my Division Director, Mr. Leon Brunk and voiced my objection to that particular paragraph being deleted.

He said he would talk to Dr. Van Houweling in an effort to have that put back and possibly rescind the instruction that had been given to us. Subsequent to that conversation with Mr. Brunk, an additional paragraph was put into the memo stating that we could now talk to either USDA or the Bureau of Foods in this particular matter.

Senator SCHWEIKER. I have a copy of an addendum here in front of me. I would like to read it to see if we are talking about the same thing.

After consideration of all the facts brought out during the meeting of 7–22–75 and the subsequent telecon with [Bureau of Foods], it was the conclusion of Dr. C. D. Van Houweling that BVM would initiate no action against meat or meat products because of residues, unless requested to do so by APHIS. There would be no bar in the future, however, to an exchange of information concerning residues with [the Bureau of Foods] whenever, in the opinion of Division of Compliance, this would be desirable since [the Bureau of Foods] has the primary responsibility for human food in FDA.

Is that the addendum you are talking about?

Mr. EVANS. Yes, sir.

Senator SCHWEIKER. This was put in at your insistence?

Mr. EVANS. No.

That was put in by Dr. Van Houweling.

Senator SCHWEIKER. Dr. Van Houweling's insistence?

Mr. SHEELER. It was put in at my instigation with Mr. Brunk.

Senator SCHWEIKER. We want to keep the record straight as to what actually had happened.

He specifically was the one who had developed this policy which some of you questioned.

Mr. SHEELER. Right.

Additionally, this addendum, this paragraph, was more consistent with the current policy as stated within the Food and Drug Administration in their policy guides relating to these matters.

Senator SCHWEIKER. Mr. Sheeler, was there a second batch of contaminated turkeys?

Mr. SHEELER. There was a report—that is correct—I believe, from Cincinnati District to the effect that there was some contaminated turkeys which was possibly being shipped to Germany and Canada, and in an effort to find out what to do in that particular area, I wrote a memorandum to my division director; namely Mr. Leon Brunk, as to whether or not we should investigate this more fully, and also to inform the Office of International Affairs to inform these countries of the possible shipment of tissues containing ipronidazole to those countries.

I believe this was in June or July 1975. I subsequently got a response from Mr. Brunk to the effect that he saw no need for this and that it was not consistent with prior policy within the Bureau, and to let it drop at that point.

Senator KENNEDY [presiding]. Just before I ask a question, I want to express my appreciation to Senator Schweiker and apologize to him for keeping him delayed and to the members of the panel and our second group.

We called a special meeting of the Finance Committee on some particular taxing provisions, which both Senator Schweiker and Senator Hathaway and members interested in tax justice have been very much concerned about. We started there just a few minutes actually before 9, and had been told that my presentation would be 5 minutes and Senator Proxmire's 5 minutes. It lasted 1 hour and 45 minutes.

There is not much satisfaction in the fact that Senator Proxmire's witnesses are waiting, too, in another part of the building.

But I apologize to you. These things do happen.

I know Senator Schweiker read the comments, my opening statement, which I mean very sincerely.

I feel there are extraordinary amounts of heroic work being done in the various departments of Government today to protect the health, well-being, and safety of the American citizens. But this work is generally not even understood or known to the American public. The American public owes an extraordinary debt of gratitude to the professionalism, to the competency, and dedication of people that work in these various agencies.

You are among that group that I am really referring to.

Your help to this committee has been of great value in the past—some of you and our second Panel go back two years—as your testimony here today has been helpful to us. I know that your comments and statements today are made for the same reason we are having these hearings. That is, to attempt to make the Food and Drug Administration, the very, very best agency that we can possibly make it in it's work to protect the health of the American people. That is motivating our interest today, and I know it is motivating your being here.

We want to give you the personal assurance that we will do everything that is essential and is necessary to strengthen the FDA, both from a legislative point of view and from the point of view of your own personal interest.

The situation in the FDA is not an easy one for you to come up here and tell us about, but you are helping us fill our own responsibility.

We made some important progress yesterday, I think, in terms of the establishment of the Panel to review various procedures in the FDA. We are going to work closely with them. To the extent that previous testimony is reaffirmed and supported and some of the problems that exist today are discussed, I think today's testimony will be very valuable in reviewing FDA procedures.

So this is an extremely important meeting.

I just want all of you to know my own personal appreciation. I know I speak for members of the committee. We will make those comments at an appropriate place in the record.

We will come back to the contaminated turkeys.

Can you tell us about the Brunk response to your memorandum?

Mr. SHEELER. Mr. Brunk felt that no other action was indicated, that was contrary to prior policy, that he just did not feel that it was necessary at that point to either make an additional investigation or to inform the Office of International Affairs.

Senator KENNEDY. Why did you feel it necessary?

Mr. SHEELER. Well, we are dealing with a carcinogenic substance within the tissue of edible animals. I did not feel that it was fair for

the United States to ship contaminated material to the rest of the world.

Senator KENNEDY. At any time were you told that cooking could eliminate the residues?

Mr. SHEELER. We have been informed there have been some studies by USDA to the effect that cooking may have an effect on these particular materials and they could consequently be removed by cooking.

Senator KENNEDY. And did you write to General Counsel about that?

Mr. SHEELER. Yes; I wanted clarification on section 409 of the act because section 409 says specifically that an animal shall be free of the carcinogenic agent at the time of slaughter. It did not address itself to any subsequent process in relation to carcinogenic agents and their removal.

I believe it was in December 1975 when I wrote that memo.

Senator KENNEDY. What was the main thing you heard from Mr. Brunk?

Mr. SHEELER. I believe in December of 1975 I got a memorandum, I am not sure whether Mr. Brunk signed it or Mr. Friedlander did—but it said that in the future all communication between consumer safety officers and General Counsel would have to be passed through Mr. Brunk.

Senator KENNEDY. It says, "Henceforth, all requests to General Counsel for legal opinions be forwarded through me so I may determine whether the Office of the Director will be needed to be notified or whether question has been raised and answered . . ." and so on and so forth.

What did the General Counsel say?

Mr. SHEELER. I do not completely recall, but I believe he did state something to the effect that this could be used for that particular area.

Senator KENNEDY. Pardon?

Mr. SHEELER. That such steps could be entered into, that is, subsequent processing, but I cannot recall the full contents of the memorandum.

Senator KENNEDY. Did you receive a series of memos from Mr. Brunk restricting your correspondence with veterinarians and your contact with the USDA, and ordering additional reviews for responding to requests for advisory opinions or in casework?

Mr. SHEELER. Well, from the period of April 21 through 23, I got three memos, one on each day.

Senator KENNEDY. Which year is that?

Mr. SHEELER. 1976.

I believe the first memo related to the fact that I could not, nor could any Consumer Safety Officer in the division communicate directly with an outside veterinarian. It would have to be signed out by Dr. Van Houweling or an appointee of his office.

The second memorandum related to the fact that I could not speak to USDA unless it involved a tissue residue report.

The third memo related to the fact that all previous medical opinions were no longer in effect and that all or subsequent cases would have to be reviewed, re-reviewed actually, for their current status under the Food and Drug Act.

Senator KENNEDY. What was your reaction to all of this?

Mr. SHEELER. Well, my reaction, going back to the December memo, of course, was that I felt that these four memos tended to erode my job description, which specifically stated that I could have free intercourse with General Counsel in obtaining a legal opinion, that I could not do the job appropriately nor could any members of my staff do the job appropriately in determining regulatory actions without contacting the General Counsel.

I felt that this was the beginning of some sort of a procedure to limit the activities of my branch in relation to its compliance work.

Senator SCHWEIKER. You felt certainly that this was contrary to public policy and the public interest, I gather, from your discussion here earlier?

Mr. SHEELER. Well, since my job is intended to defend the public interest as stated in the statute, yes, that is correct.

Senator KENNEDY. As a result of these various memorandums, you effectively were being cut off from communications with veterinarians, you were being cut off from communications with General Counsel's office, and you were being cut off from your communications with the Bureau of Foods. Originally, all you were attempting to do was keep contaminated turkeys off the market?

Mr. SHEELER. Originally that was the case. But I was much more interested in subsequent cases that would be coming up, and whether this would infringe on the flexibility of my branch in reacting to situations in an appropriate manner. And communication with General Counsel for the purpose of getting clarification of the law of certain sections, and communication with USDA in determining what followup should be pursued, and communication with USDA in relation to setting up a viable tissue residue program, I felt these were within the obligations of my particular branch.

Senator SCHWEIKER. Why do you feel that someone above you, one of your superiors, would be advocating a policy contrary to the public interest like this?

Did you have any idea why someone further up the ladder might pursue such a policy?

Mr. SHEELER. I believe that would be pure supposition on my part.

Senator SCHWEIKER. Did they give you any rationale?

They must have given you some explanation.

Mr. SHEELER. No; there was absolutely no rationale. In fact, in several instances, I went to Mr. Brunk and requested that he explain the necessity for such memos since the individual that had my position prior to me did not have such restrictions placed on him.

Senator SCHWEIKER. You never heard any explanation or rationale or reason as to why the policy seemed to be reversing itself in terms of your responsibilities?

Mr. SHEELER. No.

I must assume by the chronology of the situation that this was in fact a sequelae of the tissue residue problem involving ipronidazole.

But this is an assumption on my part, and it seemed to be a rational assumption based on the chronology of the situation.

Senator SCHWEIKER. It seems to me the burden of proof would be on your superior when he asked a subordinate to implement policy or to make case precedent that would implement policy, that the burden of proof would be on him to show why you should not be doing your job.

But I gather he did not come forth with any explanation or logical reason?

Mr. SHEELER. I attempted several times for an explanation of the memos, and I received none.

Senator KENNEDY. Sometime after, there was a petition that was endorsed by a number of employees which really commended you for the kind of work that you have done, and mentioned—

> We have worked with Mr. Sheeler and know him to be a conscientious, industrious individual, knowledgeable and experienced in food and drug, and makes him particularly well qualified, and individuals in your group benefited greatly from his association.

These people—I suppose 25 or 30 people signed that petition—are obviously people that work closely with you. I know it was not instigated by you. I did not mean to embarrass you. I think it is important that the people you work with—all professional people—recognize the quality of work which you do. I think it was a great tribute to you.

In subsequent actions, the limitations of restrictions were withdrawn?

Mr. SHEELER. That is correct, Senator Kennedy.

However, there are a few steps in between the instance where I requested clarification from Mr. Brunk to the knowledge that I had that this petition had been issued.

After I had made several unsuccessful attempts to clarify the situation with Mr. Brunk, I felt that these memos eroded my job description and put my job in jeopardy as far as its grade scale was concerned.

Consequently, I had no recourse but to submit a grievance against Mr. Brunk and clarify why he felt it was necessary to issue such memos. And it was at that time that I was informed of the particular petition.

I had no knowledge of the petition. I was extremely grateful for the petition. But at that time I was involved in a discourse with the per-

sonnel branch of the FDA, and the petition was brought to their attention.

Personnel additionally took a copy of the petition, I do not know what they did with it.

Also, at that same time, I felt that these four memorandums, had they been seen by an impartial observer or any other observer, would be extremely embarrassing to the agency.

Obviously I prophesized what has come to fruition.

I felt it was within my obligation to inform the Commissioner of these four memos and what they portended. I wrote a memo delineating the entire situation to the Commissioner chronologically pointing out that these memos could be construed in a bad light for the agency, for the Bureau, and everyone else involved.

I brought this to the Executive Secretariat who serves as the clearinghouse for such memorandum.

I do not know what happened.

Subsequent to all these various ramifications, a meeting was held by Dr. Houweling, at which time all people that had signed this particular petition were called into a general meeting and everyone present was informed that these four memorandums had been rescinded.

Senator KENNEDY. I think it is very helpful to have that story recorded.

All you were attempting to do was keep contaminated turkeys off the market, yet you were running into prohibition of communicating this concern to the Bureau of Foods and your way of proceeding was constantly restricted. Your own fellow associates recognized your own professional competence, and came to your defense.

And, ultimately, these matters were resolved.

Mr. SHEELER. Yes.

[Information supplied follows:]

MEMORANDUM

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

TO : Health Subcommittee

DATE: August 9, 1976

FROM : Bureau of Veterinary Medicine (HFV-236)

SUBJECT: Suggested Legislation
Re: To Eliminate Abuses Alleged at the Hearings.

At the conclusion of my questioning on July 20, 1976, at the referenced hearing, I was instructed by Senator Kennedy to submit directly to the committee my personal suggestions relating to needs for legislation which would increase the effectiveness of the agency and possibly preclude the defects alleged at the hearing.

I have the following comments to offer:

1) The alleged failure of the Food and Drug Administration to fulfill its mandate cannot always be placed at the doorstep of inadequate legislation.

In the last 10 years, the FDA has had 5 Commissioners and DHEW has had 5 Secretaries. Additionally, additional legislation has been foisted on the agency further debilating its already depleted resources. Because of this, the agency has been in a period of chaos and turmoil since each new designee "rediscovered the wheel" and a great deal of repetition and duplication of effort went into the education of these people rather than towards fulfilling our mandate under the Act.

2) Each Commissioner since Commissioner Larrick was appointed from outside the agency.

Such appointments had two effects:

(a) It lowered the morale of the working level of the agency who had aspired to the top position.

(b) It placed at the head of a complex organization, an individual uninformed as to the internal working of FDA. Consequently, this individual could be "snowed" as to the agency's true priorities, resources, and abilities to do the job.

Health Subcommittee

3) Therefore, in an effort to cover ineptitude, more legislation and resources were requested from Congress even though adequate legislation existed to completely fulfill the Congressional intent if sufficient knowledge existed.

4) In each new passage of legislation, more personnel was hired. This drew trained people away from assigned duties to train the new employees. It led to promotion of people to positions for which they had not yet been adequately trained. It led to a general weakening of the field force and headquarters.

5) The agency must be asked to consolidate its resources, and not extend its authority, until it can be shown that it can do the already assigned missions.

6) All the legislation in the world will not cause the appointment of people with the proper mental attitudes to critical, policy-making positions involving consumer protection.

All persons in the agency from the Commissioner to the sample custodian must be fully inculcated and indoctrinated as to the true missions of the agency towards consumer protection. Unless this is done, the agency will continue to have the problems which were outlined at the hearing.

7) Since I can see little chance of nomination of such people to these top positions, I can only recommend one legislative act take place.

This would be in the creation of an Ombudsman or Consumer Interest overseer in each regulatory agency which has the statutory authority to institute litigation against those agencies and individuals which are not operating in accord with the public interest.

Philip Sheeler
Chief, Case Guidance Branch
Division of Compliance
Bureau of Veterinary Medicine

MEMORANDUM

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

TO : Leonard Jay Farr, Supervisory Investigator
Investigations Branch, Cincinnati District 9HFR-5250)

DATE: July 15, 1975

FROM : Kenneth B. Ganote (HFR-5250) .

SUBJECT: Illegal Residue in Turkey Meat

(Journey Wagon Poultry)
(Slaughterer:) Hartwig's Poultry, Inc.
Burrville Road
Fort Recovery, Ohio 45846

On July 8, 1975, Dr. Homer R. Smith, D.B.M., and I visited the above slaughterhouse. This visit was prompted by a TWX, dated 6/25/75, from Philip Sheeler, Chief, D.C.G., Bureau of Veterinary Medicine. This wire said that U.S.D.A. sample #17960, collected on 5/27/75 at the above slaughterhouse, revealed 5.20 parts per billion of ipronidazole in the muscle tissue of turkeys. These turkeys were offered for slaughter by a Harold Brubaker of Hamler, Ohio.

Our credentials were shown to Dr. John W. Ross, D.V.M., at the slaughterhouse on 7/8/75. Also present during this interview was Paul E. McDaniel, Official Grader for the firm. Dr. Ross showed us a copy of the Lab Report for sample #17960 which is attached to this memo as an exhibit. Dr. Ross stated that this sample record shows that Harold Brubkaer brought in 5-month-old male turkeys on 5/27/75 and that samples 7 thru 12 were collected. The sample was received on 6/4/75, and the analysis was completed on 6/6/75. Dr. Ross stated that Mr. Brubaker had offered a total of 500 turkeys to the slaughterhouse on 5/27/75, and the sample represented 6 turkeys. He said that these birds were sampled as part of a survey and that the other 494 birds went out to the marketplace.

Dr. Ross stated that turkeys are received for slaughter from the states of Ohio, Indiana, Illinois, Georgia and Texas. He stated that most of finished dressed turkeys are shipped to the East Coast as well as exported to Canada and Germany.

Philip Sheeler, Chief, D.C.G. (HFV-220) 7/15/75
Bureau of Veterinary Medicine

This is part of the investigation requested of Harold Brubaker of Hamler, Ohio.

Leonard Jay Farr
Supervisory Investigator
Cincinnati District

Dr. Ross stated that the corporation changed hands about June 18 or 19, 1975. He stated that originally the firm had been operating under the name of Wayne Poultry Co., Division of Allied Mills, Inc. The name was changed to Hartwig's Poultry, Inc., at about June 18, 1975.

Dr. Ross stated that when the sample was collected, on 5/27/75, that a total of thirty turkeys were sampled, six turkeys collected at random from five different turkey producers. Dr. Ross stated that only Mr. Brubaker's sample proved positive.

Dr. Ross stated that Mr. Brubaker bought in 30 birds for sampling as required by U.S.D.A., for sampling on 7/7/75. Dr. Ross stated that these thirty birds had been slaughtered and he was keeping them frozen until shipping cartons could be obtained for shipping them to U.S.D.A. Scientific Services, 12th and C Street S.W., Washington, D. C.

While we were talking to Dr. Ross, he received a phone call from U.S.D.A. reporting that his last shipment of turkeys to Washington had spoiled due to lack of proper handling. Dr. Ross stated that he wanted the complaint verified in writing. He stated later that lately he has been shipping a lot of samples and that it is very time consuming and he has difficulty making arrangements of shipping cartons and arranging for delivery to the U.S.D.A. lab in Washington, D.C.

Dr. Ross stated that Mr. Harvey C. Worthington is the firm's plant manager. He stated that the firm's phone number is 419-375-4141. He said that the firm's U.S.D.A. plant number is 473.

Dr. Ross stated that these birds would be shipped to Washington, D.C. and that he would receive the result of analysis in about two weeks.

Kenneth B. Ganote

Kenneth B. Ganote (023)
Investigator, Cincinnati District

Enclosure

HFR-5250:KBGanote:rjg 7/15/75

Phil - FYI

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7/31/75
FROM: R. A. Zenk		OFFICE HFV-250
TO: DR. CAZIER HFV-400		DIVISION BVM

SUBJECT: Ipronidazole 48.41PPB USDA/APHIS-FDA Residue Rpt

SUMMARY

1) Preliminary results of investigation concerning above reported residue determined that Jerry Moore is part of an integrated operation of Armour & Co, Winston-Salem, N.C. Reports by the firm state that these birds received Ipronidazole only at a very young age and could not explain the cause of the high levels. I received this information by telecon Dan Cifyo, SI, Raleigh, NC on 7/17/75. Also Cifyo reported that these birds were not held and had gone into Interstate Commerce. He also stated that the Inspector had been told by Central Soya people that they too had some more residue problems. Inspections of both Armour & Central Soya are ongoing.

2) I relayed this information to Dr. Trabosh / USDA on 7/18/75. Dr Trabosh said the Central Soya

SIGNATURE	DOCUMENT NUMBER

FORM 2324 (9/73)

OHO - FYI

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE
FROM:		OFFICE
TO: Pope "2"		DIVISION
SUBJECT:		

SUMMARY

residue was the result of a "Farm Sample" collected at the Lane Price farm, who is an independent grower, however buying feed from Central Soya. Dr Trabost said that these birds were slaughter at the Harvel Poultry Co, Dayton, VA and were not condemned this was an Objective sample. He also said that birds from this plant are used in further processing such as turkey rolls, soups ect.

3) Sheeler & myself contacted Ralph Strand (7/10) CGGB Bureau of Foods who asked that we relay information concerning the disposition of these birds and that they might consider Seizure of finished products.

4) I then relayed this information by Trabost and Strand to Don Gilgo, Raleigh, NC Resident Post and asked him to TWX

SIGNATURE	DOCUMENT NUMBER

FD FORM 2034 (2/72)

PKO - FYI

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE
FROM:		OFFICE
TO: Page 3		DIVISION
SUBJECT:		

SUMMARY

a summary of reports to us as soon as possible. Calpo stated he would get something to us on Monday 7/21/75.

5) I then called Dr Trabosh again on 7/18/75 Friday afternoon to fill him in on the fact that Bureau of Foods was possibly considering seizure of finished products. Dr Trabosh said he would attempt to get further information as to destination of finished products and would notify me on Monday 7/21/75.

SIGNATURE		DOCUMENT NUMBER
RPT Jr.	CC: Shuller CC: Rinehart	

July 22, 1975

MEMORANDUM OF CONFERENCE

BETWEEN: Dr. C. D. Van Houweling, (HFV-1)
Dr. K. Johnson (HFV-400)
Dr. P. Cazier (HFV-400)
Mr. H. Friedlander (HFV-201)
Mr. P. Sheeler (HFV-220)
Mr. R. Zenk (HFV-220)
Mr. J. Evans (HFV-220)

and part time with
Dr. H. R. Roberts (HFF-8)

A meeting was held to discuss the role of BVM when meat and meat products were found upon objective sampling by APHIS to contain tissue residues over tolerance. Dr. Cazier advised that he had received a memorandum from Mr. Zenk, which outlined recent events concerning an APHIS report of Ipronidazole residue in turkeys at a level of 48 ppm. Follow-up discussions with APHIS disclosed that initially they had inadvertently obtained the wrong grower name and that the lot of turkeys which they were holding was not the lot sampled. The lot from which an objective sample was collected was combined with other lots and processed into turkey rolls and shipped out from the establishment.

FDA inspector Mr. Sitgo thought FDA should assume responsibility for the lot that was processed and shipped. Mr. Sheeler thought the Division of Compliance of BVM should inform Bureau of Foods of this fact. He and Mr. Zenk spoke with Ralph Strand on July 18, 1975, who in turn asked to be provided with all information in the possession of D/C and that they would take regulatory action if it was necessary. Dr. Cazier stated that in a similar situation involving sulfaquinoxaline in ducks he had earlier expressed the opinion that D/C should not press APHIS for information about lots passed and released by them with the possible objective of product seizure by FDA.

It was pointed out by Mr. Friedlander and Mr. Sheeler that since the drug involved is a suspect carcinogen and we were not certain as to what control USDA still maintained in the matter, or whether the turkeys should be retrieved, it was felt that BF should be aware of the situation in the event that they thought action was indicated in order to protect the consumer.

Dr. Van Houweling pointed out that there seems to be a misconception that USDA does not have jurisdiction over meats or meat products once they leave the inspection plants. He referred those present to the Wholesome Meat Act of 1967 which provided USDA with the authority to institute detention, seizure, or condemnation of meats or meat products should they find them adulterated. He did not believe that it

was the Bureau's obligation to seek regulatory action on products which were the responsibility of USDA. He stressed that if the Bureau of Foods wished to institute action, they, of course, could do so. Or if USDA asked for FDA's assistance that we should surely assist. He did not feel that BVM should initiate such action and provide such information to BF from USDA unless we were requested to. BF can communicate directly with USDA on such matters if BF wishes to pursue them. Dr. Van Houweling instructed Mr. Sheeler not to solicit further information from USDA at this time or transmit information to BF on this incident until he talked to Dr. Roberts to ascertain his views regarding BF participation.

Following this meeting, Dr. Van Houweling did speak with Dr. Roberts who essentially concurred with the BVM position. Dr. Roberts agreed that meat was amenable to the FDC Act as well as to the Meat Inspection Act. However, he agreed USDA had primary responsibility and that BF would not pursue any matters involving adulterated meat unless asked to by USDA or with their concurrence.

It was also pointed out by Mr. Evans that we must realize that as the drug residue program is now being carried out by FDA and USDA, there is the additional possibility that USDA, or for that matter FDA, may be embarrassed. That is, FDA is basing their criminal cases against growers found culpable for illegal drug residues reported by USDA through their objective sampling program. The food (meat) upon which we charge the grower as having caused a violation of the FD&C Act, in most cases is usually allowed to continue into commerce channels. Undoubtedly this will be brought out some time during a case and it could be difficult to explain why FDA is bringing criminal charges against an individual when USDA had allowed the adulterated food (meat) itself (upon which the charge is based) to enter the channels of commerce for human consumption. Dr. Van Houweling admitted that this might happen but that there was no practical way for APHIS to collect objective samples and retain several thousand birds until the assay results were returned a couple of weeks after the slaughter. Furthermore, the objective sampling program is not designed to prevent the distribution of adulterated food but to give an objective report of violative residues detected.

One additional point was brought up by Mr. Evans that USDA also operates under the Wholesome Poultry Products Act of 1968, and that both the meat and the poultry Acts may be in need of amendment since they do not define a "new animal drug" as an adulterant, as in the FD&C Act (402(a)(2)(D)).

Since the Act defines the term "food additive" as having the same meaning as under the FD&C Act, then New Animal Drugs are exempted and may have to be considered to be a poisonous or deleterious substance. Dr. Johnson made note of this.

C. D. Van Houweling, D.V.M.

ADDENDUM

After consideration of all of the facts brought out during the meeting of 7/22/75 and the subsequent telecon with BF, it was the conclusion of Dr. C. D. Van Houweling that BVM would initiate no action against meat or meat products because of residues unless requested to do so by APHIS. There would be no bar in the future, however, to an exchange of information concerning residues with BF whenever in the opinion of Division of Compliance this would be desirable since BF has the primary responsibility for human food in FDA.

MEMORANDUM

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

TO : Director
Division of Compliance (HFV-200)

DATE: August 7, 1975

FROM : Case Guidance Branch
Division of Compliance (HFV-220)

SUBJECT: Export of Dressed Turkey to Canada and Germany

Information submitted by Cincinnati District indicates a possibility of finished dressed turkeys being exported to Canada and Germany which may contain tissue residues of ipronidazole (copy of Investigation attached). We believe the International Affairs Staff of ACC should be made aware of this fact, so that they can determine whether these countries have any prohibition of turkeys with ipronidazole residues. If you concur, we should determine through USDA whether or not animals with drug residues are being shipped for export. International Affairs Staff may then make the proper notification to the foreign countries involved.

Philip Sheeler
Chief
Case Guidance Branch

MEMORANDUM

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

TO : Chief
Case Guidance Branch (HFV-220)

DATE: August 11, 1975

FROM : Director
Division of Compliance (HFV-200)

SUBJECT: Residues in Poultry and Red Meat

1. This is in reference to your August 7, 1975, memo to me. As you know, it is agency policy that responsibility for human foods rests with the Bureau of Foods - not BVM, and that Dr. Van Houweling has instructed that we are not to initiate action on those products subject to the Meat and Poultry Inspection Acts which are under the jurisdiction of USDA, unless USDA requests our assistance.

2. As you further know, USDA's objective sampling program is not designed nor conducted in such a way that the results of analysis are obtainable prior to release of the sampled carcasses. Since USDA does not ordinarily attempt, whether for domestic or export purposes, to retrieve U. S. inspected and passed carcasses or parts thereof which subsequently by analysis are found to contain residues, I see no reason to single out this instance for additional follow-up, especially in this particular case since we do not have information specifically showing that any of the product was exported.

3. Therefore, I do not concur with your suggestion that we approach USDA to determine whether or not turkeys with ipronidazole residues are being shipped for export for the purpose of informing International Affairs.

4. Incidentally, I am advised that there is a strong suspicion that ipronidazole may be heat labile. Studies are presently underway to establish whether cooking will destroy residues in turkey meat. If so, it would appear that our concern over residues would be minimized.

L C Brunk

Leon C. Brunk

MEMORANDUM

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

TO : Office of General Counsel (GCF-1)
Attn: Gary Yingling

DATE: December 17, 1975

FROM : Chief, Case Guidance Branch (HFV-220)
Division of Compliance, BVM

SUBJECT: Reconditioning of foods to meet tolerance - legal opinion requested

We are attaching a recent study conducted by a Virginia University in which a degradation of ipronidazole residues during the freezing storage and cooking of turkeys was investigated. We believe this report points out a need for legal opinion concerning residues of carcinogenic or potentially carcinogenic substances.

The study shows that turkeys when first analyzed were found to contain an average of 39.9 ppb ipronidazole. The tolerance for ipronidazole (21 CFR 556.340) is that no residues of ipronidazole are found in the uncooked edible tissue of turkey. The cooking of the birds, however, revealed that the levels of ipronidazole were eliminated and that metabolites of ipronidazole were all that were found. In this case the average of 0.5 ppb ipronidazole was in skin with zero being the average in muscle tissue. The study also indicated that raw tissue samples when stored for a period of time in a freezer would apparently contain no residues. It was felt from the study that ipronidazole breaks down at a slow rate during freezer storage.

As a result of this finding, turkeys which had been retained by USDA for ipronidazole residues were subsequently released for normal market channels. Therefore we have a situation where food when slaughtered was in violation of the Act but after storage in a freezer for a period of time was found to be no longer in violation of the Act. As you know, the Delaney Clause, (21 USC 348(C)(3)(A)(ii) in part, states:

> "That no residues of the additive will be found (by methods of examination prescribed or proved by the Secretary by regulations, which regulations shall not be subject to sub-sections (f) and (g) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal;"

It is apparent that the cooked turkey would still be subject to action under the Act since the regulation established calls for no residues in the uncooked meat. However, in the case of turkeys after freezing it is unclear whether the birds would still be actionable since the tissue could

still be considered to be edible portion of the (uncooked) animal "after slaughter." Is there a time period in this phraseology "after slaughter" when the tolerance would apply when originally tested or when tested at a later date?

With the Delaney Clause as written under section 409 and under section 512, could we conceivably allow a food which may have been seized due to residues of a carcinogenic substance or potentially carcinogenic substance to be brought into compliance by cooking? It is apparent to us that the question regarding cooking may not be readily answered at this time until further research is done to determine whether the residues are in fact eliminated or are broken down into other substances or metabolites which may be harmful in themselves.

Philip Sheeler
Chief
Case Guidance Branch

COPY

cc: HFV-1
HFV-200(Brunk) (RF)
JEvans 11/7/75/gvk
~~FT 12/17/75/mfe~~
Initialled PSheeler 12/16/75

MEMORANDUM

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

TO : All Consumer Safety Officers
Division of Compliance, BVM

DATE: December 30, 1975

FROM : Director
Division of Compliance, BVM

SUBJECT: Requests for Legal Opinions

Henceforth all requests to the Office of the General Counsel for legal opinions should be forwarded through me so that I may determine whether the Office of the Director, BVM, need be notified or whether the question has already been raised and answered. This requirement does not apply to routine casework or routine processing of regulations or new animal drug applications.

Herbert L. Friedlander

for Leon C. Brunk

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
Office of the General Counsel

TO : Phil Sheeler
HFV-200

DATE: April 6, 1976

FROM : Gary L. Yingling GLY
GCF-1

SUBJECT: Reconditioning of Foods to Meet Tolerances -- Ipronidazole

I read your memorandum of December 17, 1975, as asking two questions: The first question is whether or not a slaughtered animal whose tissue contains drug residues above the allowed tolerance can be brought into compliance by cooking the tissue and reducing the residues. The second question is whether or not a slaughtered animal whose tissue contains residues above tolerance prior to storage and then falls below tolerance can be used for human food.

1. There is no question that section 512(d)(1)(H) of the Act is talking about any edible portion of such animals after slaughter. Such language carries the implication that unprocessed animal tissue is the subject of the statute. As you pointed out, the regulation itself, 21 CFR 556.340 -- Ipronidazole, states that no residues are found in the uncooked edible tissues of turkeys. The regulation therefore appears specifically to prohibit cooking as a method of bringing the article into compliance, and the language in the statute does not appear to provide for cooking tissue.

Because the statute is unclear and the agency has authority to adopt interpretative regulations, it would appear that FDA may publish a regulation proposing to provide for cooked tissue. I think that proposal of such a regulation would be unwise at the moment, but as food chain problems become larger and more complex, it perhaps should be given additional consideration.

2. Your second question concerns the residue level after storage. The normal method of storage for a slaughtered animal, of course, would be freezing, and the attached study indicates that freezing reduces the ipronidazole level below that which would be actionable. The Act, in section 512 (new animal drugs) and section 409 (food additives), provides that a drug or food additive will only be approved if the Secretary can be assured that no residue of such drug or food additive will be found in any edible portion. This would lead one to conclude that the intention of the statute was to prevent the presence of the residue in the slaughtered

80-211 O - 76 - 3

tissue. If the statute and regulations were only intended to assure that no residue reaches the consumer from the slaughtered tissue then storage, i.e., freezing, would arguably be an acceptable method to assure this objective.

There appears to be nothing in the statutory term "slaughtered" which would prevent a taking of a tissue sample at any time after slaughter. It seems apparent that Congress intended to prevent one thing from happening when it used the word "slaughtered." It did not want tissue samples to be taken from the living animal at some time prior to slaughter, because contamination of the tissue could occur any time up until the animal was actually slaughtered. The legislative history does not reveal whether Congress wished to allow the tissue to be cooked or processed in some other way. Given the intent of the statute, i.e., the prevention of residues in the food being presented for consumption, it should be permissible to bring the tissue into compliance by holding in cold storage as long as you could be assured that the animal tissue did not contain a violative residue when it was shipped in interstate commerce. It would also be necessary to show that the residue test measured not only the parent compound but any metabolite which might be carcinogenic. Freezing may cause or permit the first step in metabolic breakdown of the residue and, therefore, approving a test only for the parent compound would be to undermine Congress' intent.

The real answer to your question is that the word "slaughtered" does not require measurement immediately after the actual slaughter. That means that the agency must determine by regulatory guidelines or regulations the procedures it will allow, i.e., tissue sample at time of slaughter, after freezing, etc. In other words, USDA's procedure for examining turkeys seems consistent with our Act.

cc: Harry Shulman
Mr. Merrill

MEMORANDUM

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

TO : All Consumer Safety Officers
Division of Compliance

DATE: April 21, 1976

FROM : Director, Division of Compliance (HFV-200)

SUBJECT: Correspondence with veterinarians

All correspondence with practicing veterinarians and members of the AVMA administrative staff will be prepared for signature by Dr. Van Houweling or Dr. Kingma. Correspondence with veterinarians representing firms in an administrative capacity will continue to be handled in the same manner as previously handled.

Leon C. Brunk

MEMORANDUM

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

TO : All Professionals
Division of Compliance

DATE: April 22, 1976

FROM : Director
Division of Compliance (HFV-200)

SUBJECT: Drug Residue Program

Dr. Cazier, DVMR, has on a number of occasions expressed concern that he is not being kept appraised of the developments occurring in the drug residue program. Additionally, he has indicated that he feels that developments such as the current effort to redesign USDA's letter which they issue to livestock producers regarding the selective sample follow-up is a policy question insofar as it might relate to our compliance activities and that he should be involved in anything dealing with policy.

Therefore, any contact between the Division of Compliance and USDA (APHIS) should be restricted to compliance activities regarding specific incidents of drug residues. All other communications, development of policy concepts, etc., should be routed through Dr. Cazier.

Leon Brunk

Leon C. Brunk

MEMORANDUM

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

TO : Chief, Case Guidance Branch (HFV-220)
Division of Compliance, BVM

DATE: April 23, 1976

FROM : Director
Division of Compliance (HFV-200)

SUBJECT: DVMR Comment on Product Status

Dr. Cazier has requested that we not rely upon previous comment on the status of a product when responding to requests for advisory opinions or in case work. Dr. Cazier explained that his people feel that earlier comments may no longer be applicable and that current status should be determined each time. Therefore, each time the Division of Compliance processes a regulatory action or replies to a request for comment on a product, we should solicit fresh views from DVMR as a basis for preparing our response.

I realize that this will increase the workload of DVMR and may result in additional delays in replying to inquiries but since DVMR feels this is essential and necessary, I believe we have no alternative but to accede to their wishes. Please implement this procedure upon receipt of this memo.

Leon Brunk

Leon C. Brunk

HF-1

MEMORANDUM

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

TO : Director (HFV-200)
Division of Compliance
Bureau of Veterinary Medicine

DATE: April 23, 1976

FROM : Case Guidance Branch (HFV-220)
Division of Compliance, BVM

SUBJECT: Drug Residue Program
(Your memo of April 22, 1976)

I have read the referenced memorandum indicating that any contact between "Division of Compliance and USDA should be restricted to compliance activities regarding specific incidents of drug residue. All other communications (regarding) development of policy concept, etc., should be routed through Dr. Cazier."

I must state my concern and objection to several points as stated in the referenced memorandum.

1) I have always instructed my people in the past to write memoranda to Dr. Cazier on any significant action taken by the Branch to keep him informed. This has been done, wherever practicable.

2) In all meetings of members of my staff with U.S.D.A. regarding policy, a member of DVMR was present. In this instance specifically mentioned, Dr. Carnevale was present and concurred that this was an avenue that would be considered to increase the effectiveness of the program. If Dr. Cazier was not informed of these discussions, it is not the fault of this branch, but of a failure in the communications within DVMR.

3) Since my branch is the primary liaison with U.S.D.A. in this division, it appears that before the issuance of this memo, I might have been contacted as a matter of courtesy, if not proper management technique, to explain the circumstances which may have precipitated its issuance.

As written the memo is unclear and disjointed. What does "etc." include? Does this include all verbal as well as written communications? Does this mean that during the exchange program with U.S.D.A, my discussion must involve only specific residue reports? Does this mean that I am unable to speak about bettering a compliance program without going through Dr. Cazier? If I receive a telephone call from U.S.D.A. requesting assistance, should I transfer it to Dr. Cazier?

Where does improvement of a compliance program end and policy begin?

Is the function of the Branch now solely clerical support in relation to this program?

4) The Case Guidance Branch has now been restricted in the last several months in the following manner:

a) We cannot write directly to practicing veterinarians or members of the AVMA.

b) We cannot write directly for a compliance opinion from General Counsel unless it specifically involves an ongoing case.

c) We cannot speak to U.S.D.A. on any policy matter and "etc." (?) without routing through Dr. Cazier.

5) This memorandum is improper, ill-conceived and ill-advised for the following reasons:

a) It renders the proper functions of the branch impossible in its relationships with the U.S.D.A.

b) In view of the recent Ipronidazole situation, the release of this memorandum as well as the memorandum of December 30, 1975 would cause any neutral observer to believe that there is a deliberate attempt by you at covering up and restraining the activities of this branch in relation to U.S.D.A. matters.

c) The memorandum is based on several false assumptions that my branch has not kept DVMR informed, and that the strenghtening of a program towards accomplishing greater compliance action output is a policy matter over which DVMR has authority.

6) In reviewing these memoranda, I find a growing, continuing, insidious attempt to prevent the proper functioning of this branch towards fulfilling its mission of compliance, under the Federal Food, Drug, and Cosmetic Act.

7) In limiting these functions, I find that I cannot continue to operate under these restrictions at any level approaching effectiveness or within the requirements of my position description.

8) Therefore, by separate memorandum, I am initiating a grievance action against you for preventing me from performing my job as described within my position description.

I am also requesting that I be reassigned and replaced by a suitable individual who is capable of operating under restrictions which I consider to be severely limiting.

9) Additionally, I feel that I am compelled to bring these repressive measures manifested by the memoranda to the Associate Commissioner for Compliance, and the Commissioner of Food and Drugs for the purpose of protecting the agency should these memos be seen by the Congress and be construed to be an attempt at limiting the compliance activity of the Bureau, and the agency.

Philip Sheeler
Chief, Case Guidance Branch

Enclosures

cc: HF-1
HFV-1
HFC-1
HFC-13
HFV-200(Brunk)
HFV-200(RF)
HFA-226
PSheeler:4/23/nmw/FT/4/26/76/gvk
Initialled: PSheeler 4/23/76

COPY

April 30, 1976

PETITION

We, the undersigned, have learned that Mr. Philip Sheeler, Chief, Case Guidance Branch, has received several memoranda limiting his freedom to function in his present position. We understand that he feels these restrictions make it impossible for him to carry out the responsibilities of his position, and that he has requested to be transferred out of the Bureau.

We who have worked with Mr. Sheeler know him to be an extremely conscientious and industrious individual, whose knowledge and experience in Food and Drug Law and Compliance procedures make him particularly well-qualified to perform effectively in enforcing the provisions of the Act. Both individually and as a group we have benefited greatly from our association with him. He has, in the short time he has been with us, elevated both the quality and quantity of Compliance activity to a level unprecedented in the Bureau. His dedication and vigorous enforcement of the Act have served to encourage productivity and improve the morale of those who have worked with him. His willingness to pursue even the most controversial regulatory matters has served to motivate and inspire his associates to emulate his example. The accomplishments of Mr. Sheeler and his Branch have become a source of pride for all of us.

We ask that you consider voiding the restricting memoranda so that Mr. Sheeler can remain in BVM and continue effectively in his position. We urge BVM management and Mr. Sheeler to make every effort to resolve their differences. Such a resolution would benefit the entire organization and have a significant positive effect on our capability, productivity and morale.

Howard Meyers
David N. Scan
Richard P. Lehmann
George Jenkins
Mukund Barkhie
Leonard A. Kunsky
Alexander Allaccod
Walter E. Unity
Andrew J. Beaulieu
Paul Lepore
Donald A. Gable
David F. Fishler
Thomas J. Dola
R. A. Baldevin
David P. Durham
Patricia Cushing
A. T. Mudell

Dan L. Sanders
Frank L. Taylor
Mary Beth Kaas
J. L. Gabriel
Emilio E. Vieira
Steve Kimbel
Gloria E. McDavid
Bob Schmidt
Myron C. Rosenberg
Ann B. Holt

TO WHOM IT MAY CONCERN: May 3, 1976

We the undersigned in light of recent developments, whereas Mr. Sheeler has found it necessary to take certain action regarding his position as Chief, Case Guidance Branch, do hereby wish to reiterate our endorsement of December 16, 1975 to the FDA Awards Officer for the FDA Commendable Service Award. We believe because of Mr. Sheeler's sustained exemplary performance, creativity in developing internal regulatory procedures and skill as a Supervisory Consumer Safety Officer that every effort should be made to mutually resolve the differences and thereby prevent what would be a recognizable loss of the Division of Compliance, Case Guidance Branch, Bureau of Veterinary Medicine.

Rodney 9 Zenk
Mark A. Arnold
Ronald L. Bayliss

John Eastman
James E. Essmer
Sarah D. Schriver

MEMORANDUM

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

TO : Commissioner of Foods and Drugs (HF-1) DATE: May 3, 1976

FROM : Case Guidance Branch (HFV-220)
Division of Compliance, BVM

SUBJECT: Repression of Compliance Activity
Re: Tissue Residue Program

I am fully aware of the ponderous burdens of responsibility under which you are presently operating, but I am compelled by conscience to bring to your attention several memoranda which have recently been issued by the Bureau of Veterinary Medicine which may serve to place the Food and Drug Administration and the Bureau into an untenable and embarrassing situation should they be seen by a neutral observer.

Copies of these memoranda are attached.

The chronology of these memoranda is significant. The December 30, 1975 memorandum which restricts my branch from having direct contact with General Counsel was issued immediately after I requested clarification of Section 409 of the Act and which indirectly involved Ipronidazole. My memo to General Counsel issued on December 17, 1975.

The April 21, 1976 memo prohibits my branch from direct communication with veterinarians except with those veterinarians operating in an administrative capacity in a firm.

The April 22, 1976 memo restricts any contact between any member of my branch and the U.S.D.A./APHIS except on compliance activities which regard a "specific tissue residue". My response to this memorandum was issued on April 23, 1976.

The memorandum of April 23, 1976 indicates that previous medical opinion may no longer be valid.

Such memoranda not only serve to make the performance of my job as Chief, Case Guidance Branch, Division of Compliance, BVM totally unfeasible, but serves to indicate an explicit and implicit, insidious attempt at controlling compliance within the Bureau and cover up the Bureau's activities and relationships with U.S.D.A.

Additionally, issuance of such memoranda in light of the recent Ipronidazole Congressional inquiry indicates a lack of awareness as to their political sensitivity in placing the agency into an untenable position.

I forward this material to your attention for whatever follow-up you may deem appropriate, but recommend that such memorandum be immediately rescinded to prevent an embarrassing situation from occurring.

Philip Sheeler
Chief

Enclosures:
As stated

cc: HFC-13
HFV-220(Sheeler)
HFV-200(Brunk)
HFV-200(RF)
PSheeler 5/3/76/gvk
Initialled: PSheeler

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFAR
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Mr. Leon C. Brunk
Director
Division of Compliance

DATE: MAY 07 1976

FROM : Director
Bureau of Veterinary Medicine

SUBJECT: Grievance

Shortly after Mr. Sheeler filed his grievance with you I was informed of it by Mr. Bunoski. It is my understanding that you and Mr. Bunoski alone or together have met several times with Mr. Sheeler, and that you felt that a verbal agreement was reached on May 3, 1976 as to how his grievance could be resolved. Even though this has not been accomplished I am pleased that this matter has been diligently pursued and I thank you and Mr. Bunoski for working closely with Mr. Sheeler in this regard. I am still hopeful that this grievance can be resolved in this Bureau.

Even if this is accomplished, it is apparent from Mr. Sheeler's memorandum to the Commissioner that he feels the memoranda he objects to are unduly restrictive. In my mind the memoranda are necessary but it is apparent that they are being misinterpreted and that the policy considerations behind them are not clearly understood.

I, therefore, am requesting that you suspend the memoranda referred to in Mr. Sheeler's memorandum to the Commissioner, namely:

1. The procedures to be followed when legal opinions are requested from OGC

2. Providing the Bureau Director and Deputy an opportunity to sign letters going to practicing veterinarians and to staff officials of the AVMA.

3. Memo which clarifies the units of the Bureau for dealing with APHIS in regard to tissue residue matters, and

4. Memo calling for updating of medical opinions prior to Bureau action or a statement of position.

I would like to make it clear that I am not asking you to suspend these memoranda because I do not agree or concur with the intended purposes and policies. However, it is clear that they are being misunderstood and misinterpreted. Therefore, there needs to be a complete and full discussion surrounding the needs for the procedures which have been outlined. After we have had this discussion I hope that we will be able to set forth policy and procedures in such a manner that everyone understands and, if not in agreement, at least understands why the management of the Bureau feels that they are necessary.

C. D. Van Houweling, D.V.M.

cc: Mr. Sheeler

It is the Bureau's judgement that your grievance is resolved since the memos have been suspended.

Richard L. Bunoski
Assistant Director for Management

Senator KENNEDY. Let me ask Mr. Zenk if this is substantially your understanding too?

Mr. Zenk, is this substantially your understanding of the series of—sequence of events of what happened, and is there anything additionally you would like to add?

Mr. ZENK. Yes, sir, just being a part of the whole thing, as a member of case guidance branch, yes, sir. But my main issue was the original Ironidazole situation——

Senator KENNEDY. The which?

Mr. ZENK. Ironidazole in the turkeys.

Senator KENNEDY. That instance, as I understand it, is as Mr. Sheeler presented it?

Mr. ZENK. Yes, sir.

Senator SCHWEIKER. I would like to ask Mr. Sheeler, to his knowledge, if any reprimand or any disciplinary followup action was ever taken against any of his superiors for the situation just described?

Mr. SHEELER. No; there has not been any reprimand of any of my superiors. However, in the Bureau's reorganization, there have been several promotions.

Senator SCHWEIKER. That was my next question. I think it is important to get that in the record.

Senator KENNEDY. Dr. Karusaitis and Dr. Seife now. Dr. Seife, these committees have been concerned with FDA's handling of DES for a very long time. I know of the great interest of Senator Schweiker, and we have worked very closely together on this issue.

Let me ask you, Dr. Karusaitis, first of all, did you draft a letter to the Medical Letter about their report on DES?

Dr. KARUSAITIS. Yes, sir.

Senator KENNEDY. Let me read the last paragraph to you. It says that, "This agency would view with serious concern the use of any DES product for emergency use postcoital contraceptive which was not specifically approved without * * * which [approval] as a result did not provide for all labeling and packaging safeguards which had been specifically identified for purposes of insuring safety and effectiveness of the drug product for that specific indication."

On the bottom of that page, Mr. Leventhal wrote these words: "Last paragraph was not strictly accurate. The agency does not officially view unapproved uses with concern. It believes that products should be properly labeled for their intended use. We regulate manufacturers, not doctors."

As you are very much aware, we had extensive conversations with Mr. Schmidt. We have had Dr. Rauscher up here about implications of DES. FDA has taken procedures in the past to try and limit DES use. We passed restrictions in the Senate on several occasions. We have had extensive private meetings with the Director of the FDA and with others about what steps could be taken. And Schmidt himself said, "You are making a very important point, one I tried to make." The issue of unapproved use and the issue of rarely occurring adverse reaction are terribly important issues and ones we have not addressed well in this country.

Well, now, let me ask you: Were you surprised when you read Mr. Leventhal's paragraph?

Dr. KARUSAITIS. Both Dr. Seife and myself do share great concern, so we do not go with that at all, that there is no concern.

The initial thrust was simple. The Medical Letter, which is addressed to 50,000 practicing physicians stated on February 27 that the product was available, that it was approved. In conversation with Dr. Seife and myself we thought that we would address ourselves to the editor for a correction. Following channels, we wrote a short letter, a longer letter, and from a half page we got three and a half, and 9 weeks I believe went by.

Senator KENNEDY. On the one hand you get the Director of FDA, the Commissioner of Drugs, talking about the danger of DES and working closely on the use of this drug, and you get the Deputy Director writing a paragraph like that. What sort of sense does that make? I mean it is directly contrary to Commissioner Schmidt's testimony before these committees. I'm just wondering whether you can help us in any kind of explanation about why the Deputy Director has taken one position and the Director has taken another. From your own statement or comment or letter you are evidently in line with the Commissioner, but Mr. Leventhal is not. Do you have any explanation, understanding or awareness of why that is the case?

Dr. KARUSAITIS. No, sir.

Dr. SEIFE. I think Dr. Leventhal felt that the drug was being used anyhow since in March 1975 by Federal Register the indications postincest, postcoitus, et cetera, had been approved. We have not approved any particular pharmaceutical drug firm for marketing this drug because no firm has as yet met the regulations. That is they have not submitted the recommended patient package insert, proper insert for the physician, plus all the manufacturing controls. We still have the only one firm as an incomplete applicant. Our last letter to them was over 3 months ago and the agency has not heard from them. What Dr. Leventhal was alluding to was that doctors were using the drug in the practice of medicine since FDA had issued a Physician Bulletin prior to the Federal Register publication. We have gone over all this before the Federal Register statement and Physician Bulletin telling them how to use this drug postcoitus, 25 milligrams twice a day, 5 days a week, Monday through Friday. Then you have your fun on Saturday and Sunday and start over again.

Since our hearing on February 27, 1975, which both Dr. Karusaitis and myself appeared before Senator Schweiker and Senator Kennedy, I have had phone calls from Ann Arbor, a hotbed for the use of this drug, from the Washington Post or Parade Magazine and from the very company who wants to market this drug concerning the availability of a DES 25 milligrams in Philadelphia. They asked me how this was so? How can the 25 milligram tablet be available when it is only allowed for a particular use, postrape, postincest, and so forth? I said I guessed perhaps there were some supplies left from the previous marketers of this drug on the shelves of drug warehouses and when a pharmacy ordered it or hospital ordered the drug, they got the 25 milligrams.

Lo and behold last month one of our inspectors wandered into a wholesale drug house in Atlantic City and found 7 bottles of 100 tablets each, 25 milligram strength, sitting on a shelf.

Senator KENNEDY. Should it be there?

Dr. SEIFE. These were made by Eli Lilly by the way. Eli Lilly stopped making these drugs in 1973, latter part of 1973, stopped shipping them in 1974. But there were over 3 million tablets out there from

Eli Lilly figuring to be about 300,000 patient doses, postcoital doses or postrape doses. This is why I probably had those phone calls that the drug was available at that strength and was being used for postcoitus, and was available on campus.

Senator KENNEDY. Should it be there now?

Dr. SEIFE. No. When the inspector, FDA inspector, contacted Eli Lilly, he asked Eli Lilly whether they had recalled the drug when they had stopped marketing it. They said no, and they did not intend to recall it.

In a way I do not blame Eli Lilly. It is up to FDA to recall a drug. When we no longer approve it for a particular use, 25 milligram dose for use during pregnancy and other uses, why the heck is it out there? Why should we not recall it?

Senator SCHWEIKER. FDA has seizure power?

Dr. SEIFE. Exactly. The first thing we do is write to the firm and ask them to recall it. If they fail to do so, we seize it. We never did that. Eli Lilly chose to let the drug peter out. It did. There is probably little left out there.

Two of the seven bottles in Atlantic City were outdated as of June 1, 1976. The inspector took two bottles back to the office, and that left three on the shelf to be shipped to local drug stores in Atlantic City. How many remain throughout the country, I do not know.

Senator KENNEDY. That is the question. It is out there now?

Dr. SEIFE. Yes. Some of Lilly's and some from other companies, yes.

Senator KENNEDY. You do not know how much is out there?

Dr. SEIFE. No.

Senator KENNEDY. Nothing has ever been done?

Dr. SEIFE. Nothing has ever been done.

Senator KENNEDY. Have you tried to find out, has FDA tried to find out?

Dr. SEIFE. The inspector's report was sent to the Bureau of Drugs, Office of Compliance. I assume somebody is perhaps looking into it at this point.

Senator KENNEDY. You would know if they were trying to find out, would you not?

Dr. SEIFE. Well on this particular drug maybe they would not choose to tell me because of our previous testimony. I just happened to know about this incident. I received a copy of the inspector's report I guess by mistake.

Senator KENNEDY. Let me ask Dr. Seife about a different issue. In January we held hearings on estrogens. At that time we knew that

in 1974, Premarin was the fourth biggest selling prescription drug in the United States. Now we know in 1975 it was the second biggest selling prescription. At the January hearing the Commissioner promised prompt labeling revisions. Do you know whether that has been accomplished?

Dr. SEIFE. We have not seen any labeling for estrogens as yet. Now this has disturbed me a great deal because my division has, at this point, over 60 estrogen preparations, mostly conjugated estrogens similar to Premarin that are being marketed, actively marketed. Although Ayerst has the largest percentage of the market, these other drugs are being marketed with improper labeling. So, since your committee was promised in approximately 4 to 6 weeks some sort of labeling to be published in the Federal Register, I was quite anxious to see it. I wanted to process these generic estrogen preparations, and if they did meet all criteria, approve them.

Unfortunately nothing came about. We watched the Federal Register quite carefully toward the end of February all through March. On March 30, 1976, we requested a meeting with the Bureau of Drugs' Director and present I believe was the Deputy Director, Dr. Karusaitis, myself, my supervisory chemist, I think another chemist from our division and other people. At that time I told Dr. Crout of the necessity of having the labeling promised to the subcommittee, on estrogens, whereby they mentioned carcinoma of the cervix and the uterus and possibly of the breast.

He stated he understood the problem and that I would have a prepublication copy, pre-Federal Register publication copy by the end of April. Came April 30, nothing was sent forward.

Throughout May we tried to obtain a copy. Nothing came forward. We heard that a 21-page package insert had been drafted and had gone to the Bureau Director's office. We had never seen it.

This draft has been back and forth between the Division of Metabolic Endocrine Drug Products and the Director's office. But as yet, 6 months after your hearing, there has been no package insert.

Senator KENNEDY. We heard earlier in January the statement by the Commissioner that we could revise professional labeling—actual drug labeling—within a matter of a week or two. Getting the right language in the patient package insert is a most difficult thing to do and I think it probably would take a little longer.

We still have not received it yet.

[Information subsequently supplied for the record follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

August 9, 1976

Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
Committee on Labor and
Public Welfare
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

At the July 20, 1976, hearing of the Subcommittees on Health and on Administrative Practice and Procedure under your Chairmanship, some editorial notes which I had made on a draft letter from one of our staff members were discussed. I feel that the brief discussion failed to provide sufficient background to place my informal remarks in the proper context and consequently gave a somewhat distorted impression of my views.

By way of background, the draft letter which was the subject of discussion during the hearing, was handed to me by an Associate Director of the Bureau on Thursday, July 15, prior to the start of a Bureau of Drugs staff meeting with the Commissioner. As you know, the letter was addressed to the Medical Letter for signature by Dr. Karusaitis. The subject of the letter was a Medical Letter article of some five months earlier concerning the use of diethylstilbestrol (DES) for post-coital contraception. I had not previously seen either the article in question or the draft letter. I read the letter quickly over, jotted some notes at the bottom of its third page and returned it at that time.

As you heard during the hearing, I made several brief comments on the proposed draft. First, I pointed out that the Medical Letter usually does not publish letters to the editor and only rarely makes corrections and/or retractions on previously published articles. With that in mind I then noted that perhaps the best response one might reasonably expect was a very brief one--perhaps one line--note in a future issue. My third comment addressed a paragraph in the draft letter which dealt with the practice of prescribing estrogens for post-coital contraceptions despite the lack of a product subject to an approved new drug application accompanied by appropriate dosage and restricted indications and warning information in the labeling.

The Medical Letter had suggested that an approved product was available when in fact, our Federal Register notice had only given the terms for approval; this error warranted correction. It was my view that the corrective letter should be cast to place less emphasis on exhorting the prescriber and more on our anticipation of an application for marketing of an approvable product for this widely accepted, though highly restricted, use. At the time of the Medical Letter article a new drug application conforming to our previously stated requirements had not been approved by the Agency, nor has the Agency approved one to this date.

The non-availability of an approved product means, however, that a physician wishing to prescribe DES for post-coital contraception under the indicated circumstances could not obtain a product packaged and labeled in the way FDA considers proper because none exists. Alternative or interim use of an available product is not illegal and may be justified in the responsible practice of medicine provided that appropriate cautions are exercised and the patient is properly informed. Thus I felt that the original statement that "FDA views with serious concern the use of any diethylstilbestrol product ....etc., etc." as incorrect because it over-emphasized the physician's role rather than the responsibility of manufacturers to assure that their products are properly labeled for their intended use.

My fourth, and final point was to indicate my endorsement of the proposed letter with the editorial suggestions outlined above, and to urge that the letter be signed by the Division Director rather than by a staff member in order to give it greater weight as an official Agency position.

The matter was not further discussed during the next several days and, given the informality and casual comment nature of the whole episode, I did not give it further thought. My reaction on the whole was that the letter was a good one and that the drafter had done a commendable job.

While my note was, in part, discussed at the hearing, its context was not, with the result that my views on an important issue may have been misrepresented. I, therefore, respectfully request that you make this letter a part of the record on this matter to provide clarification of the issue raised.

Sincerely yours,

Carl M. Leventhal

Carl M. Leventhal, M.D.
Deputy Director
Bureau of Drugs

Enclosure

MEMORANDUM

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

TO : Associate Director for Drug Monographs

DATE: August 9, 1976

FROM : Deputy Director
Bureau of Drugs

SUBJECT: Diethylstilbestrol letter to the Medical Letter

On Thursday, July 15, 1976, we attended the Commissioner's staff meeting with the Bureau of Drugs. Before the meeting began, you handed me across the table an unsigned undated colored-paper draft of a letter to the Medical Letter prepared for Dr. Karusaitis' signature. The letter commented upon a Medical Letter article of some five months earlier concerning the use of diethylstilbestrol (DES) for post-coital contraception. I had not previously seen either the article or the letter. I assumed that you were sharing the letter informally with me for my thoughts as to substance, style and policy.

The letter, as I recall, was about two and a half pages long and I jotted some notes to you at the bottom of the third page. I have not seen the note in question since I wrote it but my recollection of it is that it made several points. First, I pointed out that the Medical Letter usually does not publish letters to the editor and only rarely makes corrections and/or retractions on previously published articles. This comment was intended to give advance warning to your staff that their well-intentioned letter might elicit little response from the Medical Letter. Second, I remarked that the best response one might reasonably expect was a very brief--perhaps one line--note in a future issue six months or so after the original article. Third, I commented on a paragraph in the letter which dealt with the practice of prescribing estrogens for post-coital contraception despite the lack of an FDA approved product with appropriate dosage and appropriately restricted indications and warning information in the labeling. I found the tone of this paragraph unduly threatening to the practitioner.

The paragraph appeared to say that a physician using a non-approved dosage form of DES for post-coital contraception was doing something reprehensible. This is a stronger position than I would think warranted from our official statements in the past. The Agency has stated that post-coital DES is a safe, effective, and valuable therapeutic modality in certain cases and has described labeling and a dosage form that would be approved. At the time of the Medical Letter article no such dosage form with the required physician and patient labeling had been approved, but that does not negate our announced position that the restricted emergency post-coital use is

safe and effective. The non-availability of an approved product means, however, that a physician wishing to use DES for post-coital contraception under the indicated circumstances could not obtain a product packaged and labeled in the way FDA considers proper because none exists. Is his use of an available product, one not labeled for post-coital use, (really his only alternative) then wrong? I think not if the patient were properly informed of the risks involved.

The Medical Letter had suggested that an approved product was available when in fact, our Federal Register notice had only given the terms for approval; this error warranted correction. I thought, however, that a strong argument against physician prescribing of available DES products made too much of a technicality, especially in the absence of a detailed promulgated Agency policy on unapproved uses of marketed drugs, when we ourselves had stated that use of DES was sometimes important and a possible alternative to abortion. For this reason I suggested less emphasis on exhorting the prescriber and more on our anticipation of an application for marketing of an approvable product for this widely accepted, though highly restricted, use.

My fourth, and final point was to indicate my endorsement of the proposed letter despite the minor editorial suggestions outlined above, and to urge that the letter be signed by the Division Director rather than by a staff member in order to give it greater weight as an official Agency position.

I then handed the letter back to you and watched you and Dr. Seife, nodding in apparent agreement, read my notes. We did not discuss the matter further over the next several days and I did not give it further thought. I would note the informality and casual comment nature of the whole episode. The letter was on the whole a good one and commendable effort had gone into its drafting. My comments were intended to be supportive and constructive and not intended to be critical in any way.

It seems from subsequent events that the draft letter with my notes on it found its way to Senator Kennedy and was one of the subjects addressed in the hearing on Tuesday, July 20, just five days later. I would very much appreciate your ascertaining just how and, more importantly, why this happened. Do we have a memorandum of the meeting with the Senator's staff at which this "document" was transmitted in accordance with Department and Agency policy on Congressional contacts? Does your staff take issue with my comments? If so, why didn't they discuss these points with me?

At the hearing in question Senator Kennedy questioned Dr. Karusaitis about the letter and my comments. The questioning quoted my comments out of context, without benefit of the background I have detailed above, and suggested that my views were markedly at variance with Agency policy, which I do not believe them to be.

Dr. Karusaitis stated that "Following channels, we wrote a short letter, a longer letter, and from a half page we got three and a half, and nine weeks I believe went by." I am not aware of the earlier history of the letter in question but I would point out that, until the hearing, your showing it to me on Thursday, July 15, was the first and last time I saw it or heard of it.

I hope that this memorandum will serve to set the record straight on this episode which was discussed out of context at the hearing in such a way as to misrepresent my views.

Finally, I do feel that the letter to the Medical Letter, with appropriate revision as you see fit, should be sent and without further prolonged delay.

Carl M. Leventhal

Carl M. Leventhal, M.D.

MEMORANDUM

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

TO : Gene Knapp, Director HFD-500
Office of Drug Monographs

DATE: June 7, 1976

FROM : V.V. Karusaitis, M.D.
Through: M. Seife, M.D., Director HFD-530
Division of Generic Drug Monographs

SUBJECT:
Misleading Statements on DES (Post-Coital Use)

The medical letter on Drugs and Therapeutics, February 27, 1976, issue stated:

> Diethylstilbestrol (DES) - "The estrogen diethylstilbestrol is approved for emergency use as a contraceptive agent following intercourse. The major hazard of diethylstilbestrol is the development of vaginal carcinoma in the female children of women who received the drug early in pregnancy."

FACTS:
1. Diethylstilbestrol is a nonsteroidal estrogen.
2. To date, no approved NDA or ANDA exists. One ANDA is pending approval.
3. "Approved for emergency use as a contraceptive agent following intercourse" is too broad in scope and misleading.

RECOMMENDATIONS: Correction of statement in "Medical Letter".

V. V. Karusaitis

Enclosure:
FR Statement

cc:
HFD-1
HFD-100
HFD-130

The Medical Letter, Inc.
56 Harrison Street
New Rochelle, N.Y. 10801

Gentlemen:

In the February 27, 1976 issue of The Medical Letter on Drugs and Therapeutics you stated:

> "Diethylstilbesterol (DES) - the estrogen diethylstilbesterol is approved for emergency use as a contraceptive agent following intercourse. Major hazard of diethylstilbesterol is the development of vaginal carcinoma in the female children of women who received the drug in early pregnancy."

While this statement is essentially correct, I believe it needs clarification in order to explain to your readers the exact current status of diethylstilbesterol for emergency contraceptive.

In the Federal Register of February 5, 1975, the Commissioner of Food and Drugs announced his conclusion that substantial evidence supports the safety and effectiveness of diethylstilbesterol administered as one 25 mg. tablet twice a day for five consecutive days, beginning preferrably within 24 hours and not later than 72 hours following sexual intercourse. This order was effective on March 7, 1975.

Moreover, the safety and effectiveness of the drug for this use is subject to strict conditions, such as: to be used only in emergency situations and not as a routine method of birth control; repeated courses of therapy are to be avoided; the course

of treatment must be as recommended and completed; failure of postcoital treatment with the drug deserves serious consideration of voluntary termination of pregnancy; and if the patient has any special health problems, such as migraine, mental depression, fibroids of the uterus, heart or kidney disease, asthma, high blood pressure, diabetes, or epilepsy, she should so inform her physician.

It was also stated in the Federal Register of February 5, 1975 that complete information for the physician, drug packaging containing only the number of 25 mg. tablets required for the one emergency treatment, a printed leaflet directed to the patient describing in detail how to use the drug, limitations on its use (contraindications, warnings, precautions, and possible adverse effects), would have to be provided with any diethylstilbesterol product before it could be marketed for this use. In addition, a drug application approval by this Agency is required before the product can be marketed.

The current situtation is as follows: although the Commissioner has approved diethylstilbesterol in specific potency and regimine for postcoital emergency use, there are at present no such products which have met all the requirements for approval of a drug application, and thereby can be legally marketed for this use.

This Agency would view with serious concern the use of any diethylstilbesterol product for emergency use as a post-coital contraceptive which was not specifically approved for that indication, and which, as a result, did not provide all the attendant labeling and packaging safeguards which have been specifically identified for the purpose of ensuring the safety and effectiveness of the drug product for that specific indication.

Sincerely yours,

as per Dr. Lasagna's request ← MARVIN SEIFE
~~Vincent V. Karusaitis~~, M.D.
Medical Officer
Division of Generic Drug Monographs
~~Office of Drug Monographs~~
Bureau of Drugs

Check with Art Temple re excellence of the single dose – post coital dt in pharmacy area of college level

(1) Medical Letter does not publish letters to the Editor or corrections of earlier articles – best one can expect is a very brief one-liner or one sentence note that no properly labelled product is currently available.

(2) An approved product may come to market before they get around to publishing note

(3) Last ¶ is not strictly accurate – the Agency does not officially view unapproved uses with concern – if believes that products should be properly labelled for their intended use – we regulate mfrs. not D's.

(4) would shorten letter greatly for above reasons.

ave

E MEDICAL LETTER, INC.
56 HARRISON STREET
EW ROCHELLE, N.Y. 10801
(914) 235-0500

THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

September 20, 1976

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Rockville, Maryland 20852

Dear Dr. Seife:

We have decided to publish the enclosed in an issue of the Medical Letter that goes to press Friday, September 24. If you have any comments or corrections, please call me collect before that date.

Sincerely,

Mark Abramowicz, M.D.

MA:ps

For Issue 463
September 20, 1976

DIETHYLSTILBESTROL AS AN EMERGENCY CONTRACEPTIVE

Some physicians may not realize that although diethylstilbestrol (DES) has been approved by the United States Food and Drug Administration for use as a "morning-after" postcoital contraceptive, and although various formulations of DES are available, no available product is approved for use as an emergency contraceptive. To ensure safe and effective use of the drug, the FDA required that for contraceptive use the package should include only the number of tablets needed for one emergency treatment, and that complete information for the physician (including contraindications, warnings, precautions, and possible adverse effects), and detailed instructions for the patient be provided in the package. No such package is available in the U.S., and physicians who prescribe DES from other packages for use as an emergency contraceptive should realize that such a practice is equivalent to prescribing an unapproved drug or an approved drug for an unapproved purpose.

LIMITATIONS AND HAZARDS OF DES AS A CONTRACEPTIVE - Diethylstilbestrol is effective as a postcoital contraceptive if it is given at the recommended dosage within specified time limits (Medical Letter, 15:58, 1973). Contraceptive failures can occur, however, especially if more than 24 hours elapses between unprotected intercourse and DES ingestion, if dosage is inadequate, if the severe nausea that can occur results in vomiting the pills, if a second sexual exposure occurs, or if pregnancy has already been established. Because a teratogenic effect is possible, early therapeutic abortion should be considered if emergency contraceptive treatment with the drug fails, and continuous or repeated

courses of therapy should be avoided because of the danger that a second course may have a teratogenic effect on a pregnancy that the first course failed to terminate.

AVAILABLE PRODUCTS - Products now on the market at a much lower dosage for other indications, such as estrogen deficiency states, postpartum breast engorgement, and palliation in carcinoma of the prostate or breast cancer, bear the statement "This drug product should not be used as a postcoital contraceptive

CONCLUSION - Physicians should be aware that no preparation of diethylstilbestrol available in the U.S. is approved for use as a postcoital contraceptive.

HFD-530

ESTABLISHMENT INSPECTION ENDORSEMENT

Page of Pages

1. ESTABLISHMENT

a. ESTABLISHMENT NAME: Eli Lilly & Company

b. DISTRICT: Detroit

c. CENTRAL FILE NO.:

d. ESTABLISHMENT ADDRESS (Include Zip Code, Area Code and Telephone No.): 645 S. Alabama Street, Indianapolis, Indiana 46225

e. DATE INSPECTED: 6/18&22/76

2. ROUTING

a. HEADQUARTERS UNIT TO WHICH REFERRED (Use organizational symbol): HFD-313: Attn: D. Plumb; HFD-530

b. REASON FOR REFERRAL: F.R. 2-5-75 Certain Estrogens For Oral Use - Notice of Withdrawal of Approval of NDA's.

HEADQUARTERS USE ONLY

c. DATE REFERRED:

d. AF NUMBER:

3. DISTRICT REMARKS

a. DISTRICT ENDORSEMENT

This limited inspection was conducted as F/U to NWK-DO/DET-DO TWX of 6/11/76 which reported the finding of 7/100 tablet bottles of Lilly's DES 25 mg. at a wholesaler in Atlantic City, New Jersey. The NDA for this product had been withdrawn by Federal Register announcement of 2/5/75.

Inspection showed Lilly delated both DES 25 mg. tablets (Tablet No. 1724) and the enteric coated 25 mg. tablet (Enseals No. 90) in March 1974. The last shipment was made 3/13/74. They did not recall either product and do not intend to at this time.

F/U: Attachment B Information was obtained and forwarded to DET(RME Coordinator) for consideration of requesting an FDA initiated recall, if indicated. NWK collected samples 76-37-230/231.

Copy of EIR to HFD-313 and HFD-530 for review.

HGW/RHS/bg

b. REVIEWING OFFICER (Name and title): Raymond H. Stutzman, Supervisory Investigator

c. SIGNATURE: R H S

d. DATE: 6-29-76

e. DISTRIBUTION: Or: DET(Zoscinick then EF), cc: Indy, HFD-313, (HFD-530), 481,481a to DET-DPU, DET(Rom)

FORM FD 481a (11/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Eli Lilly & Company
645 S. Alabama St.
Indianapolis, Indiana 46225

EIR 6/18&22/76
HGW

SUMMARY OF FINDINGS:

This inspection was conducted as a F/U to Trenton, N.J. R.P./DET-DO DIB TWX 0001 1631530 of 6-11-76 concerning Eli Lilly's DES 25 mg. tablets. A Trenton R.P. (NWK-DO) investigator had noted 7/100 tablet bottles of this product on a shelf at a local wholesaler, D. Kaltman Co., Atlantic City, New Jersey. Lilly's NDA on 25 mg. DES tablets had been withdrawn by Federal Register announcement of 2/5/75, a copy of which is attached as exhibit 1.

Lot numbers observed and samples collected were:

Lot Number	Exp. Date	Bottles of 100 on Hand at wholesaler	Sample No.	Sample Size
7HF35A	10/1/78	1	76-37-231	1/100
6WF00A	2/1/78	4	76-37-230	1/100
?	6/1/76	2	---	---

Purpose of this inspection was to determine whether Lilly had recalled outstanding stocks of the product when the NDA was withdrawn, and if not, to obtain Attachment B Information.

(Note: Federal Register announcement did not require recall).

Inspection revealed that Lilly had deleted this product and also the 25 mg. enteric coated DES tablet from their price list on 3/18/74, 11 months prior to the Federal Register announcement. A copy of this deletion notice is attached as exhibit 2. Firm did not recall outstanding stocks and does not plan to at this time.

Attachment B Information was obtained for both the 25 mg. tablets and 25 mg. enteric coated tablets:

1. PRODUCT INVOLVED: 1) Diethylstilbestrol Tablets U.S.P. 25 mg., Eli Lilly & Company, Indianapolis, Indiana (Tablet No. 1724).
   2) Diethylstilbestrol 25 mg. tablets, U.S.P. (Enteric), Eli Lilly & Company, Indianapolis, Indiana (Enscals No. 90).

   Labeling for both products attached as exhibit 3.

2. LOT NUMBERS: All lots.

3. ESTIMATED AMOUNT ON MARKET: None. The only lots manufactured in the last 5 years were:

Tablet 1724:	7HF35	Oct. '73
(lot size	6WF00	Feb. '73
400,000 tabs)	6PN95	Jul. '72
	5DD83	Jun. '71

Eli Lilly & Company
Indianapolis, Indiana 46225

EIR 6/18&22/76
HGW

Enseal 90:	7HF90	Aug. '73
(lot size	7CC80	Jun. '73
560,000	6RN72	Sep. '72
enseals)		

Tablet 1724 had been on the market since 3/21/47 and Enseal 90 since 8/14/51. Level of distribution was 100% wholesale, nationwide. Date of last shipment was 3/13/74. The Lilly Regional Distribution Centers were told to return all stocks for destruction. A total of 499,200 tablets of Enseal 90 were returned and destroyed, and 229,400 tablets of Tablet 1724.

4. ESTIMATED RATE OF USE: Essentially none now. In 1972-73, the rate of use of each product was approx. 50,000 tablets or enseals per month.

5. MANUFACTURER: Eli Lilly & Company -
Indianapolis, Indiana 46206

6. RECALLING FIRM: N/A.

7. REASON FOR RECALL NOTIFICATION: Approvals of the NDA's on these products were withdrawn by Federal Register Announcement of 2/5/75 (40 FR 25, p. 5384).

8. INJURIES, DEATHS: None. (In the past 5 years, no therapeutic complaints were received on either product. Enseals 90 received 2 minor technical complaints, Tablet 1724 had none in the past 5 years).

9. HOW FIRM LEARNED OF PROBLEM: Firm deleted products in March, 1974 because they knew the NDA's would be revoked.

10. HOW FDA LEARNED OF PROBLEM: 1) FR announcement of 2/5/75 withdrew approval of the NDA's. 2) DET-DO learned that Lilly's product was still in trade channels on 6-11-76 by Trenton R.P./DET-DO TWX of that date, #0001 1631530.

11. DISTRICT PLAN FOR FOLLOW-UP:

Inspection was terminated at this point.

NWK-DO has collected samples 76-37-230/231 of DES tablets 25 mg. (Tablet 1724).

EXHIBITS:

1. Federal Register Announcement of 2/5/75 withdrawing approval of Lilly's NDA's on DES Tablets and Enseals, 25 mg.
2. Price List deletion of these 2 products.
3a&b. Labeling of DES Tablets and Enseals, 25 mg.

Helen G. Wright

Helen G. Wright, Investigator
DET-DO, Indianapolis Resident Post

The Top 200 Drugs

1974 vs. 1975: Generics Rise By 3.2%, Despite 1% Dip in Total Rx Volume

Refills drop again, falling to 50.2% of all prescriptions

For the second year in a row, the total number of prescriptions filled in retail pharmacies *declined*, according to the National Prescription Audit (NPA) which is conducted by IMS America, Ltd., Ambler, Penna. Rx totals for the past 3 years:

- 1973—1,518,462,000 Rxs;
- 1974—1,504,535,000 Rxs;
- 1975—1,489,856,000 Rxs.

The 1975 vs. 1974 decline represents a 1% dip. However, in the face of this decline, and unlike the 1974 vs. 1973 survey —reported in the April 1975 issue of PHARMACY TIMES—generically-written prescriptions *increased* by 3.2%:

- 1974—138,664,000 generic Rxs;
- 1975—143,163,000 generic Rxs.

In its April 1975 issue, PHARMACY TIMES noted that, compared with 1973, the 1974 total Rx volume dropped by 0.9%, and that generics *also* dropped by 0.9%.

In 1975, new generically-written prescriptions continued their slow and steady 10-year climb, accounting for 11.1% of all new Rxs—1 out of every 9. (See Tables on pages 38 and 44.)

The growth of new generically-written Rxs is reflected in a review of generic Rx volume during the past 10 years when it increased by a whopping 178%:

- 1966—29,741,000 *new* generic Rxs;
- 1975—82,608,000 *new* generic Rxs.

Year-by-Year Increases

Year-by-year increases for the past 10 years—based on NPA data—are reflected in the table at the top of the next page.

During this same 10-year period, the *total* number of generically-written prescriptions —*new and refills*—has increased from 69,592,000 in 1966 to 143,163,000 in 1975 (a 105.7% increase).

More ►

Top 200 Drugs *(continued)*

Year	# New Generic Rxs	Total New Rxs	Generic/ New Rxs
1966	29,741,000	475,928,000	6.4%
1967	34,500,000	492,183,000	7.0%
1968	43,293,000	533,542,000	8.2%
1969	48,425,000	561,692,000	8.8%
1970	53,605,000	603,411,000	9.0%
1971	58,570,000	645,617,000	9.3%
1972	66,675,000	687,060,000	9.7%
1973	76,234,000	720,536,000	10.6%
1974	79,196,000	741,007,000	10.7%
1975	82,608,000	741,539,000	11.1%

And during this same 10-year period, *all* prescriptions (*brand and generic*) have increased from 1,054,917,000 in 1966 to 1,489,856,000 in 1975 (a 41.2% rise).

Thus, according to this 10-year data, *all* generically-written Rxs have increased at more than 2½ times the rate of the total Rx volume—105.7% compared with 41.2%.

Refills Drop Again

Prescription refills were responsible for the 1% drop in Rxs in 1975 compared with 1974. This is evident in the table on page 39, which shows that *new* Rxs increased by 0.1%, but refills fell by 2%.

In the last 3 years, the ratio of refills to total Rxs has been declining—as is reflected in the following percentage listings:

- 1973—52.5% of Rxs;
- 1974—50.7% of Rxs;
- 1975—50.2% of Rxs.

Reasons for the decline in refills include:

(1) Tightened regulations by the Drug Enforcement Administration restrict refills.

(2) The efforts of 3rd parties to increase allowable quantities per prescription have resulted in more doses of medication per Rx, resulting in a reduction in refills.

(3) Today's inflation-recession has reportedly caused people to postpone refills, to stretch their medication by skipping doses, or to eliminate refills altogether.

(4) Hospitals fill more outpatient prescriptions—both new and refills.

From 1 to 200

In addition to listing the Top 200 Drugs in units of 50 each, PHARMACY TIMES also provides the rank for each of these drugs—from 1 to 200. Thus, Valium—with a rank of 1—is the top drug of the Top 200. In a similar vein, Robaxin-750 has a rank of 200, just making the Top 200. This information is included in the 4 tables on pages 40 and 41—under the heading "Rank."

On pages 42 and 43, the Top 200 Drugs are listed in *alphabetical* order.

Comparing 1975 with 1974, we note the following information:

- 80 drugs rose in rank;
- 97 dropped in rank;
- 8 were unchanged in rank;
- 15 were not in the Top 200 in 1974.

A total of 15 generic drugs showed up in the Top 200 Drugs for 1975—as follows:

- 1st 50 drugs—6 generics (ampicillin, erythromycin, phenobarbital, prednisone,

NUMBER OF GENERICS AMONG TOP 200 DRUGS
(New Rxs—1966 thru 1975)

Drugs	'66	'67	'68	'69	'70	'71	'72	'73	'74	'75
1st 50	3	4	5	5	6	7	5	6	5	6
2nd 50	4	4	3	4	3	2	4	4	5	4
3rd 50	5	4	6	5	3	4	5	5	4	2
4th 50	1	3	4	2	4	2	2	0	1	3
Total	13	15	18	16	16	15	16	15	15	15

	1974	1975	% Change
New Rxs	**741,007,000**	**741,539,000**	**+0.1%**
Brands	661,811,000	658,931,000	−0.4%
Generics	79,196,000	82,608,000	+4.3%
Refills*	**763,528,000**	**748,317,000**	**−2.0%**
Brands	704,060,000	687,762,000	−2.3%
Generics	59,468,000	60,555,000	+1.8%
TOTAL	**1,504,535,000**	**1,489,856,000**	**−1.0%**

*In 1974, refills accounted for 50.7% of all Rxs; in 1975, refills dropped to 50.2%. In 1975, generically-written Rxs rose by 3.2% compared with 1974.

tetracycline hydrochloride, and thyroid);

- 2nd 50 drugs—4 generics (digoxin, meprobamate, penicillin G potassium, and penicillin VK);
- 3rd 50 drugs—2 generics (nitroglycerin and quinidine sulfate);
- 4th 50 drugs—3 generics (nicotinic acid, paregoric, and reserpine).

The Past 10 Years

The table (at left) shows the number of generics in the Top 200 in the past 10 years.

With respect to new prescriptions, the top 5 generics (ampicillin, tetracycline HCl, erythromycin, penicillin VK, and prednisone) all increased in 1975 compared with 1974. These 5 generics accounted for 52.1% of all new generic Rxs in 1975.

A newcomer to the top 20 generics is hydrochlorothiazide—in the No. 20 spot—accounting for 644,000 new Rxs in 1975.

Some of the prescriptions written generically can *only* be dispensed in the form of brand-named drugs. However, most generically-written Rxs are available under *both* brand and generic names—and, in many cases, pharmacists dispense brand-named drugs for generically-written prescriptions.

Top 200: 69% of All Rxs

The Top 200 Drugs for 1975 accounted for more than 2 out of every 3 prescriptions—new Rxs *and* refills. To be exact, these Top 200 drugs represented 69% of all Rxs. Interestingly, the top *100* drugs accounted for *over half* (54%) of all prescriptions.

More ►

38% Of All New & Refill Rxs

First 50

Drug & Manufacturer	Rank	Drug & Manufacturer	Rank
Valium (Roche)*	1	Elavil (MSD)	26
Premarin (Ayerst)*	2	Inderal (Ayerst)	27
Ampicillin (Unspecified)	3	Keflex (Lilly)	28
Lasix (Hoechst-Roussel)	4	Ilosone (Dista)*	29
Tetracycline HCl (Unspecified)*	5	Diuril (MSD)*	30
Darvon Compound-65 (Lilly)*	6	Butazolidin Alka (Geigy)	31
Librium (Roche)*	7	Librax (Roche)	32
Empirin Comp./Cod. (B-W)*	8	Lomotil (Searle)	33
V-Cillin K (Lilly)*	9	Fiorinal (Sandoz)*	34
Aldomet (MSD)	10	Erythromycin (Unspecified)	35
Ovral (Wyeth)	11	Dilantin Sodium (P-D)*	36
HydroDiuril (MSD)*	12	Aldoril (MSD)	37
Lanoxin (B-W)	13	Prednisone (Unspecified)	38
Actifed (B-W)	14	Mellaril (Sandoz)	39
Dimetapp (Robins)*	15	Achromycin-V (Lederle)*	40
Indocin (MSD)*	16	Antivert (Roerig)	41
Dalmane (Roche)	17	Ovulen 21 (Searle)	42
Donnatal (Robins)*	18	Ortho-Novum 1/50-21 (Ortho)	43
Benadryl (P-D)*	19	Triavil (MSD)	44
Darvocet-N (Lilly)	20	Ser-Ap-Es (Ciba)	45
Motrin (Upjohn)	21	Thyroid (Unspecified)*	46
Dyazide (SK&F)	22	Ornade (SK&F)*	47
Tylenol/Codeine (McNeil)	23	Aldactazide (Searle)	48
Erythrocin (Abbott)*	24	Percodan (Endo)	49
Phenobarbital (Unspecified)*	25	Sumycin (Squibb)	50

*In 1st 50 since 1966 (21 drugs).

16% Of All New & Refill Rxs

Second 50

Drug & Manufacturer	Rank	Drug & Manufacturer	Rank
Thorazine (SK&F)	51	Pen-Vee-K (Wyeth)	76
Pavabid (Marion)	52	Hydropres (MSD)	77
Hygroton (USV)	53	Mycostatin (Squibb)	78
Chlor-Trimeton (Schering)	54	Butisol Sodium (McNeil)	79
Phenaphen/Codeine (Robins)	55	Zyloprim (B-W)	80
Ortho-Novum 1/80-21 (Ortho)	56	Phenergan Exp./Cod. (Wyeth)	81
Mycolog (Squibb)	57	Atromid-S (Ayerst)	82
Diabinese (Pfizer)	58	Equanil (Wyeth)	83
Penicillin VK (Unspecified)	59	Neosporin (B-W)	84
Drixoral (Schering)	60	Equagesic (Wyeth)	85
Orinase (Upjohn)	61	Macrodantin (Eaton)	86
Digoxin (Unspecified)	62	DBI-TD (Geigy)	87
Isordil (Ives)	63	Stelazine (SK&F)	88
Talwin (Winthrop)	64	Compazine (SK&F)	89
Meprobamate (Unspecified)	65	Aristocort (Lederle)	90
Tranxene (Abbott)	66	Tofranil (Geigy)	91
Valisone (Schering)	67	Sinequan (Pfizer)	92
Benylin Cough Syrup (P-D)	68	Tuss-Ornade (SK&F)	93
Gantrisin (Roche)	69	Coumadin (Endo)	94
Synthroid (Flint)	70	Serax (Wyeth)	95
Darvon (Lilly)	71	Esidrix (Ciba)	96
Afrin (Schering)	72	Polycillin (Bristol)	97
Cortisporin (B-W)	73	Penicillin G Potassium (Unspecified)	98
Vibramycin (Pfizer)	74	Combid (SK&F)	99
Tenuate (Merrell-National)	75	Norlestrin-21 (P-D)	100

8% Of All New & Refill Rxs

Third 50

Drug & Manufacturer	Rank	Drug & Manufacturer	Rank
Marax (Roerig)	101	Azo Gantrisin (Roche)	126
Vasodilan (Mead Johnson)	102	Regroton (USV)	127
Kenalog (Squibb)	103	Phenergan Expect. (Wyeth)	128
Naldecon (Bristol)	104	Diupres (MSD)	129
Parafon Forte (McNeil)	105	Tylenol (McNeil)	130
Phenergan VC Exp./Cod. (Wyeth)	106	Decadron (MSD)	131
Periactin (MSD)	107	Apresoline (Ciba)	132
Nitroglycerin (Unspecified)	108	Ortho-Novum (Ortho)	133
Pentids (Squibb)	109	Bentyl (Merrell-National)	134
Bendectin (Merrell-National)	110	Mysteclin-F (Squibb)	135
Norgesic (Riker)	111	Monistat (Ortho)	136
Demulen-21 (Searle)	112	Cleocin (Upjohn)	137
Quinidine Sulfate (Unspecified)	113	E-Mycin (Upjohn)	138
Ionamin (Pennwalt)	114	Dimetane (Robins)	139
Teldrin (SK&F)	115	Isopto-Carpine (Alcon)	140
Salutensin (Bristol)	116	Synalar (Syntex)	141
Omnipen (Wyeth)	117	Placidyl (Abbott)	142
Actifed-C Expect. (B-W)	118	Pro-Banthine (Searle)	143
Gantanol (Roche)	119	Ritalin (Ciba)	144
Principen (Squibb)	120	Vistaril (Pfizer)	145
Doriden (USV)	121	Cordran (Dista)	146
Atarax (Roerig)	122	Ambenyl Expectorant (P-D)	147
Tandearil (Geigy)	123	Demerol (Winthrop)	148
Sudafed (B-W)	124	Poly-Vi-Flor Chewable (Mead Johnson)	149
Amcill (P-D)	125	Vioform/Hydrocortisone (Ciba)	150

7% Of All New & Refill Rxs

Fourth 50

Drug & Manufacturer	Rank	Drug & Manufacturer	Rank
Proloid (Warner/Chilcott)	151	Butazolidin (Geigy)	176
Paregoric (Unspecified)	152	Pyridium (Warner/Chilcott)	177
Feosol (SK&F)	153	Novahistine Expect. (Dow)	178
Pediamycin (Ross)	154	Robitet (Robins)	179
Flagyl Oral (Searle)	155	Etrafon (Schering)	180
Nembutal (Abbott)	156	Artane (Lederle)	181
Tedral (Warner/Chilcott)	157	Tigan (Beecham)	182
Polaramine (Schering)	158	Quibron (Mead Johnson)	183
Novahistine-DH (Dow)	159	Bentyl/Phenob. (Merrell-National)	184
Minocin (Lederle)	160	Norinyl-1/50-21 (Syntex)	185
Elixophyllin (Cooper)	161	Kaon (Warren-Teed)	186
Nicotinic Acid (Unspecified)	162	Tri-Vi-Flor Drops (Mead Johnson)	187
Hydergine (Sandoz)	163	Peri-Colace (Mead Johnson)	188
Medrol (Upjohn)	164	Reserpine (Unspecified)	189
Aldactone (Searle)	165	Peritrate SA (Warner/Chilcott)	190
Kwell (Reed & Carnrick)	166	Cyclospasmol (Ives)	191
Phenergan (Wyeth)	167	Sorbitrate (Stuart)	192
Septra (B-W)	168	Norlestrin FE 28 (P-D)	193
Provera (Upjohn)	169	Nitrobid (Marion)	194
Tolinase (Upjohn)	170	Garamycin (Schering)	195
Phenergan VC Expect. (Wyeth)	171	Noludar (Roche)	196
Seconal Sodium (Lilly)	172	Novahistine Singlets (Dow)	197
Enduron (Abbott)	173	Oracon-21 (Mead Johnson)	198
Ovral-28 (Wyeth)	174	Lidex (Syntex)	199
Terramycin (Pfizer)	175	Robaxin-750 (Robins)	200

More ►

Alphabetical Listing of The Top 200 Drugs

ALPHABETICAL LISTING	RANK	
Name of Product	1975	1974
Achromycin-V	40	26
Actifed	14	16
Actifed-C Expectorant	118	131
Afrin	72	59
Aldactazide	48	57
Aldactone	165	175
Aldomet	10	17
Aldoril	37	39
Ambenyl Expectorant	147	144
Amcill	125	142
Ampicillin	3	2
Antivert	41	48
Apresoline	132	192
Aristocort	90	84
Artane	181	178
Atarax	122	135
Atromid-S	82	93
Azo Gantrisin	126	123
Benadryl	19	18
Bendectin	110	110
Bentyl	134	149
Bentyl/Phenobarbital	184	174
Benylin Cough Syrup	68	62
Butazolidin	176	140
Butazolidin Alka	31	23
Butisol Sodium	79	75
Chlor-Trimeton	54	51
Cleocin	137	52
Combid	99	94
Compazine	89	85
Cordran	146	151
Cortisporin	73	89
Coumadin	94	102
Cyclospasmol	191	162
Dalmane	17	21
Darvocet-N	20	24
Darvon	71	68
Darvon Compound-65	6	3
DBI-TD	87	83
Decadron	131	137
Demerol	148	159
Demulen-21	112	124
Diabinese	58	54
Digoxin	62	61
Dilantin Sodium	36	36
Dimetane	139	145
Dimetapp	15	13
Diupres	129	121
Diuril	30	25
Donnatal	18	15

ALPHABETICAL LISTING	RANK	
Name of Product	1975	1974
Doriden	121	104
Drixoral	60	67
Dyazide	22	22
Elavil	25	29
Elixophyllin	164	**
Empirin Compound/Codeine	8	8
E-Mycin	138	184
Enduron	173	**
Equagesic	85	82
Equanil	83	73
Erythrocin	24	19
Erythromycin	35	56
Esidrix	96	107
Etrafon	180	170
Feosol	153	153
Fiorinal	34	189
Flagyl Oral	155	158
Gantanol	119	118
Gantrisin	69	64
Garamycin	195	185
Hydergine	163	160
HydroDiuril	12	12
Hydropres	77	65
Hygroton	53	63
Ilosone	29	27
Inderal	27	50
Indocin	16	11
Ionamin	114	127
Isopto-Carpine	140	155
Isordil	63	66
Kaon	186	176
Keflex	28	35
Kenalog	103	97
Kwell	166	**
Lanoxin	13	14
Lasix	4	7
Librax	32	32
Librium	7	4
Lidex	199	**
Lomotil	33	28
Macrodantin	86	90
Marax	101	115
Medrol	164	148
Mellaril	39	30
Meprobamate	65	70
Minocin	160	143
Monistat	136	**
Motrin	21	**
Mycolog	57	58
Mycostatin	78	71

ALPHABETICAL LISTING	RANK	
Name of Product	1975	1974
Mysteclin-F	135	130
Naldecon	104	113
Nembutal	156	125
Neosporin	84	87
Nicotinic Acid	162	136
Nitrobid	194	**
Nitroglycerin	108	105
Noludar	196	177
Norgesic	111	101
Norinyl-1/50-21	185	**
Norlestrin-21	100	88
Norlestrin FE 28	193	166
Novahistine-DH	159	157
Novahistine Expectorant	178	179
Novahistine Singlets	197	183
Omnipen	117	112
Oracon-21	198	164
Orinase	61	47
Ornade	47	40
Ortho-Novum	133	122
Ortho-Novum 1/50-21	43	44
Ortho-Novum 1/80-21	56	49
Ovral	11	9
Ovral-28	174	**
Ovulen 21	42	33
Parafon Forte	105	117
Paregoric	152	150
Pavabid	52	53
Pediamycin	154	134
Penicillin G Potassium	98	95
Penicillin VK	59	79
Pentids	109	69
Pen-Vee-K	76	74
Percodan	49	55
Periactin	107	109
Peri-Colace	188	182
Peritrate SA	190	181
Phenaphen/Codeine	55	46
Phenergan	167	154
Phenergan Expectorant	128	129
Phenergan Expect./Codeine	81	77
Phenergan VC Expectorant	171	187
Phenergan VC Exp./Codeine	106	108
Phenobarbital	25	20
Placidyl	142	128
Polaramine	158	168
Polycillin	97	78
Poly-Vi-Flor Chewable	149	193
Prednisone	38	41
Premarin	2	5

**A total of 15 products were newcomers to the Top 200 in 1975, as compared with 1974. The 15 products ranked between Nos. 21 and 200.

ALPHABETICAL LISTING	RANK	
Name of Product	1975	1974
Principen	120	111
Pro-Banthine	143	146
Proloid	151	152
Provera	169	171
Pyridium	177	190
Quibron	183	**
Quinidine Sulfate	113	126
Regroton	127	119
Reserpine	189	163
Ritalin	144	141
Robaxin-750	200	**
Robitet	179	**
Salutensin	116	114
Seconal Sodium	172	138
Septra	168	**
Ser-Ap-Es	45	43
Serax	95	103
Sinequan	92	100
Sorbitrate	192	**
Stelazine	88	91
Sudafed	124	139
Sumycin	50	31
Synalar	141	132
Synthroid	70	81
Talwin	64	60
Tandearil	123	120
Tedral	157	133
Teldrin	115	116
Tenuate	75	76
Terramycin	175	147
Tetracycline HCl	5	6
Thorazine	51	37
Thyroid	46	42
Tigan	182	165
Tofranil	91	92
Tolinase	170	167
Tranxene	66	86
Triavil	44	38
Tri-Vi-Flor Drops	187	**
Tuss-Ornade	93	96
Tylenol	130	99
Tylenol/Codeine	23	45
Valisone	67	72
Valium	1	1
Vasodilan	102	106
V-Cillin K	9	10
Vibramycin	74	80
Vioform/Hydrocortisone	150	156
Vistaril	145	172
Zyloprim	80	98

A quick summary of "The Top 200 Drugs"—in groups of 50—indicates that:

- The 1st 50—accounted for 38% of all prescriptions;
- The 2nd 50—16% of all Rxs;
- The 3rd 50—8% of all Rxs;
- The 4th 50—7% of all Rxs.

By keeping an adequate supply of the 200 fastest-moving drugs at hand—where they can be reached quickly—pharmacists will find that this arrangement . . .

1. Saves steps,
2. Saves time, and
3. Saves wear-and-tear.

In addition, pharmacists can bring the Top 200 Drugs to the attention of . . .

(a) Pharmacy & Therapeutics Committees—for hospital & nursing home formularies, and

(b) Federal, state, and local governments—or other 3rd party groups—for inclusion in various medical care or prepaid Rx programs.

Now in its 25th year, the NPA is a continuing study of the movement of prescriptions from retail pharmacy to patient. The data are provided through the cooperation of some 800 retail pharmacists. Pharmacists participating on the panel provide as many as 16 types of data on the Rxs they dispense.

The resulting *monthly* input of more than 100,000 prescriptions (some 1.5 million Rxs per year) forms the basis of the *copyrighted* national projection of retail prescription sales plus a host of other market characteristics. The result is a unique barometer of trends.

Significant data unveiled by the 1975 NPA with respect to Rx prices:

Top 200 Drugs *(continued)*

1975 Average price for new Rxs: $5.20 ($4.70 in 1974—a 10.6% increase);

(a) For brands—$5.34 (compared with the $4.81 in 1974—an 11.0% increase);

(b) For generics—$4.10 (compared with $3.75 in 1974—a 9.3% increase).

The NPA is conducted by IMS America, Ltd., of Ambler, Pa. 19002. Pharmacists who want more information on the NPA may write to William A. Lockwood at IMS.

Exclusive Analysis

As has been the case for the past 10 years, PHARMACY TIMES provides the nation's pharmacists with an *exclusive* analysis of the NPA's important data—covering both new Rxs *and* refills. ℞ ⇌ OTC

The Top 20 Generic Products New Rx Comparisons: 1974 vs. 1975

'74	New Rx Rank '75	Generic Product	Number of New Rxs in 1975 (Approximate)	New Rx Volume % Change '74 vs. '75
1	1	Ampicillin	15,908,000	+ 3%
2	2	Tetracycline	11,985,000	+ 3%
3	3	Erythromycin	6,091,000	+26%
5	4	Penicillin VK	4,967,000	+27%
6	5	Prednisone	4,071,000	+ 7%
4	6	Phenobarbital	3,943,000	− 6%
7	7	Penicillin G Potassium	2,585,000	− 5%
8	8	Meprobamate	2,155,000	+ 3%
9	9	Digoxin	1,849,000	− 8%
11	10	Thyroid	1,705,000	+ 4%
10	11	Paregoric	1,601,000	−10%
12	12	Nitroglycerin	1,295,000	− 3%
20	13	APC/Codeine	812,000	+41%
16	14	Quinidine Sulfate	797,000	+ 7%
14	14	Codeine Sulfate	797,000	0%
15	14	Chloral Hydrate	797,000	+ 2%
17	17	Ferrous Sulfate	710,000	− 3%
18	18	Terpin Hydrate/Codeine	688,000	+ 5%
13	19	Reserpine	656,000	−24%
22	20	Hydrochlorothiazide	644,000	+28%
		All Generic New Rxs	82,608,000	+4.3%

In 1975, new Rxs for the top 20 generics accounted for 77.5% of the new generic Rx total, 44.7% of all generic Rxs, and 8.6% of all new Rxs.

The number of generic Rxs (new & refills) totalled 138,664,000 in 1974 and 143,163,000 in 1975—a 3.2% increase.

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NITROGLYCERIN IN ACUTE MYOCARDIAL INFARCTION

Nitroglycerin has traditionally been contraindicated in patients with acute myocardial infarction because of the danger that lowering the blood pressure could increase the area of infarction. Some recent reports have suggested, however, that sublingual or intravenous administration of nitroglycerin might reduce the degree of ischemic injury in some patients with acute myocardial infarction. Nitroglycerin is not commercially available for intravenous administration.

MECHANISMS OF ACTION - Nitroglycerin causes general venous dilatation and peripheral pooling of blood. This reduces venous return, which diminishes the work of the heart and myocardial oxygen consumption. In a study of 34 patients undergoing coronary artery surgery, intra-aortic infusion of nitroglycerin decreased collateral coronary resistance and increased flow in collateral coronary arteries (RE Goldstein et al, Circulation, 49:298, 1974). An excessive reduction in coronary perfusion pressure, however, could lead to ischemia in segments of myocardium supplied by obstructed arteries (SE Epstein et al, N Engl J Med, 292:29, 1975).

NITROGLYCERIN AFTER MYOCARDIAL INFARCTION - The effects of nitroglycerin in acute myocardial infarction have been evaluated primarily by observing the effects of the drug on ST segment abnormalities in precordial "surface map" electrocardiograms. ST segment changes have been shown to correlate with ischemic damage in dogs, but have not been validated as a means of assessing such injury in man. There are no published data on the effect of the drug on mortality or morbidity of patients with an acute myocardial infarction.

Sublingual Nitroglycerin - Administration of 1.5 to 2.5 mg of sublingual nitroglycerin to five patients with acute myocardial infarction and left ventricular failure reduced ST segment abnormalities (JS Borer et al, N Engl J Med, 293:1008, 1975). In the same study, administration of sublingual nitroglycerin to six patients without left ventricular failure reduced ST segment elevation in four patients, and had no effect in one. The sixth patient developed hypotension, with an increased heart rate and ST segment elevation. In another study a small dose of 0.4 mg of sublingual nitroglycerin led to a potentially harmful decrease in cardiac output and systemic blood pressure (DO Williams et al, Circulation, 51:421, 1975). The rate of absorption of sublingual nitroglycerin is unpredictable, and the effects are short-lived.

Intravenous Nitroglycerin - Intravenous infusion of nitroglycerin in 17 patients with acute myocardial infarction and left ventricular failure also reduced ST segment abnormalities (JT Flaherty et al, Circulation, 51:132, 1975; PC Come et al, N Engl J Med, 293:1003, 1975). In a more recent study of intravenous nitroglycerin the drug appeared to decrease ischemia in a few patients without cardiac failure as well (JT Flaherty et al, Br Heart J, in press).

ADVERSE EFFECTS OF NITROGLYCERIN - Nitroglycerin can cause sudden, severe hypotension, especially with sublingual administration, and particularly in patients not in left ventricular failure. This effect might increase the extent of ischemic injury (CE Delgado et al, Br Heart J, 37:392, 1975), so that continuous monitoring of arterial and pulmonary wedge pressure is advisable. Hypotension can be reversed rapidly by leg raising, or by intravenous administration of phenylephrine, but the effects of phenylephrine are difficult to control and an excessive hypertensive response may occur.

CONCLUSION - Preliminary studies in a small number of patients suggest that nitroglycerin might diminish the extent of myocardial ischemia in patients with an acute myocardial infarction. The cardiac effects of sublingual nitroglycerin are unpredictable, and severe hypotension can occur. Intravenous nitroglycerin requires careful continuous hemodynamic monitoring; the preparation is not commercially available. It is not known whether nitroglycerin given by any route reduces mortality or morbidity in patients with acute myocardial infarction.

✱ DRUGS FOR IMPROVEMENT OF CEREBRAL FUNCTION IN THE ELDERLY

Advertisements for several drugs suggest that they can reverse or halt symptoms of mental deterioration or dementia in elderly patients. Deterioration of intellect, memory, self-care, judgment, and orientation in most elderly patients is now thought to be due to progressive degenerative changes in the brain itself, and usually not to faulty circulation through atherosclerotic blood vessels.

✱ PAPAVERINE - Papaverine hydrochloride (Pavabid; Cerespan; and others) and its congeners, ethaverine hydrochloride and dioxyline phosphate, are offered for the relief of cerebral vascular disorders. In current advertisements it is claimed that Pavabid (Marion) helps preserve cerebral circulation and "Often relieves and reduces symptoms of cerebral ischemia associated with arterial spasm." Advertisements for Cerespan (USV) claim that it "can increase cerebral blood flow" as shown by "improvements in the thermograms."

No well-controlled trials have shown that any papaverine product will prevent or relieve ischemic cerebral vascular disease in man or improve the mental or physical state of elderly or senile patients. Adverse effects of oral papaverine drugs include nausea, drowsiness, rash, headache, and vertigo.

✱ CYCLANDELATE - Cyclandelate (Cyclospasmol - Ives), an oral vasodilator like papaverine, is claimed to be effective "for 'smaller artery disease' — whether peripheral or cerebral" and to help Gladys and Amy, "actual" patients pic-

MEMORANDUM OF CONFERENCE

Marion Laboratories, Inc.
Kansas City, Missouri
NDA 16-575
AF 2-108

DATE: June 18, 1975

BETWEEN: Mr. Merle E. Wood, Director, Government Services, Marion
Mr. Dewey Alexander, Manager, Institutional Relations, Marion
and, Mr. Thomas W. Cavanaugh, Acting Director, Division of Drug Advertising

SUBJECT: Pavabid Status

The Marion representatives came in without an appointment to discuss the regulatory status of Pavabid, particularly with regard to advertising. They stated that their visit was prompted by their recent receipt of the minutes or report of the Geriatrics Subcommittee to the Neuropharmacological Drug Products Advisory Committee. The report outlined Dr. Rheinstein's presentation of various promotional activities involving drug use in the aged, which included those activities of Marion Labs promoting their drug, Pavabid, for symptoms of senility, stroke, etc.

Mr. Cavanaugh told the visitors that behind any ad problems was the fact that the drug is a new drug on the market without an approved NDA, and that the basic question was not the advertising of claims, but whether the drug should be marketed at all in the absence of substantial evidence of effectiveness for any claims. The visitors were told that the problem also extended to competitive products such as USV's Cerespan.

A brief discussion then ensued concerning various efficacy claims made by Marion for Pavabid and by their competitors for similar products.

The Marion representatives said they wished to do whatever necessary to prevent removal of the drug from the market. Mr. Cavanaugh advised them to consult with Dr. Scoville and/or Dr. Hayes in the Division of Neuropharmacological Drug Products, who are very much aware of the problem. They thanked Mr. Cavanaugh for his assistance and the meeting concluded.

Thomas W. Cavanaugh
Acting Director
Division of Drug Advertising
Bureau of Drugs

TWCavanaugh:bjt 6/19/75

cc: Orig.(HFD-120), Dup., Trip.(Kan-DO)
HFD-170

MEMORANDUM OF MEETING

Marion Laboratories
Kansas City, Missouri
AF 2-108

DATE: November 26, 1975

BETWEEN: Mr. James McGraw, President, Pharmaceutical Division, Marion Labs.
Mr. Gene R. Sperry, Senior Vice President, Marketing, Marion Labs
Gerald L. Beckloff, M.D., Vice President, Medical Research & Development, Marion Labs.
Mr. Merle E. Wood, Director, Government Services, Marion Labs
and
Dr. Peter H. Rheinstein, Director, Div. of Drug Advertising
W. C. Drury, CSO, Division of Drug Advertising
T. W. Cavanaugh, CSO, Division of Drug Advertising

SUBJ: Marion's Presentation of Current and Proposed Labeling and Promotion of Pavabid.

The Marion representatives came in at their request to inform FDA of their current and proposed activities concerning labeling and promotional material for Pavabid.

At the outset, the Marion representatives were reminded, as in the November 11, 1975 meeting (see files), that the Division of Drug Advertising was not in a position to approve any material for Pavabid, nor to offer comment on the legal status of the marketed drug.

The Marion representatives indicated they were not seeking "approval" of any advertisements or labeling, but just wanted to be open with FDA, inform FDA of their actions and intentions, and informally discuss current and proposed actions by Marion concerning their "service" or "educational" pieces as well as their labeling and other promotional material.

Marion indicated that their intentions were to:

1. As a voluntary gesture, retrieve from the field all promotional material except those pieces consisting of essentially package insert information.

2. Limit advertisements to a "reminder-type," i.e., a promotional section which stresses packaging, etc., but makes no claims of safety or efficacy, plus a "Brief Summary" or "Full Prescribing Information."

3. Promotional material will carry a warning or precaution concerning the reported antagonism between papaverine and L-dopa.

4. Submit a 1961 FDA letter informing Marion that Pavabid is regarded as "an old drug."

5, Submit revised promotional material.

6. Revise films and brochures dealing with vasodilation, TIA's, strokes, etc. to omit the "full disclosure" for, as well as the name of, Pavabid. They will also delete any references to Pavabid. This would,theoretically, convert this material to "service pieces" when not used in conjunction with any Pavabid promotion.

Dr. Rheinstein agreed that the foregoing steps appeared prudent.

Dr. Rheinstein stated that the Agency has set a precedent of requiring in labeling an affirmative disclaimer where there is a widespread belief that a product is good for a particular indication and there are no adequate and well-controlled studies to support this. Dr. Beckloff agreed that Marion has no adequate and well-controlled studies to support the use of Pavabid either as prophylaxis for stroke or in the post CVA patient.

The America Heart Association is reprinting #24830.

Marion proposed several ads, none of which was acceptable. One compared the cost of Pavabid to the cost of Vasodilan, Hydergine and Cyclospasmol. DDA commented that this suggests that Pavabid is as effective as products which have been rated effective under DESI.

Pending further Agency study, Marion was told that this Division will defer action on ads which do no more than repeat the package insert and show an illustration not related to a product indication. Ads which refer to manufacturing practice and dosage schedule do not imply safety or efficacy providing Pavabid is not compared to other products which are safe and effective.

Promotion related to widespread physician experience is a claim for safety and efficacy.

The Marion representatives were provided a copy of the attached handwritten notes by Dr. Rheinstein at the conclusion of the meeting.

T. W. Cavanaugh

T. W. Cavanaugh
Consumer Safety Officer
Division of Drug Advertising

Attachment

TWCavanaugh:na 12/30/75
cc: Orig (HFD-120, Dup., Trip.KAN-DO)
HFD-170

Attachment to Memo of 26 November 1975 FDA/Marion Meeting Re Pavabid (NOTE: These are Dr. Rheinsteins notes, and a copy of these notes was provided to Marion Labs at the conclusion of the meeting).

Marion is adding L-dopa interaction.

Marion will modify educational systems in an attempt to make them not labeling.

Logos carrying over to promotion will be discontinued. All mention of papaverine HCl will be deleted. There will be a brief mention of vasodilators as a stroke Rx.

Dr. Rheinstein stated that the Agency has set a precedent of requiring in labeling an affirmative disclaimer where there is a widespread belief that a product is good for a particular indication and there are no adequate and well-controlled studies to support this. Dr. Beckloff agreed that Marion has no adequate and well-controlled studies to support the use of Pavabid either as prophylaxis for stroke or in the post CVA patient.

American Heart Association is reprinting # 24830.

All current Pavabid promotion has been recalled. Dr. Rheinstein agreed this was prudent.

Marion proposed several ads. One compared the cost of Pavabid to the cost of Vasodilan, Hydergine and Cyclospasmol. DDA commented that this suggests that Pavabid is as effective as products which have been rated effective under DESI.

Pending further Agency study, this Division will defer action on ads which do no more than repeat the package insert and show an illustration not related to a product indication. Ads which refer to manufacturing practice and dosage schedule do not imply safety or efficacy providing Pavabid is not compared to other products which are safe and effective.

Promotion related to widespread physician experience is a claim for safety and efficacy.

Division of Drug Advertising remarked that it could not comment on the legal status of the marketing of Papaverine HCl.

PHRheinstein:na 12/30/75

MEMORANDUM

FOOD AND DRUG ADMINISTRATION

TO : Director, Bureau of Drugs
Through: Deputy Director _____
Through: Director, Office of Compliance_____

DATE: August 8, 1974

FROM : Director
Office of Scientific Evaluation

SUBJECT: Papaverine and Ethaverine - Mr. Byers memo of July 8, 1974

In May 1974 Dr. Leventhal asked us to devote a "rounds" for HFD-120 to a discussion of the advertising claims for "cerebral vasodilators" such as Hydergine and Pavabid (papaverine HCl). Dr. Rheinstein was invited and so was Mr. Vodra.

There was general dismay at the excessive, unsubstantiated claims of the Pavabid ads which proclaim the drug for almost every area affected by impaired circulation. Papaverine is a "grandfathered" drug which did not come under DESI review. Some individuals attending "rounds," including Dr. Rheinstein, wanted to tackle Pavabid independent of a systematic program to review all "grandfathered" drugs for efficacy. Dr. Leventhal and I felt strongly that pulling one drug from the stack just because we happened to notice the excessive promotion was illogical and non-orderly. (Through the years I have received promotional pieces on other grandfathered drugs sent to me by physicians who were just as outraged at the claims being made as we are with respect to Pavabid. Admittedly, none of those drugs were as well known and as widely promoted as Pavabid. Nevertheless, I have also seen many examples of other grandfathered drugs where it is clear that efficacy has not been established for their claims.)

Mr. Vodra agreed with Dr. Leventhal and me that Mr. Hutt's philosophy is opposed to singling out one offender in the absence of a concerted plan to deal with all offenders on a systematic basis. Accordingly, following the "rounds" I sent a memo to appropriate individuals with respect to the promotion of a Task Force to identify and review the efficacy of non-NDA'd prescription drugs on the market, be they pre- or post - 1938 drugs. (Attachment A). The first meeting of this Task Force was scheduled for August 7, 1974. Members, in addition to myself, are Dr. Bryan, Mr. Batts, Miss Mansur and Mr. Apodaca.

Unless you feel that the Pavabid situation is so flagrant that it must be dealt with immediately, I would like to suggest that no action be taken on Mr. Byer's memo of July 8, 1974.

Attachment B consists of the minutes of the first Task Force meeting.

If you feel that you would still like to proceed with papaverine and ethaverine, then I might say that I disagree with the memo prepared for my signature by Dr. Belton which suggests a F.R. announcement that we are preparing to remove the drugs because of lack of evidence of efficacy unless we hear to the contrary. I would prefer that we call for data providing evidence of efficacy based upon adequate and well-controlled studies. If we take Dr. Belton's suggested route, we would need to document our review of the literature and our findings that none of the studies are adequate and well-controlled. In addition, many patients who think they are benefiting from the drugs would be shaken by our abrupt proposal. It would not be difficult to deal with Pavabid, because it is actually no longer "grandfathered" since the labeling (and, perhaps, the ingredients) have been altered since 1938. (Under Mr. Vodra's proposed new definitions for loss of grandfather status, the above would apply to Pavabid, certainly.) Mr. Hutt and Mr. Vodra state that a firm cannot revert to its old labeling and old ingredients when challenged. Once these have changed, the drug in question is "new."

Attachment C is a preliminary report on an uncontrolled study on use of papaverine for prophylaxis of migraine which I just ran across the other day. It is possible the drug might turn out to have efficacy for something. Also, it might be mentioned that some of the new Hydergine studies in the symptoms of senility used papaverine as a "positive control" and results of the two drugs were comparable, which is not, of course, to say that papaverine is effective, since a placebo control was not used in the same study and maybe both drugs were equally ineffective in the conditions of those studies; I was merely pointing it out as another possibility that the drug might have some efficacy. I would never have believed that Hydergine was effective, either, before the studies were done.

Marion J. Finkel, M.D.

Attachment A - Dr. Finkel 5/31/74 Memo
Attachment B - 8/7/74 Task Force Meeting Minutes
Attachment C - Preliminary report - Papaverine in Prophylactic Treatment of Migraine

MEMORANDUM OF MEETING

April 16, 1974 11:00 a.m.

ETWEEN:

. Scoville, M.D., Director, DNPDP(HFD-120)
. Temple, M.D., Special Asst to the Director, BD (HFD-1)
. Hobart, M.D., DNPDP (HFD-120)
. Backrack, M.D., DCRDP (HFD-110)

ND:

. H. Rheinstein, M.D., Director, DDA(HFD-330)
. W. Cavanaugh, CSO, DDA (HFD-330)
. R. Feather, CSO, DDA (HFD-330)

CIBA-Geigy Tofranil-PM
Summit, N.J. NDA 11-836
AF 20-332

Marion Laboratories Pavabid
Kansas City, MO AF 2-108

Roche Laboratories, Inc.
Nutley, N.J. Librium
NDA 12-249
AF 14-324

UBJECT:

edical Opinion on Ads for Tofranil-PM, Pavabid, and Librium

he meeting was held in Dr. Scoville's conference room at
r. Rheinstein's request.

The first item discussed was the current promotional campaign for Tofranil-PM. It was felt that the advertising implies Tofranil-PM 150 mg. is different and better than Tofranil 50 mg., when in fact three 50 mg. tablets will produce the same effect if given in a once-a-day dosage. The discussion centered on whether a change in the Tofranil 50 mg. labeling should be initiated. Dr. Scoville said the firm did studies on 150 mg. pamoate formula as a once-a-day dosage to prove it was effective. However, as far as he knew no such data was produced on the 50 mg. HCl formula. He said before he agreed to a label change he would like to see some data. The discussion ended with Dr. Scoville stating he would review the NDA to see if data exists that the 50 mg. form could be used as a three tablet once-a-day dose. The subject will be reviewed at that time.

A Librium ad for use in ulcers then was discussed. Dr. Temple said he thought this ad went beyond the indications section of the label and implied the drug was good to treat ulcers, not just anxiety related to ulcers. A long discussion followed as to the statements in the ad and their meaning and whether or not they in fact go beyond the approved labeling. It was decided that the claims did go further than the labeling permitted, by implying Librium treated the disease (ulcer) rather than the underlying anxiety. All of the participants agreed a "Dear Doctor" letter should be issued on the entire campaign. Dr. Temple said he would discuss this with some other people and get back to us.

Pavabid and the general papaverine problem was then discussed. It was agreed that the Pavabid campaign contained excessive claims since the product was probably not effective as a cerebral vasodilator at all. As a new drug without an approved NDA it was agreed the drug should be taken off the market rather than try to correct advertising. Such a recommendation will be made to the Office of Compliance.

The meeting was then adjourned.

Kenneth R. Feather

K. R. Feather
Consumer Safety Officer
Division of Drug Advertising

KRFeather:tm 4/22/74

cc: HFD-106, HFD-305(Leon),
HFD-330,
Orig., Dup.

Senator KENNEDY. Dr. Seife, what is papaverine time release?

Dr. SEIFE. Straight papaverine is a "grandfathered" drug. But that I mean a drug used prior to 1938. Therefore it could be marketed without any drug application.

Once you make a timed release preparation, I believe according to a 1959 regulation to the Food and Drug Act, any timed-release product required a full NDA (new drug application). Therefore if somebody wanted to market papaverine in timed-release form, he would have to have a new drug application, based on safety only.

In 1962, the Kefauver-Harris amendments were passed whereby the drug had to show safety and efficacy.

Eventually, I think earlier in 1960, Marion Laboratories marketed a timed-release papaverine and never filed a new drug application, although they were required to. The agency did nothing about it because as of this date there is no new drug application for any timed-release papaverine preparation, whether it be made by Marion Laboratories or USV or many generic houses.

Senator KENNEDY. The point is there should be an NDA?

Dr. SEIFE. Absolutely.

Senator KENNEDY. There is a drug on the market now for which there should be an NDA, but for which there is not?

Dr. SEIFE. Right.

Senator SCHWEIKER. Is this contrary to existing regulation or law, or is there a loophole in the regulations and law?

Dr. SEIFE. This is contrary to our present regulations. Taking this one step further, when we gave all these drugs to the NAS–NRC (National Academy of Science and National Research Council) for review, post-efficacy, post-Kefauver-Harris, all the time-release drugs were rated no higher than "possibly effective." Papaverine timed release was not in that group, because the firm never filed a New Drug Application. Therefore, it was never reviewed by NAS–NRC. It was "Catch–22." Companies are marketing and advertising this form of the drug and doing whatever they please. The firm, Marion Laboratories, now owns the Kansas City Royals. They are multimillionaires. You have practically every old person in the United States in a nursing home taking two capsules of this drug a day. If you read Gillman and Gillman, a classical textbook on pharmacology, they call this drug of "historical" interest.

Yet it is out there without a New Drug Application. Not only Marion Labs, but USV——

Senator KENNEDY. What is the value of that particular drug?

Dr. SEIFE. There is none. There is no value to it at all. In fact I think it might be of some harm, because it removes blood by causing muscle relaxation—smooth muscle relaxation of your arteries, it removes blood from certain vital areas, heart and brain to peripheral sites. It might do damage.

Senator KENNEDY. Mostly elderly people in the country are taking it?

Dr. SEIFE. Right.

Senator KENNEDY. I suppose medicaid is picking up the tab on it?

Dr. SEIFE. Exactly.

Senator KENNEDY. Which is adding cost of millions of dollars to the health care costs.

Senator SCHWEIKER. Dr. Seife, there must be some loophole procedure or some way of getting around the regulations and law. Can you explain how this is possible?

Dr. SEIFE. I've been with the agency almost 11 years, and I have heard Pavabid discussed over and over again, that is by the Office of Compliance and our general counsel. Right now they are wrestling with what to do with Pavabid and other timed release papaverine preparations. Because the FDA failed to do something about it 10 years ago, 12 years ago, whatever, the problem has gotten greater and greater, and right now it will be quite a task to get these products off the market.

Marion Labs is quite wealthy. USV is owned by Revlon. We are talking about millions and millions of dollars and many, many lawsuits.

Senator KENNEDY. To get it off the market?

Dr. SEIFE. Yes.

Senator SCHWEIKER. Sort of like perpetual litigation?

Dr. SEIFE. That is right. This supersalesman, who is the chairman of the board of Marion Laboratories, decided to market this product; he did, and he became a multimillionaire.

Senator SCHWEIKER. Do we not need some tighter laws, then, to prohibit a drug such as this to be sold without a new drug application?

Dr. SEIFE. We have the law. This firm circumvented it and FDA did nothing. We are like a toothless tiger in many instances. This is one of the worst examples of abuse.

Senator SCHWEIKER. The law is simply not being enforced, you say?

Dr. SEIFE. That is right.

Senator KENNEDY. Can we go to Mary Bruch and Merle Gibson.

In the instance of soft contact lens, I think that as a result of their dedication, a number of individuals—Mary Bruch and Mr. Gibson, in particular—were able to resist strong industry pressure and other pressures. It is important that we recognize that dedication and I think this is a story we want to hear about. So, Mary, could you tell us how many soft contact lenses were on the market when you got involved in this?

Mrs. BRUCH. 1974, the soft contact lenses were transferred from another division to the division in which I worked, which is Anti-Infective Drug Products. At that time there was one approved lens on the market for vision correction. There was an approval, a limited approval, for Warner Lambert for therapeutic use for one indication. Shortly after the lenses were transferred to our Division, another lens made by Soft Lenses, Inc., in San Diego was approved.

Senator KENNEDY. What was your role in reviewing this?

Mrs. BRUCH. Well prior to the transfer of these lenses to my division, I had helped the Division of Dental and Surgical Adjunct who had no microbiologists, which is my background, to prepare a set of testing guidelines, so when the lenses were transferred to my Division I was put in charge of reviewing the microbiological aspects of the soft contact lenses. And just as a point of information, these new lenses are required to be kept wet at all times or they dry out and become useless to the consumer. So that the agency and recognized opthamologists and our advisory committees have suggested that they have an effective disinfection system when the lens is approved. The lens that

were approved so far have all been approved with heating at approximately boiling temperatures or lower as a means of disinfection.

Senator KENNEDY. Well now, after all was said and done, you resisted; you made a recommendation of not approving the lens because of sterility guidelines. Is that correct?

Mrs. BRUCH. This is a lens that was submitted for approval by Warner Lambert. It is licensed to Warner Lambert by another company; namely, Frigitronics. They proposed to us to use disinfectant system different from heat, that is, to use hydrogen peroxide. Their lens cannot be repeatedly heated for a cosmetic use.

Senator KENNEDY. You finally did recommend disapproval of that sterility system?

Mrs. BRUCH. That is correct.

Senator KENNEDY. Were you subjected to unusual industry pressure during this process?

Mrs. BRUCH. Are you asking me for my opinion?

Senator KENNEDY. Yes.

Mrs. BRUCH. Yes.

Senator KENNEDY. Can you tell us a little bit about it?

Mrs. BRUCH. Mainly it was an attempt on the part of both companies to attack my scientific training, my scientific integrity, the suggestion that my stand on the disinfection system was based on prejudice, my personal prejudice against chemical disinfection, and that really I was not qualified to review the applications and that I inexperienced in this area and, you know, really personal attack on my abilities.

Senator KENNEDY. Were you accused of being on the payroll of a competitive company?

Mrs. BRUCH. At a reception in New York in private conversation I was.

Senator KENNEDY. Was there unusual telephoning by the company to you and your superiors?

Mrs. BRUCH. Many phone calls from both companies and in addition something I had never experienced at FDA, I would say for close to a year hardly a day went by that we did not have a stockholder from one—mainly from Frigitronics call our office. My secretary became very adept at screening these people out.

Senator KENNEDY. You got congressional pressure as well?

Mrs. BRUCH. Many letters from Congressmen and Senators, from their constituents, and from the companies to them.

Senator KENNEDY. Did you consider this pressure to be the customary pressure on an NDA or did it exceed that?

Mrs. BRUCH. We had expected inquiries and questions, whether there is delay, why the delay? That is ordinary. We expect meetings and we expect phone calls and all of that. But this is at the level which I had never experienced with the FDA.

Senator KENNEDY. Or since then?

Mrs. BRUCH. Or since.

Senator KENNEDY. Dr. Gibson, you are Mrs. Bruch's supervisor?

Dr. GIBSON. That is correct.

Senator KENNEDY. Are you aware of the industry pressure in this case?

Dr. GIBSON. Yes; I was. We were quite aware of the unusual pressure that Mrs. Bruch was subjected to. An additional one she did not mention was pressure from her peers on the outside, which I think is the most difficult pressure to resist, her scientific peers on the outside in academic, medicine, and other areas, who were acting as consultants——

Senator KENNEDY. These were people actually acting as consultants, that were getting some remuneration for their position?

Dr. GIBSON. That is correct.

Senator KENNEDY. Was this the usual pressure that you would see over in the agency?

Dr. GIBSON. No. As Mrs. Bruch said, we expect a certain amount of pressure and interest in applications, both from the applicant, from physicians who may have used the drug as an investigational drug and who have developed an interest in it, and from Congress, as a rule from inquiries from their constituents. But this I felt when it came down to personal attacks on the integrity of the reviewers was unusual.

[Information subsequently supplied for the record follows:]

MEMORANDUM

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

TO : Associate Director for New Drug Evaluation

DATE: February 10, 1976

FROM : Director, Bureau of Drugs

SUBJECT: NDA 17-554 Warner Lambert Softcons Lens

I am returning the proposed nonapprovable letter to NDE for further consideration of the laboratory testing conducted by PRT before a nonapprovable letter is sent. My reason for this is as follows: I spoke on the phone today with Dr. Buyske of Warner Lambert to inform him that a nonapprovable letter on their Softlens was about to issue. I felt this a courteous thing to do in view of the prolonged negotiations we have had with Warner Lambert over this NDA. Dr. Buyske was, interestingly, not particularly upset by the news that PRT was unable to confirm the effectiveness of the disinfection procedure for this lens. He stated that both Warner Lambert and an outside consulting firm had confirmed the effectiveness of the disinfection system under the protocol agreed upon by FDA and felt quite confident that our inability to confirm these results was due to technical errors in conducting the tests in our laboratories. Specifically, Dr. Buyske indicated that Warner Lambert personnel had not been given the opportunity to go over in detail on a person to person basis the technique of the procedure with our laboratory personnel and PRT. He also stated that our tests had not been conducted in a laminar flow hood and therefore that the possibility of contamination was great. In stating these views, Dr. Buyske wanted to make clear he was not complaining about our staff. He simply felt confident that if certain technical matters were worked out we would rather easily confirm the effectiveness of their disinfection procedure.

Dr. Buyske asked if Warner Lambert could have a copy of the report from PRT. I indicated that he could, and indeed read to him the results section over the phone. He indicated that they would like to go over the whole report and then meet with the FDA staff about this problem. I agreed to this approach on the phone, since I could not in good conscience issue a nonapprovable letter in the face of a complaint that Warner Lambert's testing procedure had not been followed in detail. I was also concerned that our laboratory results are at variance with those obtained by Wells Laboratories, an outside consulting

laboratory, and that our own studies, if I understand them correctly, appear not to contain a negative control demonstrating lack of cross contamination. Under these circumstances, I did not feel I could take a hard position with Dr. Buyske to send a nonapprovable letter as our final position on this application.

I am therefore requesting that Warner Lambert be given a copy of Mr. Evans' report and an opportunity to meet with the staff in PRT to review the technical details of the testing procedure. Because of the prolonged controversy over this application, which clearly needs final resolution, I would also request that we permit Warner Lambert personnel to work along side our own staff in repeating any necessary lab work so they have no cause whatsoever to again claim that the proper technique was not followed. We are getting down to whether we will go to a hearing with Warner Lambert over this application, and if so our entire case will rest upon our laboratory findings. Given that, both we in the FDA and Warner Lambert must feel totally secure that our own laboratory work is unassailable and impeccably documented.

My request for review of the situation is simply to be certain that everyone agrees our position is secure. Once we send a nonapprovable letter to Warner Lambert, we have given them little choice but to go to a hearing or to start over again with a new disinfection procedure. Before forcing that decision, we should be fairly certain we can win a hearing on the effectiveness of their current disinfection procedure.

I appreciate everyone's help with this very important problem and would be glad to discuss it further as you desire.

J. Richard Crout, M.D.

J. Richard Crout, M.D.

cc:
Dr. Gibson (HFD-140)
Ms. Bruch (HFD-140)
NDA 17-554
Dr. Lamanna (HFD-400)
Mr. Evans (HFD-413)

MEMORANDUM OF TELEPHONE CONVERSATION

February 11, 1976

Between: Dr. Donald Buyske
Warner Lambert Pharmaceutical Company

and

J. Richard Crout, M.D.
Director, Bureau of Drugs

Subject: Warner Lambert Soft Lens (NDA 17-554)

I called Dr. Buyske to indicate that we would run the disinfection procedure for the Soft Lens over again and that his contact point in arranging for this would be Mr. Julian Kramer at (202) 245-1072. I further indicated that we would run only the method as described in the most recent consumer brochure and that the volume of rinse after the washing step would be 30 ml. of saline. Dr. Buyske indicated this was his understanding also and that 30 ml. of solution was in fact 3 or 4 squirts from the saline bottle offered for sale to the consumer. He also indicated that this was a critical step in the procedure and that the differing results between his laboratory and ours might have occurred because of differences at this step.

I also indicated to Dr. Buyske that Mr. Jimmy Evans was undergoing surgery today and was not expected for a week to ten days. If his recuperation would be delayed substantially longer than that, we would go ahead without his being in the laboratory but, assuming he recovers promptly as is hoped, we would wait for Mr. Evans' return. I indicated that Mr. Kramer could probably advise him better of Mr. Evans progress next week and, because of this problem, Mr. Kramer would be unable to set a definite date today for re-performing the test

In the course of the conversation Dr. Buyske asked if the application were otherwise approvable except for the disinfection system and I told him that it was with the exception of some labeling changes, particularly in the consumer brochure. He asked if he could be sent an approvable letter for all portions of the application except the disinfection system. I indicated we were not in a position to do this and that any letter sent to Warner Lambert would represent our final judgment on the application, in totality, as it stands today. He accepted this judgment, albeit without enthusiasm. Dr. Buyske also indicated, interestingly, that the procedure Warner

Lambert really wants to have for its Soft Lens is one which involves a tap water rise immediately after the washing step. I stated that they could of course consider such a change in the procedure; however, we would make a judgment on the application as it stands at the present time.

J. Richard Crout, M.D.

J. Richard Crout, M.D.

cc:
NDA 17-554
Dr. Leventhal
Dr. Finkel
Dr. Lamanna
Dr. Wright
Mr. Kramer
Dr. Gibson
Ms. Bruch

MEMORANDUM OF MEETING

February 12, 1976

Between: Merle Gibson, M.D.
Director, Division of Anti-Infective Drug Products

Ms. Mary Bruch
Division of Anti-Infective Drug Products

Carl Lamanna, Ph.D.
Associate Director for Pharmaceutical Research and Testing

William W. Wright, Ph.D.
Deputy Associate Director for Pharmaceutical Research and Testing

Mr. Julian Kramer
Division of Drug Biology (HFD-410)
Pharmaceutical Research and Testing

J. Richard Crout, M.D.
Director, Bureau of Drugs

Subject: Warner Lambert Softcon Application - NDA 17-554

I explained to those at the meeting my reasons for seeking further review of the laboratory work leading to the proposed nonapprovable letter on the Warner Lambert Softlens--namely, whether the results could be explained by contamination and whether we would be vulnerable at a hearing in the face of Dr. Buyske's allegation Warner Lambert had not had the opportunity to properly instruct our laboratory personnel in the procedure.

It was the opinion of Mr. Kramer and Ms. Bruch that Warner Lambert had had ample opportunity to instruct Mr. Evans and his staff. They indicated that the fundamental instructions were in the labeling to the consumer and that additional instructions ought not to be necessary. Furthermore, they indicated that Mr. Jimmy Evans and the technician had worked side by side in performing the test. They felt confident that we could defend our laboratory work at a hearing in spite of the differing results obtained by Warner Lambert and by Wells Laboratories.

Nevertheless, it was agreed by everyone at the meeting that a repeat run of the test with a technician from Warner Lambert in the laboratory would be valuable in bolstering our case. It was therefore agreed that I would call Dr. Buyske and indicate he could contact Mr. Kramer about arranging a repeat of the test. It was pointed out that the technician who did the original test had subsequently left FDA and therefore a new technician will be assigned to this problem. In addition, Mr. Jimmy Evans is undergoing surgery on February 13. While he is anticipated to be out only 7-10 days, it is possible that he might be out a good deal longer. If he is to be out only 7-10 days, we will wait for his return. On the other hand, if his recuperation is delayed, we may have to go ahead without Mr. Evans actually being in the laboratory. This judgment will be left to Mr. Kramer to negotiate with Dr. Buyske. It was also agreed that we will consider this application for purposes of press inquiries and administrative handling, as still under review with no final judgment imminent at this time.

Finally, it was agreed that we would test in the laboratory precisely the method offered to the consumer in Warner Lambert's latest submission using 30 ml. of rinse solution after the washing step unless a smaller volume is specified by Warner Lambert.

J. Richard Crout M.D.

J. Richard Crout, M.D.

cc:
HFD-2, Dr. Leventhal
HFD-100, Dr. Finkel
HFD-400, Dr. Lamanna
HFD-401, Dr. Wright
HFD-410, Mr. Kramer
HFD-140, Dr. Gibson
HFD-140, Ms. Bruch
NDA Orig. & NDA Dup.
JRCrout:mjl/mb 2/13/76

MEMORANDUM OF TELEPHONE CONVERSATIONS

February 17, 18 and 19, 1976

Subject: Warner-Lambert Soft-Con Lens for Cosmetic Purposes, NDA 17-554.

On February 17, Dr. Buyske telephoned to state that he had been in contact with Dr. Lamanna with respect to another microbiologic analysis by Mr. Jimmy Evans. Dr. Lamanna indicated that Mr. Evans was ill but was expected the following week and that the reanalysis would be performed beginning the first week in March. However, Dr. Buyske was concerned because the technician who had worked with Mr. Evans was no longer available and recruitment was ongoing for another technician. Dr. Buyske feared that a replacement would not be obtained in time for the new study.

I phoned Dr. Lamanna who stated that because of Dr. Buyske's concerns, the latter had asked if our people could come to Warner-Lambert and watch Warner-Lambert perform the analysis, instead of FDA doing it. Both Dr. Lamanna and I felt very strongly that the analysis should be done by our technicians in our laboratory. I indicated to Dr. Lamanna that I would inform Dr. Buyske of this. Dr. Lamanna saw no problem in his previously outlined schedule for the reanalysis.

I phoned Dr. Buyske and suggested that he call either Dr. Lamanna or Mr. Kramer to set up an appointment for Warner-Lambert's technicians to come down and redemonstrate the technique and also to watch the performance of our technicians.

I phoned Mr. Kramer on February 18. Mr. Kramer stated that there was another technician available and that Dr. Buyske should not be concerned about the performance of the new study. Mr. Kramer stated that the protocol would be run without any deviations whatsoever. He has full confidence, however, in the original analysis by Mr. Evans. I asked Mr. Kramer whether he was going to analyze the peroxide supplied by Warner-Lambert for the test and he stated that that was part of their planning.

On February 18 Dr. Buyske phoned to state that there was an article in the Medical-Devices Newsletter and there would probably be a similar article in the upcoming Pink Sheet with respect to the failure of FDA to confirm the data submitted by Warner-Lambert. Dr. Buyske stated that the phones at Warner-Lambert were jingling with respect to the Medical-Devices Newsletter and he asked whether the firm could receive an interim letter of some type. He requested a letter which would state that the NDA was approvable pending confirmation of the analysis performed by Warner-Lambert. I informed Dr. Buyske that we could not send out such

a letter since we had Mr. Evans' report and had no reason at this point to doubt there was any problem in Mr. Evans' study. Dr. Buyske then asked whether we could send a letter to Warner-Lambert which would state that the data submitted by Warner-Lambert, including presumably the clinical and chemical information as well as the microbiologic information, were adequate but we needed to confirm Warner-Lambert's findings. I stated that I would discuss this with Drs. Crout and Gibson.

Dr. Crout felt that the only type of letter he would be willing to send out at this time was one which would state, in effect, that we had been unable to confirm Warner-Lambert's microbiologic results, we are performing an additional study, and we are reserving judgment on Warner-Lambert's application until our reanalysis is completed. Dr. Gibson had no problems with a letter of this type.

On February 19 I informed Dr. Buyske of the type of letter that we would be willing to consider. Dr. Buyske again asked for a more positive letter and I stated that we could not send such a letter. I suggested that he phone Mr. Kramer tomorrow to arrange for his technicians to come down to FDA.

On February 18 at approximately 4:45 p.m., Mr. Steven Weitzmann dropped in without an appointment and indirectly asked for a letter to be sent to Warner-Lambert which would in essence be an approvable letter pending confirmation of the microbiologic studies. I indicated to him that such a letter could no longer be sent because of Mr. Evans' analysis. The conversation ended amicably.

M.J.F.

Marion J. Finkel, M.D.

cc:
Orig. NDA 17-554
HFD-1/Dr. Crout
HFD-140/Dr. Gibson
HFD-400/Dr. Lamanna
MJFinkel:eks 3/2/76/3/16/76

MEMORANDUM OF TELEPHONE CONVERSATION

March 19, 1976

Between: J. Richard Crout, M.D.
Director, Bureau of Drugs

and

Dr. Donald Buyske
Vice President for Research and Development
Warner-Lambert

Dr. Buyske called again to indicate his concern about the test to be conducted next week in PRT on the Warner Lambert Soft Lens. Specifically, he was still concerned about the use of aspergillus fischeri, an organism he stated the firm did not agree was appropriate. I asked whether he was formally protesting the use of this organism at this late date or was indicating his willingness to go ahead. After some discussion, he indicated his willingness to go ahead with the test but hoped that we would interpret any positive cultures with A. fischeri with full knowledge that the company objects to this organism on the grounds that it is not a pathogen, is not as well studied as other strains as aspergillus, and contains an encrusting outer layer which makes it admittedly difficult (unnecessarily difficult from Dr. Buyske's point of view) to kill. Dr. Buyske was also concerned about the details of his staff working with our staff, e.g., whether his technicians would actually do the test or would simply be observers. I indicated these problems should be worked out with Mr. Kramer and I felt confident that he would find a good working relationship with our laboratory people. I assured him that I had spent considerable effort on the phone with Mr. Kramer and Mr. Evans in passing along Dr. Buyske's messages, and I felt confident that everyone wanted simply a fair evaluation of the disinfection process for the lens.

Dr. Buyske indicated that Warner Lambert had a newly designed holder for the lenses to be used during the disinfection procedure, which in fact was the holder they intended to market. He asked if this is the one which could be examined in the test. I indicated that Mr. Kramer had discussed this matter with me previously, and we had no objection to using the new holder, providing it was

submitted in the form of an official amendment to the NDA before the test was started. (I later discussed this issue with Ms. Mary Bruch on the phone, who objected to a change in the holder at this point on the grounds that one should not change variables in attempting to confirm or refute a previous experiment. I agreed with this principle, but felt that the upcoming test was unlikely to be the last one with this lens and that, in my view, it was proper to test the holder intended for marketing. Ms. Bruch acquiesced to this judgment but indicated she did not agree with it.)

Dr. Buyske also asked how we would interpret the test if only one lens came out positive and indicated he hoped we would view the findings with judgment and not total rigidity. I indicated we could not predict at this time exactly what decision might result from any particular laboratory results. He also indicated he had a critique of our previous experiment in the typewriter but was uncertain as to whether to send it on. I told him he should send it in; I had thought this had occurred already.

After my reassuring him again that I had full confidence in his having a cooperative reception in PRT, the conversation closed.

J. Richard Crout, M.D.

cc:
NDA 17-554
HFD-100
Ms. Bruch (HFD-140)
Mr. Kramer (HFD-410)
Mr. Evans (HFD-413)

ORIG NEW CORRES

WARNER-LAMBERT COMPANY

DONALD A. BUYSKE, Ph.D.
VICE PRESIDENT, RESEARCH & DEVELOPMENT
PROFESSIONAL PRODUCTS GROUP

TABOR ROAD
MORRIS PLAINS, NEW JERSEY 07950
AREA CODE 201 540-2716

May 10, 1976

NDA-17-554

Dr. Merle L. Gibson
Food and Drug Administration
Department of Health, Education & Welfare
5600 Fishers Lane
Rockville, Maryland 20852

Dear Doctor Gibson:

As a follow-up to our telephone conversation of today, I am providing you with copies of my correspondence to Mr. Julian Kramer, dated March 22, and also copies of my March 22 and April 15 letters to Dr. Richard Crout. All of these letters have to do with the hydrogen peroxide verification studies performed on the Warner-Lambert lenses by the FDA laboratories. I am sending you these letters to be sure you have the benefit of what our views are on this matter.

Because of the difficulties the FDA laboratory had experienced in the first run with Aspergillus fischeri and Candida parapsilosis, Warner-Lambert immediately asked two independent microbiology laboratories, Wells Laboratories, Inc. and Hazleton Laboratories, Inc. to rerun Candida parapsilosis following the Warner-Lambert protocol. The results of these reruns were completely negative; that is, there was no growth in either the lenses or the fluids. Incidentally, when we learned that the FDA intended to subculture their lenses and fluids, we asked Hazleton to also subculture (the Wells Lab study was already completed and therefore too late to subculture). The results of the Hazleton subculturing was also negative. These reports were given to Dr. Finkel on April 13, and you no doubt have had a chance to see these data. However, for your convenience, I am also enclosing a copy of each report from these laboratories.

Dr. Gibson, I do not know why the FDA laboratories had such difficulty in performing the first run, but my letter to Mr. Kramer does offer some possibilities. I believe that these first studies, for clear technical reasons, should be discarded.

It is most instructive that the second FDA verification study was so tremendously different from the initial FDA test; i.e. --

RECEIVED
MAY 14 1976
HFD-140
BUREAU OF

	Aspergillus fischeri	Candida parapsilosis	Ps. aeruginosa
1st Study FDA	14 positive/ 45 tested	40 positive/ 49 tested	Not done
2nd Study FDA	0 positive/ 39 tested	1 positive/ 30 tested	0 positive/ 36 tested

Since Warner-Lambert technicians and Dr. Frank Turner were present during the FDA second run, we are all well aware that the environmental plates showed a heavy level of environmental contamination. Dr. Turner prepared a slide, on the spot, and demonstrated these contaminants to be yeast -- and most probably Candida parapsilosis -- that were in the air and/or on the clothes of the FDA technician due to the high levels of microorganisms she was using in this enclosed laboratory. We maintain this single contaminated lens resulted from a re-entry of this organism into the lens container, after the hydrogen peroxide treatment, and during the rinsing process. It was not a survivor of the peroxide treatment. Dr. Turner specifically requested that the FDA technician move out of the room used to contaminate the lenses to a "sterile or isolated station" for the rest of the procedure. Unfortunately, the FDA did not feel that this routine step was necessary and the inadvertent or adventitious contamination was the result.

I am providing you with all of this information because I fully realize that the FDA is now in the late stages of decision making. I can only plead that all decisions will be based on scientific facts, and I know you will do your best to assure that this will be done.

Sincerely yours,

D. A. Buyske

DAB/mh

cc: Dr. M. Finkel
Mrs. M. Bruch
Dr. R. Crout

We found these factual inconsistencies and protocol violations:

1. The cleaning procedure prior to the soaking in hydrogen peroxide was not followed properly. This cleaning is an important part of the total system and must be followed when these extremely high contamination levels are added (1,000,000 microorganisms per lens for a run of 20 lenses).

2. Sterile gloves were not used for each lens as required. Rather, a single pair of gloves were used over and over again. This very probably allowed contamination from one lens to another to occur.

3. Good microbiological techniques require that there be a physical separation in the area where deliberate contamination is performed from the area where lenses and fluids are removed for final culturing. There is no evidence that this was done in a satisfactory manner.

4. The report contains no daily readings of growth or no growth at all but only a single reading at the end of 14 days of incubation. When growth does occur, there is no data provided that demonstrates whether this growth is due to the original organism or due to adventitious contaminants due to the environment. Again, this is a violation of the protocol and good laboratory microbiology techniques and practices.

5. In 60 out of 60 cases there was no organism of any kind in the final rinse fluid bathing the lenses. However, the lenses were found to be contaminated. This is an inconsistency that we have never experienced.

6. Warner-Lambert provided lenses, containers, Lensept and Lensrins to the laboratory. The Evans report showed that 60 lenses were run. Each lens requires, by protocol, the use of 7 ml of Lensept - or a total of 420 ml. We measured returned supplies and found only 320 ml were actually used.

   The Warner-Lambert protocol also required that 30 ml of Lensrins be used as a precleaner, and that 4 rinses of 7 ml each (a total of 28 ml) be used post exposure to the hydrogen peroxide. The 30 ml plus the 28 ml means 58 ml is used for each lens. Sixty lenses, as reported

by Mr. Evans, would mean 3480 ml should have been used. In measuring the returned supplies, we find that only 1800 ml had actually been used. The large under-usage of both hydrogen peroxide (Lensept) and the Lensrins is a very serious error and could be contributory to the test failure in the FDA laboratory. We would be most interested in hearing an explanation on this matter.

From the above recitation I hope you can better appreciate why I have very deep concern about the verification test procedures used by the FDA.

Sincerely yours,

D. A. Buyske

DAB/mh

MEMORANDUM

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

TO : NDA 17-554

DATE: MAY 4 1976

FROM : Microbiologist
Division of Anti-Infective Drug Products (HFD-140)

SUBJECT: Testing Procedures for Warner-Lambert Softcon Lens

After development of Guidelines and Criteria for Microbiological Testing of New Contact Lenses, Warner-Lambert submitted a protocol for performing a 20-item test (October 3, 1975). This protocol was reviewed and revised twice. The final version was sent to FDA (October 17, 1975). The tests were performed after several meetings and letters discussing the testing procedure and the organisms to be tested.

The six basic test organisms were selected by the consultants to Warner-Lambert and FDA. Two organisms resistant to the specific procedure or chemical being tested were to be selected by FDA after testing data were submitted to them and the twenty-item test would be performed by the sponsor and verified by FDA.

The six test organisms and the two resistant strains were selected prior to initiation of the tests by Warner-Lambert on the basis of D-value data. The organisms which FDA and Warner-Lambert agreed to test were Candida parapsilosis and Aspergillus fisherii. These are both fungal organisms. Contrary to statements made in the press and by Dr. Buyske of Warner-Lambert, Candida parapsilosis has caused infections of the eye. In fact mycologists such as Dr. Ahearn (a contractor with FDA to study cosmetic contamination) believe that most Candida can cause eye infection of varying severity. The emphasis in testing a disinfection procedure, of course, is to use a resistant strain. Warner-Lambert did not wish to test Aspergillus fumigatus in their laboratory and contracted with Wells Laboratory to test Aspergillus fisherii. A. fisherii is the perfect state of A. fumigatus and is not normally considered a pathogen although it does cause pulmonary infection, as does A. fumigatus, but only in immunosuppressed individuals. Fungi such as A. fisherii have been isolated from packaging materials, blood bags and food products such as dates. There is some indication that it may resist attempts to disinfect or sterilize materials. It must be stressed that in this testing procedure, as is true in many

cases, not all organisms which may create problems can be tested so that indicator organisms which may predict problem groups are selected. One organism suggested to Warner-Lambert as an alternative to A. fisherii was Paecilomyces varioti or other species of this genus. This was prior to any knowledge that Paecilomyces lilacinus would in only a few months contaminate a neutralizing solution used with intra-ocular lenses and 11 serious infections and enucleation of 5 eyes would result. We are embarking on an era of new and developing technology in the area of contact lenses. There are new materials and many more individuals considering the wearing of contact lenses. The material is different and unfortunately many individuals resort to their own experience and to what they have observed conventional lens wearers do. There is no way to predict what organisms will cause trouble. It would seem prudent to look at the history. In view of this I am enclosing a copy of a paper being given by Dr. Carl Bruch at a meeting in London, England this week. I think one might reasonably conclude that eye care products and lenses are quite susceptible to fungal contamination. I would defend the selection of the fungi which are being tested on this basis, in fact, I would suggest them as mandatory.

Data covering the testing of the six test organisms in the Guidelines and the two additional organisms were submitted to FDA on December 1, 1975. These data were reviewed by FDA and consultants; essentially, all results were negative including those submitted by Wells Laboratories. Four final cultures were contaminated by adventitous organisms different from those applied to the lens as initial contamination.

FDA laboratories also performed these tests with the two organisms selected by FDA. Approximately one-half of the lenses showed survivors at the conclusion of the 20-item test.

In reviewing the results of these tests, I believed that the protocol submitted was followed. The real addition to the peroxide system originally designed as 10 minutes exposure to 3% peroxide followed with four rinses was the use of a pre-cleaner. The current testing regimen calls for 30 minutes instead of 10. Of course cleaning does remove some debris, mucous, particles and organisms. In addition to the cleaner, a rinsing step to wash off the cleaner was added. The instructions in the protocol are slightly more informative than the proposed package-insert in stating that the lens is rinsed by holding it between the gloved fingers and changing the position of the lens and rinsing again.

I have had the opportunity to observe the type of procedure used by Warner-Lambert to run these tests and am entirely amazed at this procedure. It is difficult to describe verbally, but I will try.

1. The lens is removed from the eye and placed in the palm of the non-dominant hand.

2. Cleaner is placed on the lens and the palm. The lens is rubbed with the cleaner for a few seconds.

3. The lens is placed on the tip of the index finger of the dominant hand and rinsed with about 7-8 ml of preserved saline.

4. The lens is transferred to the tip of the index finger of the opposite hand and reversed onto it. It is rinsed again with 7-8 ml of saline.

5. The lens is then transferred to the dominant hand again - the finger next to the index - and again reversed and rinsed with 7-8 ml of saline.

6. The lens is then transferred to the little finger of the dominant hand, reversed and rinsed again with 7-8 ml of saline. A total of about 30 ml of saline has been used to rinse one lens. So a total of 60 ml would conseratively be required to rinse both lens.

7. The lenses are placed in peroxide for 30 minutes and after the peroxide is removed, the lenses are rinsed with 7-8 ml of saline for a total of four five-minute rinses.

This series of steps is so time consuming, complicated and expensive that no consumer could reasonably be expected to perform it. A consumer would use a minimum of 90 - 100 ml of solution a day, requiring the purchase of a $1.79 - $1.98 bottle every other day.

The consumer is not protected with a disinfection procedure which will not be used. Other chemical systems are being tested and will likely be reviewed in the near future in which the lens is held and rinsed once and placed in a disinfecting solution for four hours (minimum). I have also witnessed the testing of this disinfection procedure and it practically represents what the consumer is asked to do.

The structuring of the test performed by Warner-Lambert is artifical and complex and designed only to result in a lens showing no growth of the inoculated organism by complicated handling and rinsing of the lens to remove as many organisms as possible prior to testing the peroxide.

The 20-item test was designed to be performed with the steps done according to the labeled patient instructions. It should be a practical test of the system containing multiple steps as the patient will perform it.

I believe that this procedure should be performed for our microbiology/sterilization consultants and that their comments should be incorporated into the record.

I can see no way in which a procedure such as the one I have described can be approved for use by the public. I do believe that an alternative solution may be available soon which could be used with the Warner-Lambert lens. It is a matter of record that other commercial solutions have been used with this lens in Canada.

Mary K. Bruch
Mary K. Bruch

Enclosures

cc:
Orig NDA
HFD-108
HFD-140 MKB 5/14/76
HFD-140/CSO
HFD-140/MKBruch:llb-5/13/76

NDA 17-554
Softcon Contact Lens for Vision Correction
Warner-Lambert Company May 14, 1976

BASIS OF NON-APPROVAL

The reviews of the medical officer, the chemist, the pharmacologist and the microbiologist have been completed. These reviews recommend approval of the application. Further data on accumulation of the tin preservative in the peroxide used in the disinfection system was requested and provided. Data from test of the mechanical integrity of the lens when exposed to 200 repeat disinfection cycles were also submitted and are acceptable.

There have been numerous meetings and reviews of the hydrogen peroxide disinfection system.

The microbiologist's review of data submitted on December 3, 1975 shows that the criteria defined in the Guidelines and Criteria for the Microbiological Testing of New Contact Lenses was met when all the data submitted by the sponsor are considered.

The Guidelines were developed after extensive meetings with expert consultants, the sponsor's consultants and the Ophthalmic Drugs Advisory Committee.

One stipulation of the Guidelines states that two organisms selected by FDA should be tested in a USP-type 20-item test.

These tests were performed by Mr. Jimmy Evans, HFD-410, in the FDA, Bureau of Drugs Laboratories. Mr. Evans' report is included with the microbiology review. The results are positive in that a number of lenses were positive in that microbial growth developed on sub-culture from a number of lenses. The results are consistently positive and cannot be an accident. The results show that the disinfection system does not work. The materials for the test, including lenses, were supplied by the firm.

A subsequent study performed in FDA laboratories by both FDA and Warner-Lambert technicians using a different and cumbersome protocol resulted in 1/20 positives by both FDA and Warner-Lambert (2/40 total) with Candida parapsilosis only. Even if our analysis had confirmed the firm's original data, the cumbersomeness of the method needed to assure disinfection is such that is reasonable to expect that most consumers would not follow it and would thus subject themselves to

NDA 17-554

the hazard of potential eye infections.

Therefore, this application is not approvable since an adequate disinfection system for the lens has not been demonstrated.

Merle L. Gibson

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Bureau of Drugs

cc: Orig NDA
HFD-140
HFD-140/CSO
HFD-140/AFScafidi:mas-5/14/76

NDA 17-554

JUN 1 - 1976

Warner-Lambert Company
Attention: James H. Weir, M.D.
170 Tabor Road
Morris Plains, New Jersey 07950

Gentlemen:

Reference is made to your new drug application dated December 11, 1973, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Softcon (vifilcon A) Corrective Lens.

We also acknowledge receipt of the following amendments to this application:

March 28, 1974	March 20, 1975	October 8, 1975
May 1, 1974	March 26, 1975	October 14, 1975
September 6, 1974	June 16, 1975	November 19, 1975
September 9, 1974	June 30, 1975	December 3, 1975
November 11, 1974	July 10, 1975	January 12, 1976
December 12, 1974	September 4, 1975	January 14, 1976
March 6, 1975	September 15, 1975	January 19, 1976
March 19, 1975	October 3, 1975	May 10, 1976

We have completed our review of this application. We find that the clinical data are adequate to demonstrate that the lens is effective for vision correction. The manufacturing controls are satisfactory. We find, however, that the application is not approvable.

The application is inadequate under section 505(b)(1) in that the safety of the lens to the consumer has not been adequately established utilizing the disinfection system you recommend. Specifically:

1) Our analyses fail to confirm your data which were submitted in support of the effectiveness of your disinfection system for the Softcon Corrective Lens and we note that your technicians, in a subsequent study performed in FDA's laboratory, also could not replicate the original results.

2) Even if our analyses confirmed your original data, the cumbersomeness of the method needed to assure disinfection is such that it is reasonable to expect that most consumers would not follow it and would thus subject themselves to the hazard of potential eye infections.

As a result of meetings between Warner-Lambert representatives and consultants and FDA representatives and their consultants, and a meeting of the Ophthalmic Drugs Advisory Committee, criteria were agreed upon for approval of a disinfection system for new contact lenses. These criteria are described in the Microbiological Guidelines and Criteria for Testing Contact Lenses Made of New Polymers. The Guidelines specify among other requirements, that six basic test organisms be tested in a USP-type 20-item test. In addition, two test organisms selected by the FDA would be tested by the manufacturer and the FDA.

After the development of the criteria and Guidelines, Warner-Lambert submitted a protocol for performing a 20-item test (October 3, 1975). This protocol was reviewed and revised twice. The final version was sent to FDA (October 17, 1975). The tests were performed after several meetings and letters discussing the testing procedure and the organisms to be tested.

The six basic test organisms were selected by consultants to Warner-Lambert and FDA. Two organisms resistant to the specific procedure or chemical being tested were to be selected by FDA after testing data were submitted to them and the twenty item test would be performed by the sponsor and verified by FDA. The six test organisms and the two resistant strains were selected prior to initiation of the tests by Warner-Lambert on the basis of D-value data. The organisms which FDA and Warner-Lambert agreed to test were Candida parapsilosis and Aspergillus fisherii. These are both fungal organisms.

Warner-Lambert chose not to test Aspergillus fumigatus or its perfect state, Aspergillus fisherii, in its own laboratories and contracted with Wells Laboratories to do these tests.

FDA Laboratories ran a 20-item test with the two selected organisms with lenses and materials supplied by Warner-Lambert. The test was run according to the directions in the protocol agreed on by FDA and Warner-Lambert (October 17, 1975). Approximately one-half of the lenses or solutions were positive. The procedures used in this first test correspond to the consumer labeling, the revision of which was submitted on January 14, 1976 and agreed to by FDA.

After the FDA test results were made known to Warner-Lambert, FDA was informed that Warner-Lambert had used further intricate steps not included in the protocol or in the consumer labeling.

These same complicated techniques were used by Warner-Lambert's consulting laboratory. FDA agreed to use these procedures and to repeat the 20-item test with Warner-Lambert performing the same tests at the same time in the FDA laboratories.

This procedure was approximately as follows:

1) The lens was removed from the vial with a sterile swab and placed on a piece of sterile paper and blotted.

2) Uninoculated lenses were placed in the left chamber of the sterile lens carrier.

3) For inoculation, the lens was placed in the left palm. The convex side of the lens was inoculated with 0.01 ml. of the test organisms in organic load and turned so that the concave side could also be inoculated with 0.01 ml.

4) Immediately after inoculation, three drops of lens cleaner were added to the concave side of the lens and three more drops were placed in the palm.

5) The lens was rubbed with the index finger in a circular motion for 30 seconds.

6) The lens was picked up with the concave surface on the end of the index finger of the dominant hand and rinsed (varying volumes up to 30 ml. for a single rinse).

7) The lens was transferred from the dominant hand to the opposite index finger so that the lens was inverted and the concave side was rinsed.

8) The lens was transferred to the tip of the middle finger of the dominant hand and the convex surface was rinsed.

9) The lens was transferred to the fifth finger of the opposite hand and again rinsed.

10) The lens was transferred from the fifth finger to the right chamber of the lens carrier.

11) With the lens in the carrier, 7 ml. of Lensept (hydrogen peroxide, 3 percent) was added and the carrier shaken vigorously.

12) After 30 minutes, during which the lens was undisturbed, the peroxide solution was removed and 7 ml. of preserved saline was added and allowed to remain in contact with the lens for 5 minutes. This latter step was repeated 3 additional times for a total of four 5-minute rinses.

13) The entire volume of the final rinse was sub-cultured in an appropriate medium.

14) Both lenses were transferred to appropriate culture media and individually cultured.

If this complicated and intricate procedure were made part of the consumer labeling, it is unrealistic to expect reasonable patient compliance. Furthermore, there are no data to indicate that such a complex procedure could or would be followed by the average consumer.

The compilation of results of the 20-item test with Candida parapsilosis and Aspergillus fisherii are as follows: Warner-Lambert found no positives nor did two consulting laboratories using the intricate procedure described above. The results from FDA laboratories were as follows:

First test (using the non-complex method)

C. parapsilosis: Thirty-nine new lenses were challenged with C. parapsilosis, 20 by direct inoculation and 19 left in the inoculated lens environment. Sixteen of 20 inoculated lenses and 14 of 19 uninoculated lenses were test organism confirmed positives on culture. Ten used-lenses of the 10 tested were also confirmed positive.

A. fisherii: Of the 35 new lenses challenged with A. fisherii (20 inoculated and fifteen uninoculated, but left in the contaminated environment), 13 were confirmed positive, 10 of 20 inoculated and 3 of 15 uninoculated. One of 10 used-lenses tested was found to be positive for growth.

Second test (using the complex method)

In the second FDA test, 1/20 positives were found by both FDA and by Warner-Lambert (2/40 total) with Candida parapsilosis only. There were no positives with A. fisherii.

In view of the fact that the microbiological criteria were not met and that, even if they were met, the complexity required to achieve such results precludes reasonable compliance in daily use by the consumer, we find that the application is not approvable, as noted above.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated, and within 60 days of the date of receipt of such request (or such additional period as you and we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc: NWK-DO

Orig NDA
HFD-1
HFD-100
HFD-140
HFD-140/CSO
HFD-140/MKBruch
HFD-140/AESmith
HFD-140/AFScafidi
HFD-140/ARCasola
HFD-140/HCZell
HFD-140/JMDavitt
HFD-140/NJBrowder
HFD-140/DCBostwick:llb-2/5/76
HFD-140/MLGibson:mas-5/14/76
R/D initialed by:MLGibson-2/4/76; 5/13/76
MJFinkel,M.D.-5/13/76

NOT APPROVABLE

80-211 O - 76 - 8

Senator KENNEDY. Do you think, Dr. Gibson, that a lesser person could have withstood this kind of pressure?

Dr. GIBSON. I think it is quite possible that someone who was not quite so secure as far as their training and experience and "stick-to-it-iveness" are concerned, might have succumbed.

Senator KENNEDY. We want to really commend you, Mrs. Bruch, for your exemplary performance and for the work that you have done. No public servant should be put into the kind of pressure cooker that you were obviously and unfortunately put in. I think you responded much more than adequately.

You and the FDA are to be commended.

Dr. Dunham, you are one of the main members of the cardiorenal group, one of the members who testified here previously. Two years since our August 1974 hearing, has the cardiorenal division been strengthened and stabilized?

Dr. DUNHAM. No, sir, it has not.

Senator KENNEDY. I might read into the record some of the things you brought in your interview memorandum, May 1976.

Dr. DUNHAM. I have a restatement of that.

Senator KENNEDY. Briefly.

Dr. DUNHAM. My answers must in some aspects be commonsense personal observation. Documentation is difficult if not impossible if one has not deliberately, with malice aforethought, prepared to document a case.

The situation in the division constitutes a new low in inefficiency and morale. The volume of work is the same, but the distribution is heavier from loss of personnel because of unpleasant and frustrating working conditions.

Our best three CSO's have transferred and the one experienced replacement is seeking a way out.

After the Division Director and one group leader medical officer left, two other medical officers moved to other loci to avoid exasperation and conflict.

The clerical staff is rumored to be alert to other positions.

In such situation, the reputation of the Division as a wretched place to work prevents recruitment of knowledgeable qualified replacements.

The situation is exacerbated by the obviously unstable, ambiguous, and inefficient management practice of a deliberately scheduled rotation for more than 8 months of caretaker personnel as Acting Division Director. Only one of these is qualified by experience, rank, or management credentials for such position. None, however interested or qualified, could plan or execute remedial action because of brief tenure and caretaker status.

In the same context, it is questionable how sound management practice is improved by substituting for normal Deputy Division Directors and branch chiefs—duly qualified and classified as supervisory personnel—so called group leaders who have no supervisory classification

status and are exploited by serving at pleasure in a complex supervisory position.

The entire cardiorenal medical staff responsible for review of potent and complex drugs impinging on three-fourths of the human physiology is now reduced to only six full-time reviewing medical officers who are experienced in agency procedures.

The situation is further aggravated by the absence of a Division Director and one of two putative group leaders.

The one remaining is junior in seniority and agency experience, lacking in formal qualifications and, by his own statement, interest in management techniques, resulting in discoordinated assignments and decisions, requiring time- and effort-consuming rectification.

As a natural human avoidance of potentially more abrasive interaction with supervision in which they have no confidence, necessary communication is avoided and productivity is obstructed.

With an overloaded, frustrated, disaffected residual staff that perceives no hope of either stable management or professional personnel replacements to reallocate and alleviate the workload, the quality and quantity of staff work is bound to deteriorate.

Immediate remedies are available. The restoration of morale, confidence, and image that can attract recruitment of quality staff replacements requires not an elaborate technical knowledge of the field, but an acting or permanent Division Director, generally qualified in the field, who has experience and qualification in the procedures of the agency and demonstrated skill in maintaining those procedures punctiliously to implement their best efforts from a group of very knowledgeable professionals.

The most brilliant medical scientist recruited from outside the agency would require a minimum of 6 months to a year to master the deputy who possessed all the previously stated skills.

There are such qualified people already in the Bureau—some, who could be transferred from segments which are stable enough to operate on existing resources, and others, who stand in disfavor or lack full qualification in one remediable aspect or another.

The crisis in this Division is one of sensitive management dedicated to excellence, regardless of facilitation of approvals, when such are in fact premature or not warranted.

Qualified persons, acceptable to the Division, are presently in the Bureau, available by transfer. It must be recognized, however, that for such senior medical officers, neither extra rank nor salary is available as inducement for the truly qualified to assume the onerous labor and responsibility of rebuilding a destroyed Division. Outside recruitment is even more heavily deterred by this same circumstance.

I have another brief analysis of the situation, which I would be pleased to place in the record.

Senator KENNEDY. Yes, if we could make that a part of the record.

[The following was received for the record:]

STATEMENT

Inquiry into the operation of Agencies, in focusing necessarily upon documentable instance - on symptoms and signs of disease - on the non-specific attributes - frequently fails to identify the essence of the problem - the disease and its pathogenesis.

The exhibited conflict arises out of the social, psychological, and philosophical motivations that operate to produce in every person some bias that eludes the insight and deludes the biased into the profound selfrighteousness of the "true believer" - so that my bias is "good, and my adversary's bias is "bad".

In the present instance we have a classic case in point. Heirarchial control has fallen into - or been placed in - the hands of those who are, no doubt, trapped by motivations of self image that seek to identify with the power and privilege of powerful commercial entities. They truly believe that proliferation of articles of commerce to the unsupervised use of the fallible ordinary physician - whom they also identify with - truly serves the public good.

Few of these persons, however, have actively cared for non-institutional individual patients, and their choice of eventual career exhibits a disinclination to identify with such individual patient. The talent that contributes scientific rigor to the medical scientist may not necessarily parallel in the same individual a talent for compassionate identification with an ailing patient.

The "good" and the "bad" of the situation lies not in the bias - but in the psychological impossibility of selfawareness of such bias. One surmises that their own rigors are such that they would be the first to perceive a classical personal or financial "conflict of interest," and, either disqualify themselves, or deliberately render decision against their own personal gain in financial or interpersonal terms. In the sincere belief that they wear a white hat, they are made angry and aggrieved by the equally biased and selfrighteous who espouse an antithetical policy and philosophy that identifies with the victims of the marginally responsible or insufficiently knowledgeable physician and the drug vendors impersonally irresponsible corporate power and greed.

The causative virus of these conflicting viewpoints is the class concious spectrum of identifications upon which the self images of persons are constructed.

Since in human nature such bias is inescapable, exclusive control of any Agency of Equity by either, or any, bias is a disservice to its full public mission. In the Anglo-Saxon tradition, that finds justice best served by finding a viable course in fair - and I emphasize fair - contest

between advocates, both advocacys must be represented throughout each staff level of an agency up to the decision signatory.

The contest can only be fair if the procedures are even handed and make clear record of the advocacy and responsibility of each person engaged in the necessary internal debate.

Decisions must nevertheless be rendered timely and without undue delay. Strange as it may seem, the observation of experience confirms that the exercise of manipulation, guile, arm twisting, and subterfuge within an organization to avoid identified and explicit advocacy responsibility consumes vast amounts of time and staff recirculation. As any attorney recognizes - delay itself is a powerful manipulative weapon.

Explicit responsibility of record for each persons contribution, security from supervisory reprisal, strict limits on the "power to shred" and the recruitment and suitable recompense of individuals of intellectual breadth and excellence for technical and managerial staffs, constitutes the key to efficient and equitable performance of Agency missions.

Intellectual breadth and excellence, suitably respected and rewarded at all staff and management levels, is the best of all insurances against unselfconscious bias and zealotry of either sort, since such persons are least likely to be susceptible to dependency motivations whereby the flawed self image of the marginal power seeker identifies with images of power.

R. Brown Dunham, M.D.

16 July 1976

MEMORANDUM

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

TO : Senate Subcommittee on Administrative Policies & Procedures

DATE:

FROM : R. Brown Dunham, M.D.
Medical Officer, Division of Cardio-Renal Drug Products

SUBJECT: Recommendations concerning prospective legislation.

Pursuant to the request of the Senate Subcommittee on Administrative Policies and Procedures, as continuing testimony under subpoena of July 13, 1976 that I submit recommendations concerning aspects of legislation to alleviate the problems which impede this agency's performance of its public mission, the following analyses and suggestions are submitted.

In the existing situation a three cornered contention exists between the intended mission of the agency that the general public, and its individuals, who cannot be capable of making informed choice of complex and technical articles of commerce, be provided with protection from fraud and harm; the purveyors of these products; and, sad to relate, the institutional interest of the agency created to perform the stated mission.

To paraphrase Professor Harper - institutions in becoming institutionalized are required to be "consistent." To accomplish such consistency, Procrustean Beds of Policy are promulgated. A major aspect of the purpose of such policy is the properly selfserving interest that it should promote the efficient functioning of the institution. In response to the immutable laws of Dynamics, the institution interacts with and reacts to the large active vectors most immediately affected -the regulated clients-, and is only stimulated in minor degree by the diffuse, unperceptive and disorganized reactions of its intended primary client, the individuals comprising the general public.

The most carefully considered policy, in being inappropriate to the myriad variable individual situations is, in being irrationally inappropriate to some individual instances, tyrannical. If the policy has been susceptible to human bias or incapacity to imagine beforehand the ramifications of such policy, it becomes unjustly tyrannical for many. It follows that all institutions in becoming institutionalized are tyrannical and inherently exposed to dynamics that increment the self serving clientistic motivations, so that, more often than not, an institution becomes tyrannical towards its lesser clients and the general public, and utterly betrays the interest of the individuals of that general public that constituted the mission that called the institution into being.

Ergo -an axiom, "all institutions, in becoming maturely institutionalized are inherently selfserving and unjustly tyrannical. In invoking more net individual grievance than they preclude, they must never be allowed to become institutionalized and their policies and judgements must be provided with corrective supervision or appeal to assure individual justice and equity."

The traditional corrective is protection of the individual's rights of petition, hearing, and ultimate appeal to the courts.

These mechanisms served a parochial Republic reasonably well, but in the megapolitic of today the traditional safeguard of "due process" has become synonymous with the abuses of political and economic power to the detriment of the peace and prosperity of the individuals of the general public. Just as abuse of the procedures of legal due process have come to serve the interest of the ordinary overt criminal, they also, in other larger settings, have come to serve the interest of the criminal capabilities of irresponsible and exaggerated supranational economic power.

In their preoccupation with curbing the abuse of power of herediatry monarchs the good founding fathers forgot one of the ancient Anglo Saxon and Feudal magisterial functions of the Crown, to secure the peace and general well being of all subjects against fraud and riot, overriding the rights and property interest of all local powers, whereby the Crown granted "markets," not as a property right-but as "grace and favor" "privilege", supervised by the Kings Officers, rendering summary judgements. In a preoccupation with rights, the proper usages of "privilege", in which no property right inheres, was overlooked.

Accepting that a pecuniary, if not a property, right is infringed upon by regulating the vendors of any item of common commerce in which the nature and quality of the goods is evident to the purchaser of ordinary wit and education, there has developed a general principle of regulatory law, whereby -in exchange for "regulation", which prescribes certain matters as misdemeanors and sets relatively trivial penalities thereon -the regulated vendor is rendered relatively safe from criminal prosecution for the actual fraud that most of these "misdemeanors" constitute.

In addition, such "regulation" by statute and rule making authority, invoking safeguards of both right of petition and of due process, infinitely recycled, effectively precludes timely regulatory action against any but the most flagrant sharp practice by the most trivial of malefactors.

It is clear that, for even such articles as clothing, utensils and, most importantly, comestibles, this mechanism fails to secure the generality of individuals against technological fraud.

How much more removed from the capability of caveat emptor, then, are those products which are chosen and designated by a physician, whose education cannot realistically encompass either the technology or data evaluation involved, which are to be consumed by another person, and which are paid for, either by that person -or as is frequently the case -by a third party, that will likely be the taxpayer in many instances.

It is quite true that under the existing legislation -rigorous and aggressive enforcement can abate some of the present abuses, but it also increments the tyrannical aspect of an institutionalized agency, while doing nothing to diminish the abuse of due process by concentrated economic power.

New applications of very old legal principles must be utilized to frame legislation that can reduce technological fraud upon physician, patient -and taxpayer, -and at the same time reduce the institutionalization that eats away the substance of both the taxpayer and the honest vendor of needed articles.

New legislation should explicitly undertake a restatment of the overriding principle of inherited English law relating to the privilege of the granting of markets and chartering of Guilds, that in securing the general welfare by applying the magisterial function of the Crown/State, the usage to vend and market technically complex goods and services is a retractable "grace and favor" privilege, in which no property right inheres. The implication of this principle of the accepted powers of the state to regulate underlies the Insterstate Commerce Clause and is exemplified in the definition of and regulation of Public Utilities, but the failure to identify the privileged nature of this limited market, in allowing assertion of an inappropriate property right, has, in this field, as well, bogged down effective exercise of the public interest against regulatory agency clientism and abuses of "due process."

It is therefore proposed that such legislative restatment should delineate the rationale whereby the purveyance of technologically sophisticated goods and services, which require the application of manifold special technical knowledge to assess their appropriateness, quality, utility, and value, in requiring arbitrage outside the capability of the ordinary knowledgable citizen and/or for which payment or indemnity is provided by a third party or by a public agency, constitutes a special privileged market, by its nature reserved from the exercise of ordinary individual competitive right to vend.

In order to conserve the finite economic resources of the public, and to preclude wasteful duplication and proliferation of expensive competitive technical facilities, and to provide assurance that the goods or services vended are in fact of a the quality and value represented, those intending to manufacture and vend such goods and services should be required by this new legislation to obtain a license to such privilege, acknowledging thereby both tacit and explicit relinquishment of any property right claim.

Such license would be obtained by submission of a proposed contract to the appropriate agency. As example -for a New Drug Product - modification to contractual form of the present New Drug Application processes and criteria would build on the existing evolved procedural and legal base. As a condition of contract, the contractor, in exchange for the privilege of making and vending, engages to be bound to maintain delivery under each and every term of such accepted contract, including range limits on the delivered base price to whatever next immediate echlon of distribution might be. If such price limits are contracted to be related to costs, then full disclosure accounting of such costs, documenting them to be within the cost of similar contractors for similar goods, must be proffered.

Such an unamendable contract must be renewed annually by renegotiation of such terms as require amendation. Failing timely completion and acceptance of such annual renewal, the licensed privilege is voided without recourse. Moreover any failure to perform in any detail of the contract voids the privilege without recourse.

In any dispute not resolved in 30 calendar days, and failing resolution in a single formal hearing of record within the next 15 calendar days, the law of contracts shall govern, as determined by the appropriate Federal District Court, and appeals are limited to question of substance rather than technicalities of procedure. As condition of contract privilege, any unresolved dispute passing beyond Hearing automatically suspends the privilege, so that rapid non-litiginous resolution of dispute stands in the interest of the privilege holder.

Such restatement of the basis of regulatory function offers a mechanism of broad application, whereby the weaknesses and abuses of the present proliferating bureaucracy, inherently ineffectual in being hamstrung by claimed property right and due process depending therefrom, may be ameliorated. The self administering contract and its flexible applicability to extremely various particular matters should promote shrinkage of the unmanageable size of agencies.

Moreover utilization of these mechanisms can bring under cost conscious supervision, not only technological products, but a multitude of goods and services paid for by third parties or the taxpayer, including not only drugs and processed and packaged foodstuffs, but also insurance, delivery of health services, other professional services, and technical contractors.

A further general principle that the taxpayer should not bear the cost of obtaining privilege to a market of constrained competition should also be addressed. As concerning the general category of Food, Water, and Drugs, -the cost of technical review of proposed contracts should be realistically assessed, by a scale related to cost of personnel man hours actually engaged by the particular proposal, with payment required of an initial fee and accruing costs by the applicant at subsequent stage intervals. Such a requirment provides a motivational stimulus to minimize submission of ill considered, frivolous, and ambiguous proposals. Suitable exemption may be provided for those products desirable or essential to a particular public need too small to constitute a profitable commercial venture, and so defined in Requests for Proposals generated by the agency to accommodate such identified special need.

The restructuring of the regulatory agencies granting and administering these contractual privileges must be accomplished in a fashion that, instead of promoting Parkinsonion proliferation, rewards an efficiency that minimizes their need to exist. There must be flexibility to adapt to technological changes and to deal with matters on a sufficiently individual basis to avoid ridiculously "consistent" procrustean policy and the institutionalization that leads to "complaisance toward the great, and tyranny towards the small."

We again turn to the historical sources and development of the proper relation between the magisterial function of the State and its citizens. Underlying feudalism was an eminently practical and self regulatory theory of social justice, that each segment of society, and the individuals thereof, had certain duties to adjacent and interactive segments, the performance of which entitled each to certain privileges. There was realistic recognition that it was not only impossible for each person to be knowledgable in judgement of the various crafts and trades, but socially and enconomically inefficient for such to be. Accordingly, the Crown not only granted markets as grace and favor privilege, but chartered Guilds in similar privilege laying on them the duty of assuring the quality and worth of their technical product. This is, in fact, the origin of the theory of technological "peer review." We are only too familiar with the abuses of adherence to obsolescence, lowest denominator of mediocrity, manipulation by cronyism of Masters, repression of initiative, and abuse of monopoly that are inherent in such un-supervised self regulation. The system, however, actually worked very well until the guilds, in periods of unstable Crown authority, grew powerful enough to escape the continuing supervision of the Chancellor and Privy Council. Adaptation of the general principle of self regulation within groups contracting for performance of their subconstitutents may be feasible if such contracts are rigorously drawn, monitorage of such contracts by technologically knowledgable representatives of the public interest is equally rigorous, and enforcement of the autoregulatory terms of the contracts is even handed and timely.

Supervision of any of these contracts is inescapably an Executive Branch function which must be exercised by an array of special capabilities, including review by applicable technical experts of the special technical aspects of the contracts' privilege, to ascertain the veracity thereof, also including the legal determination of contractual aspects. Most importantly, such Agencies must posess independent legal and investigative capacity and legal authority to hold hearings and to initiate and plead court actions in enforcement of the agency's regulatory determinations of breach of contract.

As concerns the functions of the present Food and Drug Administration extended over those technical processes impinging on the quality, quantity and honest measure of these products, and including the purity of potable water, in any new legislation we should be careful to retain the useful and

demonstrably effective criteria, mechanisms, and procedures that have evolved through decision and precedent and become accepted by the regulated industries.

As developed in other papers, equity and justice are best served by a healthy dynamic between adversary champions, without subterfuge, under fair arbitrage and with personally identified accountability, so long as decisions are achieved without undue delay, and those, once rendered, are considered not renegotiable.

The present disservices to the taxpayer general public lie in the insufficiently checked evils of clientism and institutionalism that proliferate selfservingly in order to diffuse and conceal identifiable personal accountability for clientistic judgements and inefficient administration, that diverts personnel from primary mission to supernumary superstructures, then requests additional appropriation to accomplish its failing mission.

The dynamics of this category of organization, in which technological considerations govern, is such that, given a finite budget and number of personnel to perform its primary mission, which requires the exercise of maximum professional talent and capability at the primary working level, the limited capabilities for rewarding the clever and talented lead to creation of superstructures of management which depletes the size and quality of the effective primary working force leaving it staffed by the unmanipulable exceptionally talented under punishment, and/or the mediocre or maimed. To correct this problem by recruiting and retaining maximum talent at the primary level it is necessary to provide extra rank and rewards to primary technical and professional personnel fully equal to those enjoyed by more advanced management functions. Since such rank structure is not standard Government practice, legislation will be necessary. It will also be necessary to prescribe ratio limits for distribution of technical and professional personnel between those performing primary mission functions, along with the minimum line function management thereof; and those diverted to supernumerary organizational superstructure and ancillary or supportive functions, which, instead of diverting the talented, frequently can utilize a certain number of otherwise valuable personnel who have proved to be inadequate to the intellectual and temperamental rigors and demands of the primary function.

As consequence of the "Peter Principle," no organization can perform consistently or very long above the level of competence and dedication of the personnel it is able to recruit and retain.

The mission accomplishing operatives on the firing line must therefore be provided with valuable incentives.

They must be provided rank and pay realistically comparable to their academic and industry peers with whom they must negotiate and communicate. The present differential between $37800 and $65-75000, with no correction for inflationary shrinkage would be ludicrous were it not so painful.

They must be provided sufficient clerical support to efficiently and rapidly convert their technical labors into operational product and be relieved of wasting technical working time fighting for or performing menial services of typing, filing, or seeking out working materials. "The impetus of supply is from the rear!"

Their personal and professional integrity and independence must be respected and safeguarded. Since promotion to higher management or staff functions is counter productive to mission efficiency, other rewards of seniority and exceptional competence or service in the form of perquisites, additional leave, extra retirement credits, tax protected bonuses or other tangible rewards must be legally provided for by legislation.

Mechanisms need also to be provided whereby those marginal personnel who had been recruited in past periods of expediency and retained in career status may be honorably removed from critical mission positions and utilized in performing useful and necessary service functions.

Utilization short of premature retirement needs also to be authorized for those senior staff that can no longer carry the full overload that is common in such agencies.

The common knowledge common practice whereby powerful spokesmen of regulated clients exercise covert -and in being covert undocumentable -veto power over individual personnel assignments must be specifically prohibited and penalities be prescribed for all discoverable participants in such contravention of agency mission.

As discussed in other papers, prescribed management organizational simplicity and rigid adherence to procedures explicitly identifying personal responsibility and documentation for judgements is the key to cost-effective operations.

An additional measure to minimize clientism is to state explicitly in any legislation that the interests of the individuals comprising the general public is paramount, making demonstrable adherence to that interest the prime test of feasance of individual officals administering such legislation.

In the same interest of those individuals as taxpayers, and equally important test of feasance is demonstrable cost effective efficiency as determined by efficient management of personnel resources. Specific individual penalities for such mal and misfeasance -over and above those presently incorporated in general codes- should be provided.

As case in point, one can clairvoyantly predict that the extra appropriation obtained by FDA to staff an expanded capability to monitor Investigations will be squandered in supernumerary upper level positions rather than in providing highly qualified technical experts to perform the primary mission effort.

Touching on the cost effective efficiency of institutions to the taxpayer and promotion of the necessary latitude of individualization to prevent asinine application of procrustean policy, there must be limits to legislative prescription of internal structure and procedures. The historically efficient mechanism is exemplified by the military principle that a General Officer is provided a defined mission or set of missions, a certain force and budget for its accomplishment, while overall, and at each command level, considerable latitude is authorized for individualization to deal with the tactical situations, so long as the commanders exercising that latitude are held personally responsible for any misjudgement.

In civilian agencies, there is need for greater flexibility to rapidly remove Executive Appointees throughout the organization when they, and their superiors, become identified with inefficient function or questionable judgements tainted with clientism. Legislative confirmation of such appointments is meaningless unless a legislative oversight remedy less drastic than suspension of Appropriation can be invoked. This is a complex constitutional issue for which innovative legislation is urgently needed.

Reverting to the latitude and independence of any agency in performing its stated mission and the problems of clientism -balances and restraints need to be defined legislatively to protect it, not only from the direct, and more proper, attempts of the regulated to obtain special treatment, but also from excessive interest exerted in behalf of a particular powerful constituent by the Executive and/or members of the Legislative branch. The "right" of constituent inquiry and petition must be held within prescribed bounds that prevent it from becoming harassment, contravening the agency's prescribed mission responsibility to the public at large that lacks such special pleading.

The special problems of Food and Drug Regulation, as conditioned by the Science and Technology related to it, have organizational requirements for efficiency of mission accomplishment and consistency that need to be recognized by any proposed Legislation.

The same problems of the interface of complex products of industrial chemistry impacting numerous individual and group biological functions, ranging from chronic and long latent tissue cellular dysfunctions through explicit poisoning, to long latent genetic and congenital consequences, are common to drugs, to foodstuffs contaminated or deliberately adulterated in their production and/or processing, and to human water resources.

The limited resources of this technical knowledge are ill utilized by dispersal among separated agencies, e.g. separation of Foods from Drugs and from Environmental, (Air and water) Administrations. On the contrary, the same organized pool of technical knowledge and information capability serves all coordinatively better.

Moreover, this entire field is too important to the present and future human condition to be relegated to a subordinate segment of the already unmanageable Dept. of H.E.W.. Its present subordination to the Public Health Service, rather than the inverse, is ridiculous, particularly since the PHS function is more properly primarily concerned with delivery of health services whereas the Food and Drug mission is antecedent even to the common prophylactic and epidemiological matters PHS concerns itself with.

In order to provide the requisite immediacy of oversight and to hold the management structure within size limits to secure satisfactory accountability for efficiency and to afford necessary latitude of command judgement in operation, such mission directed agency must have independent reportage and authority directly to the highest Executive level. It must also be provided with independent investigative and subpoena powers on a level parallel with those enjoyed by the Internal Revenue and its independent capacity to bring effective actions in the courts must be sufficient to render it independent of permission or assistance from the limited resources of the Justice Department.

The ability to accomplish acceptable due process rapidly enough to prevent mass disasters triggered by obscure technological innovations is too important to be delayed by procedural pettifogging and the ability to "nol pros" a matter that might appear to the strictly legal understanding to be an incomprehensible wrangle among technical experts.

Actual efficiency requires a mission directed flexibility of structure that brings the same chemical, industrial, and biological technological knowledge to bear on all these products and processes to identify the same problem in several places and expeditiously proceed to effective intervention.

Rather than fractionation of various requisite Technical Review and Regulatory Compliance functions, the organization prescribed should be a flexible skeleton which promotes the interdisciplinary communication and coordination between technical disciplines and between the technical, administrational and enforcement functions, so that, from the moment of identification of a problem the full coordinated resources of the agency are brought to bear on its rapid resolution.

Both cost effectiveness and capability for rapid resolution of potential catastrophic technological hazards require that a prescribed pattern of "due process" be set forth with rigid time limits for each step along with an enforceable preclusion from pettifogging and recycling.

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Summary and Recapitulation.

In order to minimize the present problems of securing the individual interest of the taxpayer individuals of the public at large and to curb the present inequities of clientism, abuse of due process, and self serving agency expansion and rigidity, and to promote cost effective operation, and to provide capability to act rapidly and forcefully to prevent potential technological disaster, some legislative remedies are needed. Such legislation should:

I. Restate the constitutional basis of the legislation specifically excluding property right from the licensed "grace and favor" privilege enjoyed by the regulated vendors. It should further specify that:

a) Vendors applications for such contractual licences, in being both knowing and voluntary, further removes any claim of property right.

b) The contractual mechanism allows individualized flexibility to deal with diverse technical matters on a problem oriented individual basis.

c) Default of contract automatically invokes contract specified penalties without recourse.

II. Specifically restate the paramount agency mission as the protection of the public interest of the individuals of that public to defend them from both physical harm and any aspect of fraud.

a) It should further charge that, inherent in the mission, is protection of the taxpayer that requires demonstrably cost effective administration of that charge and prescribes contribution to the cost of that administration by those that seek privilege to profit by vending to this regulated market.

b) To accomplish all this, the legislation should set tests of feasance of officials and provide penalties for their failure over and above those currently incorporated in existing code.

c) Since the technical facts govern this function, the organizational efficiency depends on maintaining maximum quality and quantity capability at the working level, which requires that

limits be set on the relative distribution of professional personnel between line effort and service staff superstructure. Authorization must also be provided for rank and rewards that prevent drain of quality technical talent from direct mission into Management as the only currently available reward.

d) It should require that procedures be established and be adhered to assuring personal identification accountability of all officials for both tactical judgement and cost effective administration throughout all organizational levels. These procedures should include safeguards against covert interference-particularly by veto of personnel assignment -in agency operation and functions.

e) It should also require that procedures be established limiting and channeling to only particular accountable officals the exercise of constituent inquiry and petition in order to minimize arm twisting and constituent special pleading mediated through the Executive or Legislative Branches.

III. Reposition this function of regulating the quality, worth, and measure of Food, Drugs, Water and other consumed or encountered industrial products conditioned by a common spectrum of technical information to establish a coordinated capability for administration and enforcement, reporting directly and independently to the Executive, provided with independent means of investigation, enforcement, and litigation. Provision to this end should recognize that the dispersion of technological problems over all of these products governs, and that the capacity to move quickly and decisively to avert incipient disaster requires prescription of limits on "due process" by rigid application of minimum time limits on each step and curbs set against recycling and procedural pettifogging.

Respectfully submitted.

R. Brown Dunham, M.D.
Aug. 4, 1976

Senator KENNEDY. Mr. Pipari, did you work in the Cardio-Renal division?

Mr. PIPARI. Yes, from July 1973 until March of this year.

Senator KENNEDY. You transferred out?

Mr. PIPARI. That is correct.

Senator KENNEDY. Can you tell us why you transferred out?

Mr. PIPARI. I think the memo that Dr. Dunham read is adequate for the reason. I think the unit could qualify for Federal disaster relief.

Senator KENNEDY. I'm sorry?

Mr. PIPARI. The unit could qualify for Federal disaster relief.

Senator KENNEDY. The unit qualifies for Federal disaster reilef?

Mr. PIPARI. Yes.

Senator KENNEDY. I thought I heard you.

This obviously is an enormously serious situation which you have outlined. The Cardio-Renal Division within the Food and Drug Administration has an important responsibility in areas of kidney and heart diseases and drugs that will be used in treatment of them. The Division's work is of enormous importance and consequence to the health of the American people. If we are not going to have the kind of qualified people in that department, it is not terribly reassuring for us. Those that have responsibilities for the health care policy know that. For this reason, the testimony that Dr. Dunham and you have provided is very valuable.

You have stated it in your words much better than I can do in mine.

Dr. Gyarfas, you have written a very strong letter to the HEW drug panel dated December 30, 1975. Perhaps we could go through the major points with you.

I will make this a part of the record.

On page 1 you talk about attempts to discredit and ridicule our witnesses.

How was that done, and do you still believe that most employees concur with that?

Dr. GYARFAS. I feel it was done very subtly. Of course, these are brilliant people from the drug industry, and they use their intelligence to reflect their feelings. Very subtle comments in various conferences with industry where they ask: How are the dissenters getting along or conscientious objectors?

Senator KENNEDY. Dissenter and conscientious objector?

Dr. GYARFAS. Yes. That is what people who have testified here have been branded by various trade publications, namely the Pink Sheet.

Senator KENNEDY. You talked about an effort to stonewall the dissenters. What do you mean by that?

Dr. GYARFAS. Well, I was in a position more or less on the outside watching the work of the people that testified before you to gather their information and documentation of their charges. Frequently I received requests from them to see what assistance I could give them even in obtaining such things as secretarial assistance and typing up the reports that they were required to submit.

Senator KENNEDY. You mean they were being, in some instances, denied the support of secretarial assistance to file reports and to complete their work?

Dr. GYARFAS. It appeared that way to me, yes.

Senator KENNEDY. So you do not believe that there really was full cooperation with a number of these people that had been witnesses? At least that was your impression?

Dr. GYARFAS. Yes.

Senator KENNEDY. You have an overview kind of position; specifically what is your responsibility?

Dr. GYARFAS. Currently I am the Director of the Division of Radioactive and Oncological Drugs.

Senator KENNEDY. At this time what was your position?

Dr. GYARFAS. At this time I was in a position with the title of special assistant to the Director of the Bureau of Drugs, at which time there was no position established.

Senator KENNEDY. Were you, in your opinion, removed from a position because of your recommendation to disapprove a drug?

Dr. GYARFAS. That is my conviction.

Senator KENNEDY. That was Discase, as I understand?

Dr. GYARFAS. Yes.

Senator KENNEDY. Did you get offered a job at Travenol Lab at the time you were handling the NDA for Discase?

Dr. GYRAFAS. Yes, sir.

Senator KENNEDY. You were actually offered a job by a company at the time you were considering their drug application, is that right?

Dr. GYARFAS. Yes, sir.

Senator KENNEDY. Is that usual or unusual? Is that the way things are done? What is your reaction to that?

Dr. GYARFAS. Well, very frequently members of our staff have been offered positions——

Senator KENNEDY. When they are considering drugs of companies——

Dr. GYARFAS. Well, they may or may not be at the time.

Senator KENNEDY. But in this case it was?

Dr. GYARFAS. Yes.

Senator KENNEDY. You were considering a new drug application, Discase, and you were charged with prime responsibility in this area at the same time the company was offering you an employment opportunity with that company. Did you gather the impression that it was contingent upon what recommendation you made for that drug?

Dr. GYARFAS. I cannot say that I did.

Senator KENNEDY. Well, do you in your own mind think they would be more likely to hire you if you approved it than if you disapproved it?

Dr. GYARFAS. I would hope they would hire me regardless of the outcome.

I have no way of knowing. I know that they were very pleasant, very friendly.

Senator KENNEDY. But there is no question in your own mind about the inappropriateness of either that recommendation or suggestion?

Dr. GYARFAS. No; there was not.

Senator KENNEDY. As a final request, I want to ask this Panel if they would very briefly make written recommendations to our com-

mittees as to how the circumstances you have described could be dealt with. We will make these recommendations part of the record. That is what we are really interested in. Obviously there will drafting and fashioning of rules and regulations. We are going to have legislation as well. We welcome receiving from those of you that are interested, any specific recommendations about how we could deal effectively with the problems you have outlined. It is ultimately the purpose of these hearings to deal with these problems, either from a legislative or regulation point of view.

I want to again thank you very much for your appearances here.

[Information supplied for the record follows:]

Crystal House II, Apt. #215
2000 South Eads Street
Arlington, Virginia 22202
December 30, 1975

Lionel M. Bernstein, M.D., Executive Secretary
Review Panel on New Drug Regulation
HEW North Building, Room 4617
330 Independence Avenue, S. W.
Washington, D. C. 20201

Dear Doctor Bernstein:

In reply to your letter of December 5, 1975 inviting my participation in the Review Panel on New Drug Regulation's review of Commissioner Schmidt's report on his investigation into the specific allegations regarding the internal management of the Food and Drug Administration made by eleven present and former FDA employees and three agency consultants on Health and on Administrative Practice and Procedure, I respectfully submit the following comments concerning the conclusions reached in the Commissioner's Report, and I do so directly without recourse to legal counsel.

First of all, I do want to register a complaint regarding the way that the Review Panel's letter was delivered to me. While the letter was in a sealed envelop and addressed to me, presumably a personal letter, I received it opened and routed to me with a routing slip.

I wish to point out to the Review Panel that I am not a novice in the Bureau of Drugs, but have been with the Bureau of Medicine (now Bureau of Drugs), Food and Drug Administration since July 21, 1963. Since 1968 I have served in responsible positions as Director of various division as well as for a 23 month period as Acting Director, Office of New Drugs. Also, for a period of 20 months, I was detailed as Special Assistant to Director, Bureau of Drugs, a non-established position. I am knowledgeable of the events that have happened within the Bureau and am cognizant of the allegations made by the "dissenters" at the Senate Hearings of August 16 and September 25, 1974. Also, I am cognizant with requests by the Administration made of all "dissenters" to document their allegations and charges, and the difficulties encountered by them to collect data and to reply to the requests for documentation, including the difficulty even to obtain necessary secretarial assistance.

In my opinion, I feel that some of the "dissenters", being acquainted with them and knowledgeable of the events that lead to their allegations, were using the Senate Hearings merely as a forum to air their personal grivances purely for invective reasons while others were deeply sincere and did present charges that should be brought to light and explained. I do ~~admire~~ admire their courage in placing their positions and reputations in jeopardy in making their charges and withstanding the campaign to discredit and ridicule them by some members of the Food and Drug

Administration, various members of the drug industry, and in publications of the drug industry such as the "Pink Sheet" which tagged them with the name "Dissenters". While some of their fellow employees do not concur with their testimony, by far the large majority could have added to the allegations, from knowledge and experience, if only they would have had the courage to do so.

I hereby submit my evaluation of the conclusions reached in the Commissioner's Report and do so without submitting documentation to support my evaluation, and without any intent even to collect documentation. Any part of my evaluation that is not agreed with or is challenged, let the disageer or challenger produce documentation to the contrary.

My over-all evaluation of the Commissioner's Report is that during its preparation, every effort was made to "stonewall" the "dissenters" and the conclusions reached in the Report are merely as "whitewash" of the charges and allegations made. Also, I feel that the conclusions are incomplete as they respond only to the allegations made at the hearings of August 15, 1974 and includes no responses to the allegations made at the September 25, 1974 hearings. Very little evidence or documentation is presented in the Report to support the Commissioner's conclusions and much of the documentation presented is after the fact, so to speak. For example, while the Commissioner concludes that he saw no pattern of harassment of employees in unexplained removals or transfers, new policy and procedure guideline were drawn up for future use, when there were policies and procedural guideline already in existence to prevent unexplained transfers at the time they were occurring.

While the Commissioner concludes that he saw no pattern of harassment of employees in unexplained removal or transfer, no effort is made to explain the removal or transfer of the employee, often to area outside of his training and experience. While he calls for the "dissenters" to produce evidence that their transfers were because of their positions unfavorable to drug companies, the Commissioner offers no explaination of reasons for their transfers. In my own case, I was removed from a position of decision making and I sincerely feel that I was removed from the position because of my opposition to approval of a New Drug Application (NDA). I am of the conviction that I was removed from the position because of my stand against approval of the new drug, though I would have great difficulty in supplying documentation. While opposing the approval of the NDA forDiscase (Chymopapain), referred to by Dr. John Gerda in his testimony before the Senate Committee, I convened an Advisory Committee consisting of three experts recommended by the Academy of Neurosurgery and three experts recommended by the Academy of Orthopedics to evaluate the data submitted by the drug firm for Discase. Since the recommendations made by this Advisory Committee was unfavorable to the Administration, the new drug, and to the drug firm, I was suddenly "promoted" from Director, Division of Surgical and Dental Drug Products to a not-established position as Special Assistant to the Director, Bureau of Drugs and a new Advisory Committee was appointed to review the data submitted for Discase.

(My belief that there was inadequate data to support safety and efficacy of Discase as claimed by the sponsor, Travenol Labs, was substantiated when a later, controlled study revealed that Discase is no more effective for herniated nuclei pulposus than was the placebo and the NDA was withdrawn by the firm.)

Though the Commissioner, in his conclusions, states that he saw no pattern of harassment of employees, or transfers or removal of people for punitive reasons, or of pressure to approve new drugs, he does not supply any evidence to the contrary. For a rational person, it is difficult to explain the reasons for some of the transfers or removals of employees, often from their areas of expertise and even to non-established position. Among his conclusions, the Commissioner states that in his investigation he found no industry domination of the Bureau of Drugs. In my opinion, I feel that he did not search diligently enough to find domination by industry. I feel that just about everyone in the Bureau, at one time or other, must have felt some degree of pressure for approval, more than likely pressure from industry. Many times this pressure comes in the form of disagreement, but not to what is considered "good science". Differences are most commonly resolved by industry by proceeding to the next higher position and settling the differences not by additional new data but merely reaching an "agreement" with the next highest authority.

In spite of the public relations efforts made by the Administration to publicly list all meetings with industry, often the "differences" are settled by telephone and even meetings held out of town at chance meetings or at various scientific meetings and conferences. The Commissioner states that Agency files are remarkedly complete in documenting the events discussed in reaching decisions about a new drug, a personnel disagreement, or even disputes over what should be put in Agency files, I content that many decisions are reached within the Agency that are not documentable. Many times, decisions are reversed by a short memo written on a routing slip, and not contained in the files, or even through a telephone call from a superior.

There have been times when a new drug was approved wtih definite pressure, whether by the Administration or by industry. Demulen was one such new drug. The instructions were to approve the new drug within one week, and no question asked if it was approvable or not. Signatures for approval were collected under stress and in a rush even though there existed at the time a long memrorandum from Dr. Daniel Banes stating the new drug, Demulen, should not be approved as there was not presented by the firm adequate methodology for regulatory purposes. I feel that such pressure to approve Demulen was improper and probably reflected a bias toward the drug industry.

While current guide-lines for steps in the process to approve, or disapprove, a new drug is well spelled out to produce a well documented, sound, institutionalized decision. I feel that in daily practice, it does not work as promoted by public relations. Decisions are often

reversed by higher levels, and often without the courtesty to discuss differences with the reviewing medical officers except in a cursory way, if that. Advisory Committees are often quoted, but I feel that the selection of Consultants is very bias. Recommendations are adopted that are favorable and recommendations not favorable to the Administration and to drug industry are rejected.

For a regulatory agency, in my opinion I feel that it has acted in conflict of interest with the industry that it seeks to regulate. Very close liaison has developed in scheduled meetings with industry and especially meetings to which attendance has been restricted. While joint meetings between the regulators and the regulated are good if they are to discuss scientific questions, and are not used to determine what industry desires to do and to what regulations they will submit. Routinely meetings are held with members of the Pharmaceutical Manufacturers Association, but not always to resolve scientific questions.

Without letting my response to your inquiry becoming too long and rambling in nature, and to respond to your inquiry directly as to my evaluations of the conclusions reached in the Commissioner's Report, I wish to state that in my opinion the conclusions reached by the Commissioner are not completely accurate or correct. With some of his conclusions I could agree but with the majority, I must disagree. I submit my comments with the sincere conviction that the Review Panel will be honest and thorough in their investigations and will reach a just conclusion.

Sincerely yours,

William J. Gyarfas, M.D.

WILLIAM J. GYARFAS, M.D.
2000 South Eads Street #215
Arlington, Virginia 22202

October 22, 1976

Honorable Edward M. Kennedy
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

At your Food and Drug Administration oversight hearings on July 20, 1976, you invited comments and suggestions for ways to improve and strengthen the FDA so that it might better accomplish its mission. After giving the matter serious thought over a period of time, and based on my 14 years of experience in the FDA, I wish to submit the following comments and suggestions. My comments are brief, but I am available to elaborate on any point as you wish.

In summary:

1. The FDA should be an independent regulatory agency out from control of DHEW and especially from Public Health Service.

2. Recommend one agency for Food, Drug, and Cosmetics rather than attempting to establish separate agencies, with their necessary resources, for each. The one agency would be responsible for regulating medical devices, insecticides, pesticides, and dangerous drugs, and also would be the principal advisor to the Envirnomental Protection Agency.

3. Scientific capabilities should be strengthened by additional well-qualified, experienced scientific personnel--and decrease the current ratio of "lay" and "public relations" personnel to scientific personnel.

4. The mission of the FDA should be redefined, with a revision of the Code of Federal Regulations, Title 21. All superficial, satellite, "public relations," make-work" programs should be abolished.

5. Appointment to the position of Commissioner, FDA, should require Senate approval, and be for a set term, not renewable. There must be a reduction in the number of positions subject to political appointment. There must be a stricter compliance with Conflict of Interest requirements.

6. Requirements for Food, Cosmetics, Medical Devices, etc. should include safety and efficacy.

7. Everything possible must be done to minimize the influence of regulated firms and individuals.

8. Whenever questions of the safety or efficacy of a product exist, the product must not be marketed. When questions of safety or efficacy are taken to court for resolution, even though the product previously has been approved, it should not be marketed until all problems are resolved.

9. All drugs, whether presciption, over-the-counter, or "me-too" should be required to have on file an approved New Drug Application (NDA). In essence, every drug sold in the United States would be sold only on the basis of FDA approval--and with the number of the approved NDA (or license, if you will) on the label of each package.

10. Development and study of new drugs should be better organized. All animal studies required must be completed and evaluated by FDA before human studies are permitted. All protocols of proposed studies must first be reviewed and approved. Before studies are permitted to advance from one phase to the next, all information and data from the previous phase must be submitted and subjected to evaluation. Frequent on-site inspections to all laboratories and investigators must be accomplished by the monitors and by FDA.

11. There must be complete periodical reporting by firms on all marketed products, with emphasis on the amount of drugs distributed and all adverse reactions reported, with the frequency of reports determined by the FDA.

12. All scientific and laboratory capabilities of the FDA must be increased.

13. There must be more use of computerized methods to record, store, and retrieve drug data and information.

14. We need a marked improvement in the FDA's management and utilization of drug adverse reaction information.

15. The compliance arm of the FDA must be strengthened and geared to immediate action in all product dangers and hazards. There must be notable increase in the field compliance activities, with greater deference to scientific and medical opinion.

16. All data and information within the FDA should be available to the public under Freedom of Information requirements. Other than true trade secrets no information should be withheld from the public, including adverse information as well as information upon which the approval of a product is based.

Discussion:

The FDA should be an independent agency. It should not be located within and under control of any department of the government, not even the Public Health Service. I have no objection to separation of the FDA into individual agencies for drugs and food, but feel such a move would only create additional agencies that would require considerable duplication of personnel, laboratories, and testing facilities. The FDA would better serve as a single, strong, scientifically competent, independent REGULATORY agency responsible for the safety and efficacy of all drugs, including all biological and veterinary drugs, cosmetics, medical devices, and foods (all with complete labeling) and also as principal advisor for the Environmental Protection Agency regarding the safety of insecticides, pesticides, and all chemicals used in our society.

The scientific capabilities of the FDA should be strengthened by the addition of more scientific and medical personnel who are completely free of any possible conflict of interest for at least three years prior to appointment, and without allegiance to any other branch of the government such as the Public Health Service, military, or NIH. On leaving employment at FDA, employees should not have dealings with FDA for at least three years. This would tend to decrease the current "revolving door" practices, especially with the newer political appointees. Employees should be protected by law from influence by industry and special interest or lobbying groups. The same requirements for employment at the FDA should also apply to all members of advisory committees. In addition, members of advisory committees should be selected on an unbiased basis as they now are. Currently, members of advisory committees are selected without a definite plan of selection, and mostly on a friendship or acquaintance basis, or with a deliberate effort to obtain a committee with a preformed opinion as judged from their writings and publications. Members of advisory committees should be selected from nominations from learned professional societies.

The medical arm of the FDA sorely requires the addition of many qualified, experienced physicians. Currently, there is a lack of physicians in the FDA, plus a marked under utilization of presently employed physicians. In 1970, for example, the Bureau of Medicine (now Drugs) had approximately 330 employees of whom approximately 160 were physicians. Currently, the Bureau of Drugs has a little over 1,000 persons of which only approximately 80 are physicians, and many of these physicians are being employed in satellite programs and projects. While the term, "drug lag," is one that has been created by the drug industry in an effort to gain earlier, less stringent reviews and approval of their NDA's, there is a backlog or delay in reviewing IND's and NDA's due to the lack of personnel whose jobs are to review such submissions. The FDA should be strengthened with the addition of more well-qualified, experienced physicians.

Being a part of the Public Health Service has created some degree of discord or low morale among the physicians of the FDA. The FDA is being used by the Public Health Service as a place to assign physicians and other personnel to keep them "occupied" and to maintain their personnel strength and numbers. For the most part, Public Health Service physicians are younger and less experienced than are the civilian physicians. Since Public Health Service physicians are eligible for additional pay as bonuses, as are military physicians, this has created additional animosity between the FDA and Public Health physicians. The FDA physicians are often supervisors of Public Health Service physicians, yet are paid by a different pay scale and receive less money. This is not to decry the capabilities of Public Health physicians, but for unity and harmony, it would seem that if they want to work for the FDA, they should become FDA physicians and be subject to the same pay and regulations.

The missions of the FDA should be reidentified and redefined. As the FDA is a regulatory agency, this should be acknowledged in no uncertain terms. In recent years, the authority and capability of the FDA to accomplish its mission as charged has been diluted by the addition of many satellite programs tending towards public relation functions, medical education, sociology studies, etc., that spread thin the scientific expertise of the agency. There has been a loss of emphasis on the medical and scientific strength of the FDA because of the proliferation of nonscientific personnel within the FDA. There has been a loss of funds because of the desire to support these various satellite programs and projects. The FDA cannot be "all things to all men" but must concentrate on its stated mission of protecting the consumer from unsafe, dangerous, ineffective drugs, medical devices and products, food, and hazardous chemicals. In addition, the FDA must sever its "bedfellow" ties to the drug and food industry and allied associations, such as the PMA, etc.

To better accomplish the missions of the FDA, the regulations should be rewritten, simplified, organized, and recodified in a way that would be advantageous to the FDA and the consumer, rather than the drug and food industry. Administrative procedures should be clarified and better defined. When there is a question of the safety or efficacy of a product, and the problem has exhausted all administrative procedures and winds up in the courts for legal resolution, until that problem has been satisfactorily resolved, the product must be withdrawn from the market immediately. A product should not be marketed just because there are no known adverse results. It should be marketed only after all questions of safety and efficacy have been resolved by well-controlled, substantial studies. Today, drug firms often take problems of safety and efficacy to the courts for legal solution knowing that they may continue marketing their questonable products for years while the problem is under litigation. Similar requirements should be developed for foods, cosmetics, medical devices, and other chemicals in our envirnoment.

One of the most important recommendations that could be offered would be that all drugs--old drugs, new drugs, prescription drugs, over-the-counter drugs, "me-too" drugs, USP drugs, etc.--that are marketed in the United States have an effective, approved New Drug Application (NDA) on file. In essence, every drug marketed in the United States would be licensed, and approved for its safety and efficacy as claimed. This would reveal just how many drugs are currently marketed: information that is sorely lacking today. With period reporting required on all drug products--information as to formulation, quanitities produced, adverse reactions, etc.--meaningful and useful data would be available.

In the past, there have been objections to the recommendation of requiring an NDA for all drugs on the basis that there would be so much data generated that the FDA could not manage it. But with hundreds of thousands of drug marketed today, what better protection could be offered the consumer? The FDA could be strengthened with additional personnel, better utilization of "good" advisory committees, and utilization of other assistance such as computors, etc. New drugs would be required to follow current procedures of investigations under IND's and then thorough review of the resultant NDA's. Drugs for which knowledge and information exists, reviews and approvals would not be of any time consuming consequence. It is felt that within a two year period of time, such a system of drug approval and management could become an operational program. Furthermore, each drug package marketed would bear the approved NDA number for identification, or license, if you will.

New drugs under study, investigation, or development would still require the sponsor to submit a Notice of Claimed Investigational Exemption for a New Drug as now, but with stronger, firmer control and enforcement of regulations. Before human studies would be permitted, even phase I studies, animal studies would have to be completed and data submitted for evaluation. Only after approval of the animal studies would human studies be permitted but only after approval of the proposed protocols of studies. All human studies would require careful and frequent monitoring, and also often on-site inspections by FDA. Before human studies would be permitted to advance from one phase to the next, the previous phase data must have been submitted and evaluated.

Once adequate studies have been performed for a new drug, or new indication, and the data is substantial to permit making a decision that the drug is safe and efficacious as claimed, the drug is probationarily approved with careful follow-up required on each patient that may receive the drug until such data has accumulated that would no longer require the initial close control and monitoring of a new drug product. Critics contend that such care and caution in developing new drug products would only add to the "drug lag." The term "drug lag" was developed by the drug industry in their attempt to gain public support and to be permitted to market a new drug prematurely, and to take short cuts in what is regarded as good science and adequate protection of the consumer. In examination of "drug lag" the drug industry is unable to

make truly meaningful and accurate comparisons between the time of drug approval in the United States and other countries because the drug laws of the other countries do not afford the protection to their citizens that the United States drug laws do.

With old and "me-too" drugs, for which there is existent data and experience regarding their safety and efficacy, NDA approvals would require very little time. Perhaps only a presentation to medical staff and advisory committee, plus a review of their manufacturing procedures and controls. There would be no drug monographs developed, each individual drug product would be the subject of an NDA. Publishing drug monographs, recipes, would permit anyone to manufacture and market the drug merely by stating that they were complying with the drug monograph, but without any real check.

For adequate protection of the consumer, we need stringent laws and controls, firmly administered by scientific, unbiased, we need individuals free from conflict of interest. By and large, the FDA is composed of such individuals, but they must be permitted to function without "pressure." Such tight requirement should be required of all drugs, foods, cosmetics, medical devices, dangerous drugs and chemicals to which our population is exposed. The mere statement that no "known" adverse reaction has occurred after exposed to a drug or chemical can no longer be adequate. Before such a drug or chemical may be marketed, the safety and efficacy must be proven by well-controlled, substantial studies.

Efforts must be made to publize any information that reveals the dangers or hazards of a drug or chemical. The mere announcement of the ones that are approved for marketing is not sufficient.

In summary, I do not feel that there is a need for a major revision of the FDA. With a few changes, good consumer protection can be secured by strengthening the scientific capabilities of the FDA, removing untoward industry pressures, and firmly enforcing existing regulations to the "letter."

In closing, I want to compliment you on your interest in the American consumer and the FDA. I feel that your work is very beneficial.

Sincerely yours,

William J. Gyarfas

William J. Gyarfas, M.D.

Senator KENNEDY. We will move to the second panel now.

Our second panel consists of Dr. John Winkler, Dr. David Lidd, Dr. Andrew Beaulieu, Dr. Klemens Johnson, Mr. Thomas Dols, Dr. Steward Frazier, Dr. Robert Baldwin, Dr. Robert Condon, Dr. Donald Gable, Dr. Larry Rollins, Dr. Robert Knox, and Mrs. Lucille Pogue.

Dr. Winkler, do you stand by your previous testimony before this committee?

STATEMENTS OF DR. JOHN WINKLER, DR. DAVID LIDD, DR. ANDREW BEAULIEU, DR. KLEMENS JOHNSON, THOMAS J. DOLS, DR. STEWARD FRAZIER, DR. ROBERT BALDWIN, DR. ROBERT CONDON, DR. DONALD GABLE, DR. LARRY ROLLINS, DR. ROBERT KNOX, AND MRS. LUCILLE POGUE, A PANEL

Dr. WINKLER. Yes; I stand by all the testimony.

Senator KENNEDY. I understand that you have been involved in a review of a drug called Proventil, is that correct?

Dr. WINKLER. Yes, sir. I was involved from the standpoint of the group leader in the group that handled this drug.

Senator KENNEDY. When was that? Give us an approximate time. Walk us through your experience with that drug?

Dr. WINKLER. My most recent experience began in the summer of 1975. The application was reviewed, the last time it was reviewed, it was completed in July 1975, at which time the medical officer and myself took the position——

Senator KENNEDY. Just before we get to that, as I understand it, the first medical officer review resulted in a recommendation for disapproval in June 1974, is that correct?

Dr. WINKLER. I am not sure about that date.

Senator KENNEDY. We have the document here that shows that it was June 19, 1974.

Dr. WINKLER. I believe that is correct.

Senator KENNEDY. Show this to him. [Indicating.]

Dr. WINKLER. Yes, sir, this is the first review.

Senator KENNEDY. Was that first recommendation acceptable?

Dr. WINKLER. Yes; it was. I endorsed that recommendation and so did the division director.

Senator KENNEDY. Now, there was the second review. I understand that it was done July 26, 1974, and again nonapproval was recommended.

Dr. WINKLER. Yes; that is correct.

Senator KENNEDY. Why did you write to Dr. Clark on July 28, 1974?

Dr. WINKLER. What was that memo?

Senator KENNEDY. Do you remember writing to Dr. Clark on July 28, 1974?

Dr. WINKLER. In July 1974, I do not have a copy of that memo.

Senator KENNEDY. We will get the particular memorandum. We have got it. It is July 26, 1975.

Dr. WINKLER. Right. July 1975 was the last time the application was called nonapprovable by reviewing medical officers.

Senator KENNEDY. Was a third medical officer review conducted?

80-211 O - 76 - 10

Dr. WINKLER. That is the one I am referring to, July 1975.

Senator KENNEDY. What was the recommendation?

Dr. WINKLER. That the application was not approvable.

Senator KENNEDY. So what we really have got here is three different reviews of it and all for disapproval?

Dr. WINKLER. That is correct.

Senator KENNEDY. Is that correct?

Dr. WINKLER. Yes.

Senator KENNEDY. Did you concur with those?

Dr. WINKLER. I concurred with the not approval recommendation.

Senator KENNEDY. Now at some time they had an advisory committee meeting, is that not correct.

Dr. WINKLER. That is right.

Senator KENNEDY. What happened to the advisory committee recommendation? What was the recommendation? What did they recommend?

Dr. WINKLER. The advisory committee recommended the drug could be approved in spite of the absence of the usually required long-term studies on the basis that the drug could be studied under phase four conditions to develop data that is missing at this time and also under the provisions of a restrictive type of labeling which would not be consistent with the type of use the drug was intended for.

Senator KENNEDY. When that action was taken, I understand, the chairman remarked that, "with considerable hesitancy this course of action is recommended to FDA." Is that your understanding?

Dr. WINKLER. That is right.

Senator KENNEDY. The drug was approved[1] with considerable hesitancy over the three negative recommendations of the medical officers?

Dr. WINKLER. That is right.

Senator KENNEDY. After that were you asked to determine whether this was a drug lag?

Dr. WINKLER. Yes, sir. After medical review was written and endorsed at the division level, and after the advisory committee recommendations there was interaction between the Division Director and the office level. One of the considerations brought up at the office level was whether or not the drug represented a drug lag item.

This was addressed by Dr. Lidd and myself in some review of the literature and of all the material that was available to enable one to determine that. It was our conclusion that there was no basis for a position that the drug represented a drug lag item at this time.

Senator KENNEDY. Dr. Lidd, what did you conclude?

Dr. LIDD. A comparison was made between metaproterenol and salbutamol, it being felt that metaproterenol, a drug recently marketed, was the closest with respect to safety and efficacy, to salbutamol. Upon reviewing the five studies, I came to the conclusion that with respect to both safety and efficacy there was not any significant difference apparently at this time between salbutamol and metaproterenol.

Senator KENNEDY. Dr. Winkler, so you believe it was not a drug lag problem?

Dr. WINKLER. That is right.

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[1] Dr. WINKLER. I believe Senator Kennedy's comment intended to state approval was recommended. The drug was not approved. See my suggested revision.

Senator KENNEDY. Did Dr. Finkel agree with you?

Dr. WINKLER. At that time I do not believe she did agree with me until later in the course of the situation when we presented memos pointing this out.

Senator KENNEDY. Dr. Lidd's report said that it was a drug lag drug——

Dr. WINKLER. That is right. That was in October.

Senator KENNEDY. On October 28, 1975, Dr. Finkel sent a note to Dr. Clark that says: "Use our SOP for drug lag drug, viz approval if that firm submits a protocol for phase 4 study," et cetera, et cetera.

Are you aware of that?

Dr. WINKLER. Yes. There was a development that occurred after the writeup by Dr. Lidd and myself. I know there was interaction between the Division Director level and the Office Director level. I recall the memo that came, the one you just read with a buck slip on it in which Dr. Finkel indicated we should issue an approvable letter under the conditions that you just went through, phase 4 studies and so forth.

Senator KENNEDY. Was that a surprise to you?

Dr. WINKLER. No; I was not surprised.

Senator KENNEDY. Were you asked to help in the preparation of an approvable letter?

Dr. WINKLER. Yes; after that memo and accompanying buck slip came to the Division there was a meeting at which I was requested to prepare an approvable letter under the conditions outlined.

Senator KENNEDY. Did you do this?

Dr. WINKLER. No; I did not. I expressed a strong disapproval of being asked to prepare the letter and the documents that would accompany it, the basis for approval, inasmuch as I had gone on record with my opinion that the drug was not approvable.

Senator KENNEDY. Did you receive any continuing pressure to do what you did not want to do?

Dr. WINKLER. For a short period of time I did.

Senator KENNEDY. Did you meet with your superiors stating you felt you were being harassed on the matter?

Dr. WINKLER. I had no contact with anyone outside the division level.

Senator KENNEDY. In the Division level?

Dr. WINKLER. In the Division level.

Senator KENNEDY. You did in the Division level—Dr. Clark?

Dr. WINKLER. Yes; as I say, for a short period of time. I indicated my disapproval of the request and asked that it be put in writing, and it was put in writing.

Senator KENNEDY. What happened after that?

Dr. WINKLER. There was several memos.

Senator KENNEDY. Did it go back to the advisory committee?

Dr. WINKLER. Yes; a series of memos, and then the matter was taken to the committee in an informal way at the next meeting.

Senator KENNEDY. What did they conclude?

Dr. WINKLER. They reversed themselves from their previous position. They decided it did not represent a drug lag and they decided they did not now feel it should be approved.

Senator KENNEDY. As I gather it, you had three medical officers who recommended disapproval and then the advisory committee hesitantly

recommended approval. Then you reviewed it to establish whether it was drug lag drug. You realized that it was not and the advisory committee supported that decision by reversing itself.

Now after that all happened, a new report comes from Dr. Fefer?

Dr. WINKLER. Yes; there was a report of an additional deficiency, and I am not familiar with all the details on this——

Senator KENNEDY. Well as I understand it, yet another medical officer review was completed in March 1976, is that correct? Well there was another one completed sometime in the spring of this year?

Dr. WINKLER. I do not believe so. I am not sure about that. There were three reviews, including the one that was completed in July 1975. That was the third medical review.

Senator KENNEDY. Is there not also a medical officer's review that was completed March 4, 1976, that you are aware of?

Dr. WINKLER. This is the same one basically. It is not another medical review. It is an expanded review. It was revised to bring it into format with—the usual format for review. There is no significant change in this review.

This review was the same one that was the basis for the position taken in July 1975, the same medical officer's review.

This is the one in which we restated our position as expressed in July 1975.

[Information supplied for the record follows:]

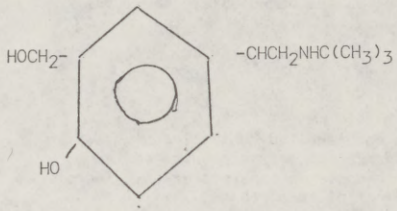
NDA 17-559 June 19, 1974

MEDICAL REVIEW NDA 17-559

COMPANY: Schering Corp.
60 Orange Street
Bloomfield, N.J. 07003

DRUG: Proventil Inhaler, Ventolin inhaler, Salbutamol, Albuterol.

STRUCTURAL FORMULA AND CHEMICAL NAME:



α' - [(tert- butylamino) Methyl]-4 Hydroxy-m-xylene-α,α'-diol

Category of Drug: Bronchodilator (beta-adrenergic stimulant)

Related INDs: 5684 - albuterol aerosol
7542 - " tablets

Proposed Indication and Dosage:

"Relief of bronchospasm in adults and children with obstructive airway disease such as acute and chronic asthma and in chronic bronchitis and emphysema when bronchospasm is a predominant factor."

Daily Dosage: 200 mcg (2 inhalations every 4 to 6 hrs.)

Chemistry: Not approvable under Section 505(b)(3)(4) and (6) of the Act. See chemist's review of March 28, 1974.

Pharmacology: Preclinical studies offer adequate support for the proposed clinical dose of the Proventil inhaler. It is noted that the propellant is more toxic than other fluorocarbons, and is currently under review by FDA. See pharmacologist's review of April 12, 1974.

CLINICAL EVALUATION:

Explanatory Preamble:

On 3/28/72 Schering submitted a discontinuance letter for their albuterol inhaler IND 5684 (Proventil). The reason stated was a problem with the dose delivery system, i.e., "With the passage of time there was a decrease in the amount of albuterol released per actuation of the metering valve."

On 6/14/72 in a Proventil IND progress report Schering stated in their discontinuance letter to the investigators that Proventil was available with a different dose delivery system which was acceptable. Thus, the fact of the discontinuance was confirmed.

EFFICACY STUDIES:

United States:

1. Dr. Joseph Dwek - This was a double-blind controlled study which began with 30 patients. Reports for 26 patients are submitted and 3 were dropped due to a paradoxical response to isoproteroneal. Therefore a total of 23 patients are the subject of this report. All of these patients also received concomitant therapy.

This study by Dr. Dwek was completed by January, 1972. Therefore, this pre-dates the discontinuance of studies due to the faulty delivery system.

2. Dr. Myron Stein: This was a double blind controlled study. 22 patients began the study and 21 completed the study - one patient being lost to follow up. Again, concomitant therapy was the general rule for all patients.

This study by Dr. Stein was completed by April, 1972 and hence the faulty delivery system was apparently involved.

SPECIAL STUDIES:

Dr. B. Calesnick: This was a study of absorption, excretion and metabolism in 4 volunteers. Plasma radioactivity peaked at 2 and 4 hours after inhalation of 84 and 220 mcg, respectively. About 72% of the inhaled dose is excreted within 24 hours in the urine. Approximately 28% of the dose is excreted as unchanged albuterol, and a water-soluble metabolite represented 40% of the inhaled dose.

SAFETY:

In the 44 patients studied by Drs. Dwek and Stein, in the United States, there was one death in a 49-year old woman whose study entrance diagnosis was "mild, stable bronchial asthma" of 18 years duration.

An autopsy revealed severe bilateral bronchiolar mucous plugs, chronic bronchitis, bilateral pleural adhesions, moderate hypertrophy of the right ventricle.

The patient entered the study on 10/15/71 and died on 11/12/71.

Check by Schering of the albuterol aerosol used by the deceased revealed "good agreement" with the reference samples. (See NDA Pg. 2301.1.18a in volume 1.12).

Dr. Dwek's review of the patient's study medical diary revealed no over-utilization of the medication. He felt the cause of death could be explained on the basis of mucous plugging with resultant hypoxemia. The role of the albuterol aerosol could not be determined. Whether it contributed to an arrythmia or whether it had any relationship to sudden death could not be determined.

SUPPORTIVE DATA:

There were 83 clinical studies conducted by 58 investigators in 1500 patients in countries other than the United States.

Six studies were done in the United Kingdom, where there was no demonstrable valve meter problem.

No case reports have been submitted for any of these studies. The sponsor states that no raw data may be permitted to leave the United Kingdom.

The sites of the other studies are Scandinavia, West Germany, and Rumania.

ADDITIONAL INFORMATION:

At the May 9, 1974, meeting of the Pulmonary-Allergy Advisory Committee meeting representatives from Schering Corporation presented an overview of their work with Proventil. While the Committee made no specific recommendations they did express concern regarding the type and caliber of studies done to date.

CONCLUSIONS:

1. Two studies done in the United States (44 patients) with a defective valve do not provide satisfactory evidence of efficacy.

2. One death among 44 patients is reported. Final conclusion regarding safety must wait the completion of additional well designed studies.

3. Protocols for additional studies should be submitted for review.

4. Review of labeling must await additional clinical data (see pharmacologist's review for preliminary comments).

RECOMMENDATIONS:

This application is not recommended for approval under Section 505(b)(1)(3), (4), and (6) of the Act.

M. Smelzer

M. Smelzer, M.D.

cc: NDA 17-559 Orig., Dup.
HFD-100
HFD-160
R/D MSmelzer(HFD-160)6/19/74
R/D Init JWinkler 6/19/74
Final typed nm 6/19/74.

JWinkler 6/19/74
MClark MD 6/21/74

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7/15/74
FROM: M. Clark, M.D.		OFFICE
TO: John Winkler, M.D.		DIVISION

SUBJECT: NDA 17-559 (Proventil)

SUMMARY

Please see Dr. Crout's memo regarding Not-Approvable letter for NDA 17-55.. Accordingly, a complete review of all clinical studies, foreign and domestic should be done.

Dr. Solymossy has been assigned to HFD-160 on detail. Since Dr. Smelzer is on sick leave, please assign NDA 17-559 to Dr. Solymossy. Since it is important to review this NDA expeidtiously, no other work should be assigned to him until this review is complete. The progress of this review should be closely supervised by you. This review should be completed by August 5, 1974. If there is any time lag please inform me as to the reasons for such lag.

Please see that the NDA and work assignment are conveyed to Dr. Solymossy today.

SIGNATURE Margaret Clark, MD	DOCUMENT NUMBER

FD FORM 2034 (2/72)

NDA 17-559

January 10, 1975

MEMORANDUM OF CONFERENCE

Between: Schering Corporation

Domenic Pezzoni, M.D.
V. P. Experimental Med.

Allison Felarca, M.D.
Project M.D.
Assoc. Direct. Res.

Leonard Dennick, M.D.
Project M.D.
Res. Fellow.

Aige Drubulis, Ph.D.
Director Pharma. R & D.

Richard T. Kach
Ass. Dir. Reg. Technical Off.

E. C. McKeon
Director Res. Services

and: Dr. Clark
Dr. Smelzer
Dr. Winkler
Dr. Jerussi
Dr. Oneson

Conference and telephone call

Subject: NDA 17-559, Albuterol

A number of items were discussed from the Chemistry standpoint. (See separate memo by Dr. Oneson).

In general, the Chemistry questions are apparently in the process of resolution.

It was agreed that a 2 year expiration date will be used initially.

The discussion of the medical aspects of this application centered around various problems encountered thus far in reviewing the case reports of the multicenter study of Hudson, Ziskind & George. Additional information was made available at this time from a summary used by the sponsor. This volume contained the data upon which the mean values reported in the NDA case report forms were based. This additional volume was submitted today for aid in our further review. Also it was determined that two additional investigators, Dr. Chodish and Dr. Siegel, are now taking part in this multicenter study, though the sponsor has not received any case

reports from these two thus far.

It was pointed out that one could not determine readily from the case reports how long patients had been on concomitant drugs when these were listed. The monitor for the study stated that such patients were only those who were stabilized on the concomitant drugs. This was according to the protocol.

It was determined that the EKG's in these studies were done only initially for screening purposes only.

With respect to the baseline pulmonary function studies it was determined that patients were entered into the study only after obtaining two "similar" values. No specific percentage variation to be permitted was stated.

With respect to the two studies by Diveck and Stein it was determined that both determined pulmonary function changes only once post-treatment at 15 minutes. It was understood that these two studies evaluate acute effects only. The multicenter study discussed earlier provides data out to six hours post-treatment.

A question was raised as to why certain patients were apparently dropped out of the study by Ziskind (patients numbered 2, 5, and 7). This is to be checked by the monitor and an explanation provided.

The sponsor provided a brief summary of a recently completed study in the U.S.A. by Dr. George Bedell. This was a comparison of Albuterol with isoproterenol in aerosols in the treatment of patients with bronchial asthma. This study is said to be supportive and consistent with results reported in the earlier trials. The data are reported to show efficacy up to six hours following inhalation of albuterol.

There was a very brief discussion of the present draft labeling. The sponsor was advised that the present claims will have to be supported by the clinical studies to be evaluated further. These include such claims as B_2 specificity (clinically); onset and duration of action, stated to be within 15 minutes and up to 6 hours; and lack of tachyphylaxis.

They were also advised that the present warning section is inadequate with respect to information on cardiovascular reactions, paradoxical reactions and deaths.

At the conclusion of the meeting, the firm was requested to make their next submission a complete package including all necessary chemistry data and the clinical data including the study by Bedell. They were

advised that we plan to present this NDA once again to our Pulmonary Allergy Advisory Committee prior to any final action.

J Winkler 1/16/75
John Winkler, M.D.

cc: NDA 17-559 orig.
HFD-108
HFD-160
R/D JWinkler 1/9/75
R/D Init. by: MClark MD 1/10/75
Final type pk 1/16/75

MClark MD 1/17/75

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-559

March 25, 1975

Between: Mr. Morgan for
Dr. Neary
Schering

and: Dr. Margaret Clark
Act. Dir. HFD-160

Initiated by: Dr. Neary (returned by Dr. Clark)

Subject: NDA 17-559

I returned a call from Dr. Neary of Schering. Dr. Neary was not in and I spoke to Mr. Morgan. He stated that Dr. Neary had wanted to talk to me about the possibility of arranging a meeting to discuss the labeling for the Proventil inhaler prior to the Advisory meeting next month. I told Mr. Morgan that I felt the Reviewing Medical Officer was not prepared as yet to discuss labeling. When we have completed sufficient amount of the review to have a useful discussion, I would be glad to get in touch with him if a meeting was indicated. Mr. Morgan felt that we might discuss the labeling with the Advisory Committee and they wanted to meet with us before that if we were going to do so. I said I did not know whether this would come into the discussion at this point because as I previously explained the Reviewing Medical Officer had not as yet completed his review.

Mr. Morgan asked if they could check with us again in about two weeks and I said yes.

Margaret A. Clark, M.D.

cc: NDA 17-559 Orig.
HFD-108, HFD-160
MClark:HFD-160:3/25/75
Typed from tape nm 3/26/75

NDA 17-559 31 May 5, 1975

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Neary
Schering Corp.

and: Dr. Margaret A. Clark
Act. Director HFD-160

Initiated by: Dr. Neary

Subject: NDA 17-559

Dr. Neary of Schering called to ask if I could provide him with any information with regard to their application. I said that the application was still under review and I had no information for him at this time. He asked if the subject had been discussed at the recent Pulmonary Advisory Committee Meeting. I explained that we only had an interim report to present to the Committee and since other items on the Agenda took up more time than we anticipated we dropped this completely from the Agenda and did not discuss it with the advisory group. He asked if there was any point in coming in to discuss labeling and I told him that we were not prepared to discuss labeling until the medical review was done so that we would know what might be appropriate for the labeling.

He thanked me and the conversation ended.

Margaret A. Clark, M.D.

cc: NDA 17-559 Orig.
HFD-108
HFD-160(2)
MClark:HFD-160:5/5/75
Final typed from tape nm 5/6/75.

NDA 17-559 May 5, 1975

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Iozoni (201) 743-6000 ext. 652
Schering Corp.

and: Dr. Margaret Clark
Act. Director HFD-160

Initiated by: Dr. Iozoni

Subject: NDA 17-559

Despite my earlier conversation today with Dr. Neary, Dr. Iozoni of Schering called again to find out the status of their NDA. He expressed dismay to find out that from Dr. Winkler that Dr. Miranda was now reviewing the application instead of Dr. Smeizer and he thought this was delaying matters. I explained that a large part of the delay was that the original application contained totally inadequate information with regard to chemistry and contained only two studies. In both of these studies the patient was followed for only 15 minutes after being administered the drug. Since then additional information has been coming in in dribbles and it is difficult to review an application that is presented in this fashion. Dr. Iozoni said he felt that the time of our January meeting that everything was in good shape and they could expect an approval soon. I pointed out to him that at that point they had not even submitted the additional clinical material which they had promised as well as answers to additional chemistry deficiencies which we told them about at that time. Dr. Iozoni wanted to know why I could not order Dr. Mirandi to produce a review within a certain number of days. I explained that in order to do a good medical review the physician needed as much time as it required to go over the material in the document and that simply ordering someone to do something within a short period of time was ~~xxxxx~~ counter-productive. Dr. Iozoni wanted to come in and meet with Dr. Mirandi and me to discuss the clinical material. I explained that I saw no point in discussing the information until the review was complete - until such time we did not know whether we had any questions or whether the material would be satisfactory. I did say that I would check with Dr. Mirandi and be certain that he had not found any gross deficiencies to date and if he had I would certainly ~~x~~ let them know. This conversation went on for well over half an hour being mainly repetitive of what has been stated above. Dr. Iozoni discussed at length material that was in the IND and I explained to him that the NDA would have to be approved on the basis of adequate and well-controlled studies that were in the NDA. I did promise to call Dr. Iozoni by the end of the week and let him know if we had any additional questions at this time.

cc: NDA 17-559 Orig.
HFD-108, HFD-160(2)
MClark:HFD-160:5/5/75
Final typed from tape nm 5/6/75.

Margaret Clark, M.D.
Margaret A. Clark, M.D.

NDA 17-559 May 8, 1975

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Neary
Schering

and: Dr. Margaret Clark
Act. Dir. HFD-160

Initiated by: Dr. Neary

Subject: NDA 17-559

Dr. Neary called with regard to their pending application for Proventil. He had called for Dr. Miranda but I accepted the call. I explained to Dr. Neary that we preferred not to have reviewing people discuss matters with the sponsors as they were very heavily loaded down with work and I felt it was my obligation to discuss the status of reviews of applications with the sponsors. He asked the status of the review on Proventil and I said I would check with the review team and call him back.

After checking with Dr. Winkler I called Dr. Neary again and said that there was still considerable work to be done and I could not at this time give a good guess as to when we might have more positive information for him or have need of a meeting. I told him I thought it would cruel and unfair to give him any estimate when I really didn't have sufficient information to make a valid estimate. He asked if he might call in two or three weeks to see how we were doing and I said that would be fine or if the meantime I have any news I would call him.

Margaret A. Clark, M.D.

Margaret A. Clark, M.D.

cc: NDA 17-559
HFD-108
HFD-160
MClark:HFD-160:5/8/75
Final typed from tape nm 5/12/75
Document room copy.

NDA 17-559
Proventil (brand of
albuterol inhaler)

June 5, 1975
2:30 p.m.

MEMORANDUM OF TELEPHONE CONVERSATION

BETWEEN: Edward R. Neary, M.D.
Schering Corporation

and

Clarence M. Nealey, Jr.
Supervisory Consumer Safety Officer
Division of Surgical-Dental Drug Products/HFD-160

Subject: Present status of pending NDA 17-559

Mr. Neary stated that on May 8, Dr. Clark advised him that he could call back in three or four weeks for the present status of this pending NDA, and that since she was not in the office, he was requesting that I obtain this information for him. I asked him if top management was after him for a response and he said yes. I told Dr. Neary that I would make inquiries and get back to him shortly. I checked with Dr. Winkler who refreshed my memory as to the clinical status in that the NDA would be referred to Advisory Committee, which we didn't want to reveal to Dr. Neary at this time, and then checked with Dr. Oneson, the reviewing chemist. Dr. Oneson advised me that the chemistry was approvable at this time except for some minor labeling that could be corrected very easily.

I returned the call within 10 minutes to Dr. Neary and advised him that the manufacturing controls was approvable at this time except for some minor label deficiencies which could be readily corrected. I explained that the inspections were all in compliance with the FD&C Act and that methods validation had been confirmed. As to the clinical status, I advised him that Dr. Clark had been in discussion with the group leader and the reviewing medical officer and that further comment in this regard would have to come from her after her return next week. I explained to Dr. Neary that I could not provide any comment at this time on the clinical status other than that it was under review. Dr. Neary said he understood completely and that he would get to Dr. Clark upon her return next week.

The conversation then ended without any further pertinent discussion.

Clarence M. Nealey, Jr., CSO

cc:
NDA 17-559 Orig.
HFD-160 HFD-160/Doc. Room
HFD-108
Dictated by CMNealey(HFD-160) 6/5/75
Final typed 6/12/75:jw

6/12/75

NDA 17-559
and NDA 17-601

June 10, 1975

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Neary
Schering Corp.

and: Dr. Margaret Clark
Act. Director, HFD-160

Initiated by: Dr. Neary

Subject: NDA 17-559
NDA 17-601

Dr. Neary of Schering called. He asked the present status of the review of NDA 17--559. I told him that the medical review was going along and I expected it would be finished in a couple of weeks. I pointed out that following ~~xxxx~~ that both Dr. Winkler and I would want to review the submission along with the medical officer's review. Dr. Neary asked if he might call in three weeks to determine the status and I said that would be fine.

He asked the current status of NDA 17-601. He said that someone had called a chemist last week and was told that they should get in touch with me. I told him that my record showed that everything had not been completed with regard to this NDA but I hoped that that too would be done within the next three weeks and we could discuss that when he calls again.

Dr. Neary thanked me and said he would call in three weeks.

Margaret A. Clark, M.D.

cc: NDA 17-559
NDA 17-601
HFD-108
HFD-160
R/D MClark,M.D. (HFD-160) 6/10/75
Final typed nm 6/10/75
Doc. Room

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-559 Proventil
NDA 17-601 Optamine

7/1/75

Between: Dr. Neary
Schering Corp.

and: Dr. Margaret Clark
Act. Dir. HFD-160

Initiated by: Dr. Neary (returned by Dr. Clark)

Subject: Status of NDA 17-559 and 17-601

I returned a call from Dr. Neary of Schering. He inquired as to the status of our reviews on Proventil NDA 17-559 and Optamine, NDA 17-601. I told him that the review on Proventil was proceeding and I hoped that within the next two weeks that we would have an in-house conference in the division to discuss the reviews of this application. Following that we will let him know if we need to have a meeting concerning any possible labeling revisions. It was agreed that Dr. Neary would call me on July 11 to check again as to the status of this NDA.

With regard to NDA 17-601, I told Dr. Neary that he could anticipate receiving a letter in the next several days. He asked whether the outcome was good or bad and I explained that our statisticians recommended that the clinical data be reanalyzed in a different fashion. I said that when they received the letter and their statisticians have had time to consider the matter, we shall be happy to arrange a conference if they feel one is indicated prior to re-working the data. I said I thought there were also some chemistry deficiencies altho without the application in front of me I could not be sure. In any event I felt that any problems with chemistry could be resolved by the submission of additional information.

Dr. Neary thanked me for the information and said he would call on the 11th.

Margaret A. Clark, MD

Margaret A. Clark, M.D.

cc: NDA 17-559, NDA 17-601
HFD-108, HFD-160
MClark:HFD-160:7/1/75
Final typed from tape nm 7/2/75.
Doc Room

NDA 17-559

MEMO OF TELEPHONE CONVERSATION 7/24/75

NDA 17-559

BETWEEN: J. W. Winkler, M.D. HFD-160

and

Edward Neary M.D.
Schering

INITIATED BY: DR. Winkler

SUBJECT: NDA 17-559 Proventil

I called Dr. Neary and informed him that the NDA for Proventil is currently under medical review and that we are interested in literature references that relate to the long term controlled clinical trials that would include appropriate frequency of pulmonary function testing. I asked Dr. Neary if they could identify by location in the NDA any references along these lines that they consider pertinent to this NDA. He stated that they would look into this and try to do so within the next several days. Dr. Neary or someone else from their medical staff will call.

J. Winkler 7/25/75
J. Winkler, M.D. 7/25/75

cc: NDA 17-559 ORIG.
HFD-108
HFD-160
R/D by J. Winkler, M.D. 7/25/75
R/D init. M. Clark, M.D. 7/28/75
T/F: kd 7/28/75

M Clark MD 7/29/75

MEMO RECORD | AVOID ERRORS PUT IT IN WRITING | 7/28/75

FROM: J. Winkler, M.D. | OFFICE: HFD-160 (NDE)

TO: Margaret Clark, M.D. | DIVISION: HFD 160

SUBJECT: NDA 17 539 IND 5684, Proventil

J Winkler signature

SUMMARY

On your request of 7/27/75 I have made an initial review of this open volume of IND 5684 (Vol. 13.1) and find that the sponsor has submitted a number of protocols only for acute effect studies and uncontrolled studies for this drug. The last progress report indicates no long-term adequate and well-controlled studies to be in progress or planned.

It is difficult to understand why they have not initiated such needed studies. At this point we will only have the one repetitive dosing study by Bedell which is limited in scope. (extends for approximately 12 days)

Also, review of the bibliography and reprints submitted with the last annual progress report of March 14, 1975 fails to identify any long-term controlled trials from the literature.

On 7/24/75 I called Dr. Neary of Schering and requested their assistance in identifying the location of any pertinent literature on long-term controlled studies with adequate testing of pulmonary function (intervals and time duration, e.g. up to 6-8 h.) that might be supportive to their NDA. He indicated they would do so.

If the extent of clinical data and literature references remain as meager as our reviews have indicated thus far, we will have great difficulty in finding support for this drug as it is proposed to be labeled.

It is my understanding that this NDA is to be included on the agenda of the next Pulmonary Advisory Committee meeting. These considerations regarding the manner in which this firm has proceeded in investigation of this drug should be of interest to the committee, particularly inasmuch as the committee was extremely critical of the firm's efforts up to the time they made a presentation to the committee at the meeting on May 9, 1974.

J. Winkler, M.D.

cc: IND 5684
HFD-108, HFD-160
JWinkler:HFD-160:7/28/75
Final typed. nm 7/28/75.

SIGNATURE | DOCUMENT NUMBER

FORM FDH-2034 (11/65)

SUMMARY OF: ☐ REPORT

☐ SUPPLEMENT

☒ NDA

2nd Neg Review

DATE SUMMARY COMPLETED: July 26, 1974
NDA #: 17-559
COMPANY: Schering Corporation
ADDRESS: Bloomfield, New Jersey 07003
ORIGINAL APPROVAL DATE: N. A.
REVIEWED BY NAS/NRC: YES ☐, NO ☒

NAME OF DRUG: Trade: Proventil Inhaler

Generic: Albuterol

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: Oral inhaler containing 20 mg albuterol. Each depression of canister valve releases 100 mcg albuterol. Dosage: 2 inhalations every 4 to 6 hours.

CATEGORY OR USE OF DRUG:
Beta-adrenergic bronchodilator agent for relief of bronchospasm.

DATE OF ☐ SUPPLEMENT

☒ ~~AMENDMENT~~ NDA: 12/26/73

REASON FOR SUBMISSION: New drug application.

MATERIAL REVIEWED: NDA 17-559. Volumes 1 through 17. (Numbering of volumes, as designated by the firm, will be shown in parentheses.)

REVIEW:

Volume 1 (Volume 1.1)

Enclosed, with the Volume 1, were:

Dr. Winkler's memorandum to Dr. Solymossy,

Dr. Clark's memorandum to Dr. Winkler,

A. J. Aronson's memorandum to Dr. Clark,

Dr. Oneson's chemistry review of this NDA,

Dr. Fefer's pharmacology review of this NDA,

New NDA assignment sheet,

Dr. Clark's acknowledgement letter to the firm,

Cover letter and application form by the firm,

Table of contents in 26 pages,

Summary and evaluation of the new drug.

This included chemistry and preclinical studies. For details refer to the appropriate reviews. Clinical investigations also were summarized. Those will be dealt separately and later.

Albuterol was investigated under IND No. 5684.

Volume 2 (Volume 1.1a)

In these pages summary and evaluation of the clinical investigations of the drug was continued.

Annotated product information sheets yielded a good background for the proposed labeling pieces, which were - in general - in agreement with FDA's labeling guidelines. For proper comments refer to Dr. Fefer's review.

Chemical controls data section of the submission started with this volume.

Volume 3 (Volume 1.2)

The rest of chemical controls data was contained here.

Volumes 4 (Volume 1.3) and 5 (Volume 1.3a)

Consisted of the first part of preclinical data, i.e., pharmacology.

Volumes 6 (Volume 1.3b), 7 (Volume 1.3c), 8 (Volume 1.3d) and 9 (Volume 1.3e)

Included the second part, i.e., toxicology and pathology.

Volume 10 (Volume 1.4)

Complete list of all investigators.

Annotated bibliography on albuterol in 79 pages.

International and domestic publications (judged as 'not available to FDA' category) in 390 pages.

The scientific literature appeared to support the safety and efficacy of albuterol as a bronchodilator agent.

Volume 11 (Volume 1.6)

Special clinical studies:

1) Calesnick - Absorption, excretion and metabolism of ^{3}H-albuterol in man.

   This was one of the three (only) American studies. It was a well executed metabolic investigation.

2) Milner - Bronchodilator and cardiac effects of isoprenaline, orciprenaline, and salbutamol aerosols in asthma.

   Twelve children participated. Double-blind design. Well controlled.

3) Riding, et.al. - Clinical trial of a new beta-adrenergic stimulant in asthma.

   Ten adults were tested with salbutamol and isoprenaline aerosols in controlled technique.

4) Schumann-Herxheimer - The bronchodilator action of salbutamol in asthmatics.

   Open design. 40 patients. Oral, sublingual and nebulized administration of the drug.

5) Spitzer, et.al. - The bronchodilator effect of salbutamol administered by IPPB to patients with asthma.

   Controlled comparison with isoproterenol and placebo involving 30 patients.

6) Streeton - Salbutamol: a double-blind, cross-over trial.

   Thirty-one patients participated. Normal saline, salbutamol, isoprenaline, orciprenaline were used by nebulizer.

7) Streeton - Salbutamol in status asthmatics and severe chronic obstructive bronchitis.

   This was an open trial with 97 patients.

8) Harrison, et.al. - The effects of salbutamol on pulmonary and systemic hemodynamics.

Twelve patients undergoing cardiac catheterization were studied. The drug was given by nebulizers.

9) Koch - Effects of a selective beta 2-receptor stimulant on lung function, intrapulmonary gas exchange and circulation at rest and during work in patients with bronchial asthma.

Salbutamol aerosal was used in 16 adults. Controlled investigation.

10) McCarthy - The prevention of exercise induced asthma.

Open trials in 9 children (9-12 years). Salbutamol aerosol was included among the drugs used.

11) Tala, et.al. - Double-blind comparison of isoprenaline, orciprenaline and salbutamol aerosols in patients with asthma.

Twelve patients participated. There was no cross-over design. Exercise tests were used in connection with FEV_1 determinations.

12) Goldman, et.al. - Bronchodilator response in asthma. Effects of salbutamol.

Histamine challenge tests in 5 patients.

Partial blocking effect was demonstrated by salbutamol.

13) Gayrard, et.al. - Comparative study of a new beta-adrenergic stimulant in asthma: salbutamol.

Challenge trials (open) with bronchoconstrictor agents. Decrease in air-way resistance was always marked after salbutamol administration.

14) Turner - Antagonism of acetylcholine induced bronchospasm by WG 253, a new sympathomimetic amine.

Double-blind trial with 8 healthy subjects. Salbutamol also were used among the drugs tested.

15) Martin, et.al. - Metabolic studies of salbutamol-^{3}H: a new bronchodilator, in rat, rabbit, dog, and man.

Specialized investigation on metabolism of drug.

Similar (partly) to Dr. Calesnick's study (q.v.).

16) Evans, et.al. - Pharmacokinetics of inhaled salbutamol in asthmatic patients.

^{3}H labeled drug was used in 4 patients. Results correspond to other metabolic studies.

17) Allen and Hanburys, Ltd. - Cardiovascular effects of salbutamol in normal volunteers.

In 2 trials 6-6 subjects were involved. Heart rate and blood pressure were not altered by salbutamol administration (contrary to isoprenaline).

18) Coleman-Leary - Cardiovascular effects of salbutamol: a comparison with isoprenaline.

Open trial with only 5 healthy subjects.

19) Tattersfield-McNichol - Salbutamol and isoproterenol. A double-blind trial to compare bronchodilator and cardiovascular activity.

The latter part of trial involved 10 healthy subjects.

Design was also cross-over and well controlled technique.

20) Phillips, et.al. - A comparison of isoprenaline, salbutamol, and rimiterol inhalation on skin temperature, heart rate, and respiration in man.

Double-blind study with 7 healthy subjects. Salbutamol in 500 mcg doses/aerosol/affected only the bronchial receptors selectively. Contrary to isoprenaline.

21) Kennedy-Simpson - Human pharmacological and clinical studies on salbutamol: a specific beta-adrenergic bronchodilator.

Six healthy subjects participated in this open investigation.

22) Palmer-Diament - Dynamic and static lung volumes and blood gas tensions in bronchial asthma.

The stated parameters were measured in 72 patients.

Salbutamol significantly increased FEV_1, FVC and decreased residual volume. No change in blood gas tensions was detected.

23) Palmer-Diament - Dynamic and static lung volumes, blood-gas tensions, and transfer factor in chronic obstructive bronchitis.

Forty-five hospitalized patients were studied. The 'irreversible' component of their air-way obstruction still could be altered by bronchodilators.

24) Kennedy - Beta-adrenergic stimulants in asthma.

In 'reversibility' test salbutamol was substituted for epinephrine. From 241 patients only 51 responded better to epinephrine inhalation.

Volume 11 (Volume 1.6)

Dose-range studies:

1) Warrell, et.al. - Comparison of cardio-respiratory effects of isoprenaline and salbutamol in patients with bronchial asthma.

Six patients were given from 10 to 500 mcg doses (in aerosol form) of the drugs. Increase in SG_{aw} was comparable to the increase in dosage.

2) Sadoul-Sentissi - A comparison of the action of salbutamol and of isoprenaline on air-way resistance in 30 patients with obstructive airways disease.

No significant changes in BP, HR and arterial oxygen saturation were detected in 46 patients while on various doses of salbutamol. This was the second of two open trials.

3) Leblanc - A comparison between the dose-response relations of Berotec and salbutamol metered-dose aerosol.

Well controlled, double-blind and cross-over trial with 10 patients. FEV_1 increased directly with the increase in dosage (number of inhalations). But vital capacity not beyond 4 inhalations, i.e., 400 mcg for salbutamol.

4) Dollery-Fletcher - Respiratory and cardiovascular effects of salbutamol in patients and healthy volunteers.

Effect of oral dose appeared to last 4 hours while inhaled dose 4-6 hours. Number of patients (4) was to small for meaningful interpretation.

5) Choo-Kang, et.al. - Response of asthmatics to isoprenaline and salbutamol aerosols administered by intermittent positive pressure ventilation.

Salbutamol was more potent in total bronchodilator effect and duration of average effect than isoprenaline.

6) Dollery-Fletcher - Refer to 4) above.

This part of the trial concerned with iv administration of salbutamol and isoprenaline.

Ratio of cardiovascular effect was 1(S):6(I).

7) Gibson-Coltart - Hemodynamic effects of intravenous salbutamol in patients with mitral valve disease: comparison with isoprenaline and atropine.

Eighteen patients undergoing cardiac catheterization were studied. Only isoprenaline increased stroke volume and mean systolic ejection rate and decreased ejection time.

8) Paterson, et.al. - Selectivity of bronchodilator action of salbutamol in asthmatic patients.

Graded rates of infusion were used in 10 patients.

Comparison was made with isoprenaline.

9) Svedmyr-Thiringer - The effects of salbutamol and isoprenaline on beta receptors in patients with chronic obstructive lung disease.

Ten patients were in the trial.

Beyond FEV_1 30% increase ten times as much salbutamol as isoprenoline has to be given to increase the heart rate the same percentage that FEV_1 values are increased.

10) Warrell, et.al. - Refer to 1) above.

This part of the trial concerned with infused drugs.

Five patients were only tested. Difference in cardiac effects of the drugs manifested in same way as in the other similar studies.

Volumes 12 (Volume 1.6a), 13 (Volume 1.6b) and 14 (Volume 1.6c)

Controlled clinical studies:

1) Dwek - A double-blind comparison of albuterol and isoproterenol used as required in asthma.

Twenty-six patients took part in a 12-week trial. The drugs were used in 100 mcg doses by aerosol inhalation technique p.r.n. Emphasis was placed on subjective evaluation by patients. This study demonstrated quite inadequate controls. Raw data were contained in the submitted 3 volumes (q.v.).

Volume 15 (Volume 1.6d) and 16 (Volume 1.6e)

Controlled clinical studies: - continued -

2) Stein - A double-blind comparison of albuterol and isoproterenol used as required in obstructive airway disease.

The design and outlay of this investigation were similar to those of Dr. Dwek's. Here 21 patients were used for 13 weeks. Drug usage also p.r.n.

The study was rather inadequately controlled thus the derived results were scientifically meaningless. Raw data were included in the 2 volumes.

Volume 17 (Volume 1.6f)

Controlled clinical studies: - continued -

3) Alliott, et.al. - Effects of salbutamol and isoprenaline/phenylephrine in reversible airways obstruction.

Sixteen patients received 2 and 6 inhalations from the commercial drug products in randomized fashion over 2 days. FEV_1 was increased more with salbutamol.

4) Riedel-Dibbern - Leblanc - Controlled comparison of Berotec and salbutamol metered-dose aerosols.

Double-blind, well controlled cross-over study involved 21 hospitalized patients. Respiratory and blood-gas parameters were studied mainly.

5) Vale - Oral salbutamol as a supplement to inhaled aerosol in obstructive respiratory disease.

Double-blind, cross-over study with 5 patients. Two mg tablets of the drug did not augment the bronchodilation elicited by the inhalation of 100 mcg dose.

6) Hambleton-Shinebourne - Evaluation of the effects of isoprenaline and salbutamol aerosols on airways obstruction and pulse rates of children with asthma.

Ten children participated in the trial. Each was given on 6 occasions single inhalation (100 mcg) of the drugs or placebo. Design was double-blind. Pulse rates were not effected by the drugs.

7) Choo-Kang, et.al. - Controlled comparison of the bronchodilator effects of three beta-adrenergic stimulant drugs administered by inhalation to patients with asthma.

Double-blind trial with 24 patients. Maximum increases in FEV_1 values were approximately the same with all 3 drugs. However, after 5 hours FEV_1 was still 26% above the control with salbutamol, but only 8% with isoprenaline.

8) Danø - Comparison of the effects of salbutamol and orciprenaline in asthma.

Thirteen patients participated in this double-blind study. Each of them was tested 2X with each of the aerosols (plus placebo).

9) Kennedy-Simpson - Human pharmacological and clinical studies on salbutamol: a specific beta adrenergic bronchodilator.

Refer also to 21) under special clinical studies.

Single-blind trial with 12 asthmatics. Results of integration of the areas beneath the response curves: Means - $FEV_{0.75}$ - Salbutamol 12,782, Orciprenaline 8,780, Placebo 1,079.

10) Lustman - A double-blind, sequential trial of salbutamol and isoprenaline aerosols in general practice.

Fifteen asthmatics participated in this 4 week cross-over trial. Only subjective evaluation by the patients was provided.

11) Racoveanu, et.al. - The bronchodilator effects of orciprenaline and salbutamol. A double-blind study.

Twenty-two hospitalized asthmatics were studied.

Maximum increase in FEV_1 was approximately 40% with both drugs during the first 2 hours.

12) Riding, et.al. - The bronchodilator and cardiac effects of five, pressure-packed aerosols in asthma.

This was a blind study involving 21 patients. Six hours after inhalation, FVC and FEV_1 values were still increased in patients treated with salbutamol (contrary to other agents). Only the other drugs elicited various cardiac effects.

13) Tattersfield-McNichol - Salbutamol and isoproterenol. A double-blind trial to compare bronchodilator and cardiovascular activity.

Refer also to 19) under special clinical studies.

In the first part of this trial 10 asthmatics participated. FEV_1 values were significantly higher at 3-4 hours with salbutamol than with isoproterenol.

14) Chapman - Bronchodilator aerosols.

Arterial oxygen tension decreased after inhalation of all the six tested aerosols.

15) Minette - Ventilatory results and side effects of salbutamol given by different routes in coalminers with reversible broncho-obstruction.

Open trial with 50 patients. Orciprenaline and hydroxyphenyl derivative of this drug also were used.

16) Scherrer-Bachofen - New developments in the treatment of asthma. Special consideration of the modern, selective beta-2 stimulating agents.

Ten patients were tested with 5 different bronchodilators. Open trial, partly controlled. Overall results favored salbutamol.

17) Dollery-Fletcher - Respiratory and cardiovascular effects of salbutamol in patients and healthy volunteers.

Refer also to 4) and 6) under dose-range studies.

Inhalation of up to 1500 mcg salbutamol had no definite effect on HR and BP in normal subjects.

18) Freedman - Trial of a terbutaline aerosol in the treatment of asthma and a comparison of its effects with those of a salbutamol aerosol.

The trial involved 12 patients. In general, similar responses were noted.

19) Freisleben - The treatment of asthma with salbutamol aerosol.

Twenty-five patients participated in a brief preliminary investigation. Orciprenaline was used as a control drug.

20) Goldman, et.al. - Bronchodilator response in asthma in partial remission. Effects of salbutamol.

Refer also to 12) under special clinical studies.

Several respiratory parameters were evaluated in 11 patients.

21) Kamburoff-Prime - Oral and inhaled salbutamol as a bronchodilator.

Forty asthmatics were involved. The effects of oral salbutamol were similar to those of the aerosol. However, its onset of action was slower (15 minutes).

22) Kennedy-Dash - The bronchodilator effect of a new adrenergic aerosol--salmefamol.

IMBC was measured in 10 asthmatics after administration of 3 different aerosols.

23) Palmer-Diament - Effect of salbutamol on spirometry and blood-gas tensions in bronchial asthma.

Thirty-seven patients were tested. All spirometry values increased significantly.

24) Palmer, et.al. - Comparison of effect of salbutamol and isoprenaline on spirometry and blood-gas tensions in bronchial asthma.

Trial with 11 patients. After isoprenaline increased HR and a fall in arterial oxygen tension occurred.

25) Riding, et.al. - A comparison of the cardiorespiratory effects of salbutamol and isoproterenol-phenylephrine aerosols in asthma.

Twenty hospitalized patients were studied. FEV_1 and FVC was significantly greater and the duration of effect longer with salbutamol.

26) Tala, et.al. - Double-blind comparison of isoprenaline, orciprenaline, and salbutamol aerosols in patients with asthma.

Refer also to 11) under special clinical studies.

Randomized trial with only 12 patients. No cross-over design.

27) Clark - Comparison of single doses of salbutamol and isoprenaline in 18 patients.

Approximately 100 mcg salbutamol was equal to 500 mcg isoprenaline.

28) Harris - Comparison of the effect on blood-gases, ventilation, and perfusion of isoproterenol-phenylephrine and salbutamol aerosols in chronic bronchitis with asthma.

Trial involved 11 patients. The combination product increased PaO2, while salbutamol decreased.

29) Sadoul-Sentissi - A comparison of the action of salbutamol and of isoprenaline on airway resistance in 30 patients with obstructive airways disease.

Refer also to 2) under dose-range studies.

First of the two trials dealt with the problem shown in the title. Salbutamol was more effective than isoprenaline (in doses 300 and 270 mcg respectively).

30) Schonell, et.al. - Salbutamol--an effective bronchodilator.

Twenty-two patients took part in this open trial. Neither salbutamol nor isoproterenol was as effective in patients with chronic bronchitis as in those with asthma.

31) Thiede-Ulmer - Inhalation therapy with catecholamines.

In the course of this trial salbutamol also was used in 13 patients as a control drug.

Other clinical studies:

1) Clark - Therapeutic use of salbutamol in 15 patients for one to 18 months.

Brief reports with spirometric data.

2) Turnbull - Therapeutic use of salbutamol in eight patients for one month.

Brief reports with expiratory peak air flow values.

3) Smith - Salbutamol aerosol - Long-term administration.

Two open, uncontrolled trials. Twenty-five patients were on the drug up to for 15 months. The degree of broncho-dilation did not decrease during the prolonged administration.

4) Zwi, et.al. - Clinical trial of salbutamol aerosol in chronic obstructive airways disease.

Seventy-four patients were in the study. Open, uncontrolled trial with spirometric determinations.

5) Bass, et.al. - Effect of salbutamol on respiratory function in children with asthma.

Trial involved 19 children. Very brief communication.

6) Velazquez, et.al. - Effect of salbutamol on lung volumes in bronchial asthma.

Open study with 23 patients. There was distinct improvement of baseline VC values following 8 days of treatment.

7) Roncoroni, et.al. - The effect of salbutamol on airways obstruction in patients with status asthmaticus.

Four hospitalized patients were in the study.

A marked and significant increase in specific conductance was observed immediately after inhalation and persisted more than 60 minutes.

8) Turnbull - The treatment of asthma in the presence of ischemic heart disease.

Brief reports on 4 patients. Salbutamol produced no adverse cardiac effects like other bronchodilators.

9) Clark - Single dose studies with salbutamol in 146 patients.

The drug, in 100 mcg dose, was used as the standard broncho-dilator (instead of isoprenaline) test in evaluation of respiratory functions.

Clinical laboratory studies related to safety:

1) Chatterjee - Study of 34 patients treated with salbutamol for 3 to 20 months.

   Before and during treatment rather detailed laboratory measurements were carried out: respiratory function, cardiovascular system, blood, metabolism, and liver functions. Neither tolerance nor adverse effects were demonstrated from salbutamol.

2) Clark - Study of 8 patients treated with salbutamol for 7 to 20 months.

   Similar to 1) above but with less laboratory tests.

3) Grant - Study of 6 chronic asthmatic patients treated with salbutamol aerosol for 9 to 18 months.

   Results of standard laboratory tests and FEV_1, FVC values were tabulated.

4) Grant - Biochemical and hematologic studies of 8 patients treated with salbutamol aerosol or tablets, or both, for up to 4 months.

   Brief tabulations of data for each patient separately.

   Biochemical tests consisted of liver profile determination.

5) Kennedy - Study of 22 patients treated with salbutamol for 7 to 18 months.

   Similar to 1) above but with less tests and also no liver function determinations.

6) Kennedy - Studies of 9 patients with reversible airways obstruction and co-existent cardiac disease treated with salbutamol for periods of 7 to 33 months.

   Similar to 5) above. No adverse effects, no tolerance were demonstrated from the drug.

7) Kelman, et.al. - Cardiovascular effects of AH 3365 (salbutamol).

The drug had no statistically significant effect on HR, fastest circulation time, and mean circulation time.

8) Hume - Blood-gas tensions and aerosols.

Arterial oxygen tension decreased on salbutamol.

9) Chatterjee-Perry - Salbutamol: clinical application as pressure-packed aerosol.

Refer also to 3) under special clinical studies and to 12) under controlled clinical studies.

In this third trial 20 hospitalized patients were involved. Fifteen minutes after salbutamol inhalation arterial oxygen tension increased in 7 and decreased in 12 patients. Rest was unchanged. However, mean values before and after treatment did not differ significantly.

COMMENTS:

1. The frequency of side-effects and the relatively short duration of action of isoproterenol/isoprenaline/ necessitated searching for other compounds of similar structure but with different substituents on the nucleus and side chain. One of these - albuterol (salbutamol) - differs from isoproterenol in that the replacement of 1 of the hydroxyl groups in the benzene ring by an ethanol group prevents the molecule from being rapidly metabolized (as is isoproterenol) through the action of catechol-O-methyl transferase, and the tertiary butyl group attached to the nitrogen atom of the side chain hinders de-alkylation of albuterol. These structural changes also modify the pharmacological action of albuterol; i.e., there is a great reduction in its effects upon the cardiovascular system. Yet it is at least as powerful a bronchodilator as isoproterenol.

2. From the compilation of data, it appears that a dose of 200 mcg of albuterol aerosol is at least as effective as, or more effective than, 1000 mcg of isoproterenol. Albeit, its cardiovascular effects amount at most only one-tenth of that isoproterenol. Bronchodilation is maintained for up to five to six hours or more following inhalation of the drug.

3. Albuterol (salbutamol) aerosol was approved for marketing in the United Kingdom in January 1969. Since that time it has been licensed for sale in 57 countries world wide. It is an 'official' article in the British Pharmacopeia, British National Formulary, British Pharmaceutical Codex, Martindale Extra-Pharmacopeia, etc.

4. The submitted exhaustive scientific bibliography and literature (domestic as well as international) clearly support the safety and efficacy of albuterol as a bronchodilator agent.

5. All the various and quite numerous international investigations - enclosed mostly as publications and partly as unpublished reports, etc. - reveal the same trend as above. Nonetheless, from the very nature of these communications follows that not enough details with actual data can be presented. Thus depriving any reviewer from the 'true' evaluation.

6. Only three domestic studies were submitted. Calesnick's concerned just with the metabolism of albuterol. Dwek and Stein failed to establish appropriate controls in their trials which were designed and conducted not in compliance with the regulations as published in the Federal Register of May 8, 1970 under "Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations".

7. According to A. J. Aronson's memorandum (q.v.) there "was a problem with the dose delivery system" of Proventil. The sponsor stated, "With the passage of time, there was a decrease in the amount of Albuterol released per actuation of the metering valve". Thus the quantity of the drug was inadequately controlled in the above cited two studies.

   The fact 'per se' is discrediting any controlled status claim.

   Furthermore, several regulatory deficiencies are also demonstrated in the quoted memorandum.

8. Dr. Oneson's review (q.v.) of chemistry of this NDA also lists numerous deficiencies those making the application not approvable under the statutes.

RECOMMENDATIONS:

1. In view of foregoing considerations the NDA - in its present status - is not approvable.

2. However, the facts pertinent to the chemical compound - albuterol - clearly demonstrate its usefulness as a therapeutic agent. So the firm should be advised to comply with the proper regulations, i.e., (1) chemistry have to be updated. This is indispensable matter for future marketing purposes; (2) labeling needs changes according to our pharmacologist's recommendations; (3) when the first two requirements are fully met the firm should initiate (sponsor) two rather limited Phase III studies closely following the cited Federal Register Notice as well as our 'bronchodilator' guidelines.

Alfred A. Solymossy, M. D.
HFD-110

cc:
ORIG. NDA 17-559
DUP. NDA 17-559
TRIP. NDA 17-559
HFD-100
HFD-110
HFD-160
HFD-110/CSO
HFD-110/A.A.Solymossy/gh/7-30-74

4.1 SEP 16 1975

NDA 17-559

7/30/75

MEDICAL OFFICER'S REVIEW

NAME OF DRUG: Salbutanol; Brand name Proventil, brand name of albuterol inhaler.

COMPANY: Schering Corporation

DOSAGE FORM: Inhalation; 100 mcg. per actuation.

ROUTE: Bronchial

CLINICAL STUDIES:

Studies were performed to support the company's labeling claims.

I. The first studies were of those of Drs. Joseph Dwek and Stein:

A. OBJECTIVE:

The study will be to compare albuterol aerosol with isoproterenol with regard to relative effectiveness of optimum dose range, pattern of PRN dosage and safety of medication when prescribed for use on a PRN basis by hour with reversible obstructive airway disease. The study will be double-blind and will be conducted in a non-crossover manner with half the patients receiving albuterol and half isoproterenol.

B. PATIENT SELECTION:

1. Before being entered into the study, patients should demonstrate a significant reversibility of bronchospasm defined as a 15% or greater improvement in FEV_1, FVC, or $FEF_{25-75\%}$ after a screening dose of 140 mcg. of isoproterenol.

2. Patients with primary diagnosis of asthma should be studied, if necessary patients with other bronchospastic disease (chronic bronchitis and emphysema) who meet the reversibility criteria may be used.

3. Patients will be between the age of 18 and 65. No pregnant women should be used. The following laboratory tests must be in normal limits or accounted for by concurrent disease: WBC, fasting blood sugar, BUN, SGOT, alkaline phosphatase, and urinalysis. Patients were allowed to use the aerosol as needed but dosage was not to exceed three inhalations every four hours. Then therapy was started according to the custom of the investigator. Each patient was asked to keep daily diary on which was recorded the following information:

(1) Amount of medication taken of both the test aerosol and concurrent therapy.

(2) An estimate of the onset and duration of effect of the aerosol.

(3) Severity of symptom, especially cough, sputum production, wheezing and shortness of breath.

insert —>

(4) A weekly assessment of overall breathing symptomatology.

The criteria for effectiveness was based on the patient diary which was primarily a subjective one. The patients were seen by an investigator every two weeks; at which time they were examined and interviewed on their daily diary review. The following subjective parameters of efficacy in the preceding two weeks were considered and entered on their case report form: degree of dyspnea, usual onset, duration and extent of relief attributed to the aerosol, the patient's and physician's impressions of the effectiveness of the aerosol. In addition spirometry and single breath nitrogen washout were measured before and fifteen minutes following two inhalations of the test aerosol. At each revisit the patient was asked about possible adverse reaction. The laboratory tests were obtained prior to the trial and after one and three months of therapy. Chest x-ray and EKG were done before and at the termination of the study.

Dr. Dwek started with 30 patients, 19 female and 11 males ranging in age from 19 to 62 years. All patients had a primary diagnosis of asthma and the duration of the disease was moderate to severe and was over one year. Of these 26 patients completed the study, three patients received isoproterenol were dropped from the study as treatment failures, one patient with albuterol discontinued due to worsening of her condition, one patient had a paradoxical rebound phenomenon with isoproterenol, and another patient assigned to albuterol expired after being in the study for four weeks. Autopsy revealed severe plugging of the bronchial by mucus.

Dr. Myron Stein had the same protocol as Dr. Dwek. He started with 22 patients and finished with 21. One patient was lost to follow-up.

CONCLUSIONS:

The value of this study is limited because only one objective measurement ($FEV_{1.0}$) was determined at 15 minutes post drug.

Tolerance and tachyphylaxis was not able to be demonstrated by the parameter used in the study.

II. MULTI-CLINICAL STUDY:

The second study is designed as a double-blind, randomized, complete crossover investigation involving 92 patients. This report is a multi-clinic report and has come from different part of the nation and different investigators.

A. The criteria for being admitted to the study: age vary between 18 and 70 years with the primary diagnosis of reversible airway disease. When screened for admission FEV_1 should be 30 to 60% of mean predicted value and reversibility of airway obstruction must be demonstrable by at least 15% improvement in FEV_1 and 20% improvement in isovolume MMEF following two inhalations of isoproterenol aerosol.

Clinical laboratory included CBC, urinalysis, fasting blood sugar, BUN, SGOT, alkaline phosphatase, and a 12 lead EKG. Concurrent therapy including steroids are stabilized. The patients selected are studied for three days, each of six hour duration per day. One of the three test preparations is administered by two inhalations on each of the days studied in random order. All bronchodilator therapy including aerosols are withheld for at least six hours prior to the test period (12 hours for sustained acting preparations). If the patient is on systemic steroid therapy dosage schedule is not interrupted. If on alternate day therapy should be done on the off day. On each study day the patient is seen and examined by the investigator and the basic pulmonary studies are done such as FVC, FEV_1, MMEF, heart rate, blood pressure, auscultation, shortness of breath, wheezing, chest pains and cough. Following administration of the test preparation pulmonary functions are repeated at 15, 30, 60, 90, 2, 4, 5, and 6 hours in total. Heart rate and blood pressure are measured also at those intervals. The patient also scores the severity of his symptoms of shortness of breath, wheezing, chest tightness, cough, and adverse reaction. The physician auscultate the chest of the patients at 2 and 4 hours after medication.

B. ADVERSE REACTIONS:

Cardiovascular system, tachycardia, heart rate greater than 100 was noted in 12 patients after inhaling albuterol, blood pressure didn't change significantly, local adverse reactions such as moderate retention of the mucous membrane, unpleasant taste and dry mouth was reported in several patients. Ectopic beat we are reporting one patient with albuterol. Headache, dizziness, or lightheadedness was reported by one patient each. Laboratory data was not repeated after the study. Pulmonary functions results: see pages 42, 44 and 46 of Volume 4.1 copies attached. As you look at the mean percent change in FVC from last baseline, by four hours the percent of change is less than 15%, our criteria for bronchodilation. When you look at the mean percent change FEV_1 by five hours the 15% criteria is not obtained.

INVESTIGATOR	$FEV_{1.0}$	MMEF
Dr. Chodosh (13)		
5 hrs.	46	13
6 hrs.	23	9
Dr. George (20)		
5 hrs.	50	70
6 hrs.	50	70
Dr. Hudson (8)		
5 hrs.	50	53
6 hrs.	50	53
Dr. Siegel (16)		
5 hrs.	56	50
6 hrs.	44	50
Dr. Tomashefski (20)		
5 hrs.	39	55
6 hrs.	39	55
Dr. Ziskind (11)		
5 hrs.	36	55
6 hrs.	36	55

III. CLINICAL STUDIES:

Studies were performed to support the following company claims (see product information also).

Actions - Albuterol is a beta-adrenergic agent with direct, selective pharmacologic action on the smooth muscle of the bronchial tree. Inhalation of albuterol promptly relieves bronchospasm and associated dyspnea and improves vital capacity in patients with reversible airway gostruction. Near maximum improvement in pulmonary function occurs with fifteen minutes of one or two inhalations of albuterol and improvement continues for four to six hours. Albuterol exerts comparable bronchospasmolytic action throughout the course of long-term treatment; tachyphylaxis has not been reported.

The effect of albuterol on bronchial smooth muscle is selective since it acts primarily on the beta-2 adrenergic receptors; it has little or no effect on the beta-1 adrenergic receptors of the cardiovascular system at the dosage used by patients. Tachycardia and blood pressure alterations have been minimal and infrequent following administration of the drug.

Studies are separated as:

A. A double-blind randomized complete crossover investigation involving 16 patients. The crossover study consists of two 12 day treatment periods during each of which one of the two test preparations is administered at random. On the first and last day of each treatment period the effect of a single dose of the test preparation will be assessed over the course of six hours.

   The two treatment periods will be separated by at least two days of washout.

   Evaluations are to be made at baseline and 15, 30, and 90 minutes; and 2, 4, and 6 hours following drugs which consist of:

   (a) Heart rate and blood pressure.

   (b) FEV_1, FVC, and MMEF.

   (c) EKG a 12 lead baseline and rhythm strips will be obtained 30 minutes and two hours following drug administration.

(d) Entries will be made of volunteered symptoms and observed signs. Overall evaluation of the status of the patients' bronchial asthma will be made by history and physical examination - compared to baseline, and two, and four hours following drug administration.

B. ADVERSE REACTIONS:

1. See Tables 19, 20.

2. See Tables 21-A, 21-B, 22-A, and 22-B.

C. EFFICACY:

Improvement or change in the pulmonary function of 15% or more from the baseline is used as the criteria of good bronchodilation. In this study the pulmonary functions used were FVC (Force Vital Capacity), FEV_1 (Force Expiratory Volume in One Second), and MMEF (Mid Maximal Expiratory Flow):

1. MMEF: ~~(See Figure 1. and Pages 1.91, and 1.92)~~ T I A + B

The improvement in MMEF are sufficient to show marked bronchodilation. However, only 2/16 or 12% of the patients show less than 15% improvement at six hours post Albuterol aerosol.

On the second evaluation at four hours 5/15 or 33% and at six hours 7/16 or 44% of the patients show less than 15% improvement. In other words 66% and 56% of the patients show improvement at four hours and six hours respectively with the Albuterol aerosol.

2. FEV_1: (See page 1.95 and 1.96)

There is significant improvement up to two hours at four hours, and six hours, 69% and 53% of the patients show improvement respectively; that is 11/16 and 10/16.

On the second evaluation at two hours 69% (5/16), four hours 44% (9/16), six hours 25% (12/16) show improvement more than 15% on bronchodilation. That is by four and six hours 66% and 75% were below 15% of improvement.

3. FVC: (See pages 1.99 and 1.00)

On the first evaluation the improvement was 25% from the fourth to the sixth hours, that is 75% or 12/16 did not show improvement greater than 15% of the baseline.

On the second evaluation the improvement varied from 25% to 44% starting on the two hours up to the six hours, that is 75 to 66% of the patients showed no improvement greater than 15% from the baseline.

Vital signs such as blood pressure (systolic and diastolic) and heart rate showed a tendency to decrease but not outside of physiological ranges.

Evaluation of other physiological parameters such as hemoglobin, white blood cells, and eosinophil count, bilirubin, alkaline phosphatase, transaminases (Sgot, Sgpt), blood urea Nitrogen (BUN), fasting blood sugar, urinanalysis and platelets all were within normal limits with minor variations of no significant pattern.

CONCLUSION:

There is no long-term study done in which we can judge tolerance and tachyphylaxis.

The drug appears to have maximum effectiveness up to four hrs. and in some patients up to six hours based on this single short-term (12 day) study.

A. Miranda, M.D.

cc: NDA 17-559
HFD-160 Document Room
HFD-160
HFD-108
R/D AMiranda (HFD-160) 9/8/75
R/D rev. by JWinkler - 9/9/75
Final typed by sm from tape and R/D - 9/9/75

JWinkler 9/9/75 mcCurdy MD 9/9/75

MEMORANDUM OF TEELPHONE CONVERSATION

NDA 17-559 July 31, 1975

Between: Dr. James Gourgis
Schering

and: Dr. Margaret Clark
Act. Dir., HFD-160

Initiated by: Dr. Gourgis (returned by Dr. Clark)

Subject: NDA 17-559

I returned a call of Dr. James Gourgis of Schering. In response to our conversation of two days ago he wanted additional information with regard to the type of submission we would like to see on the retrospective long-term studies done in England with Proventil. He wished to know if we wanted all the case reports or if we would like to see the summary and tables. I stated that for the, at least the initial submission we would like to first look at the summary and tables and if we then decided we needed the case reports we could ask for them. He wanted to know how many copies to submit and I recommended the standard three plus a desk copy for the reviewer. He also asked if this should be submitted to the NDA and I said yes.

Conversation ended.

Margaret A. Clark, M.D.

cc: NDA 17-559
HFD 108
HFD-160
MClark,M.D.:HFD-160:7/31/75
Final typed from tape nm 7/31/75.
Doc.Rm.

NDA 17-559 August 7, 1975

MEMORANDUM OF MEETING

Present: Schering Corporation
Leonard G. Dennick, M.D.
Irving Tabachnick, Ph.D.
Allison B. Felarca, M.D.
Joan M. Donovan
James J. Gourzis, M.D.
Nelson H. Schimmel, M.D.

and

Division of Surgical-Dental Drug Products/HFD-160
Margaret A. Clark, M.D., Acting Director
David Lidd, M.D., Medical Officer
A. Miranda, M.D., Medical Officer
J. Winkler, M.D., Medical Officer
A. Joel Aronson, Consumer Safety Officer

Subject: Proventil

This meeting was arranged by Dr. Clark at the request of the sponsor. At the onset it was determined that this meeting is for the purpose of preliminary discussion of what type of labeling claims might be appropriate if the application is found to be approvable.

It was clearly pointed out to and understood by the visitors that the application is currently still under medical review and they were reminded that it had been previously agreed upon that our comments and discussions at this time would not include reference to the recently submitted clinical material from the ongoing multicenter study.

Prior to a detailed review of the entire presently proposed package insert, the visitors were advised that we have at this time a number of areas of concern with respect to whether or not the application contains data supportive of certain claims or whether or not such data might be available. These points were enumerated and briefly discussed as follows:

1. Under "Actions" we noted they claim:

   a. "Near maximal improvement occurring within 15 minutes"

      It was determined that several of the studies contain pulmonary function measurements beginning at the 15 minute interval following administration of the drug and the visitors feel assured that they can support this particular claim.

   b. "Effect continues for 4-6 hours"

      It was agreed that this had only been evaluated on an acute basis.

c. "Effectiveness continues throughout long term treatment. Tachyphylaxis has not been reported"

It was pointed out to the visitors that there are no "long term" controlled studies that could be used to evaluate this claim. They acknowledged this and recognized it as a problem. Particularly, inasmuch as, following our recent request to them, they have confirmed the fact that they were unable to identify any well controlled long term studies even in the world literature as of the time of their recent literature search. In this regard the visitors stated that they are submitting on this date a volume containing some data from uncontrolled "long term experience" of two clinicians in the United Kingdom. (See the cover letter of this submission dated August 7, 1975).

d. "Little or no effect on the cardiovascular system. Tachycardia and blood pressure alterations have been minimal and infrequent".

We indicated some concern as to whether or not the data submitted thus far could support this claim.

2. It was pointed out that the present labeling under "Dosage" merely mentions Adult and Children's dosage to be 2 inhalations every 4-6 hours and does not give a lower age limit or otherwise define or establish definite pediatric dosage recommendations. It was unclear as to how extensive the pediatric experience, that is, under 12 years of age is at this time.

During the course of the ensuing point by point discussion of the labeling some of the above considerations were discussed in more detail as follows:

1. With respect to determination of duration of efficacy, which is said to be 4-6 hours in acute studies, it would be informative to evaluate the percent responders with each pulmonary function test (15% vs. 20% improvement) at the 4 and 6 hour points respectively. Thus for MEFR, it appeared that approximately half of the patients for a given acute study had a 6 hour duration (15% improvement); while the FEV_1 test for the 6 hour cut-off demonstrated that less than a majority of patients responded. In this regard, it was recommended that labeling statements regarding duration of the effect should be reflective of what was actually seen rather than a mere statement of possible range.

2. With respect to "tolerance",

a. Reference was made to an abstract by Jenne, et al (Journal of Allergy and Clinical Immunology No. 55; 96, 1975) in which 3 weeks of oral terbutaline cause a decrease in FEV_1 - "area under the curve", while there was no change in peak FEV_1 values.

b. It was noted that the Bedell study lasted only 12 days, and the retrospective long term data (to be submitted today) only had a single

pulmonary function evaluation at 15 minutes post durg administration.

3. With respect to a claim for "preferential" beta-2 adrenergic stimulatory effect, the need for supporting data was stressed by the FDA representatives. Some considerations discussed were:

   a. This may be the case in animal studies only.
   b. This may be the case where high doses (higher than recommended) are employed in patients.
   c. There is a need for data at the recommended clinical dose, with comparison to another adrenergic bronchodilator, e.g., isoproterenol.

Following the above discussions it was decided that the visitors would consider all of these points further and would prepare revised draft labeling with anotations and any pertinent supporting documents to be submitted in the future for further consideration.

J. Winkler 8/12/75
J. Winkler, M.D.

David Lidd 8/12/75
D. Lidd, M.D.

cc: NDA 17-559 Orig.
HFD-160 (2)
HFD-108
R/D dictated-JWinkler/DLidd 8/7/75
R/D Init. J.Winkler 8/12/75
D.Lidd 8/12/75
DocumentRoom(HFD-160)
r/t jw 8/11/75
finaltyepd pd 8/12/75

M Clark MD 8/12/75

John Winkler, M.D.
HFD-160

September 19, 1975

See memo and addendum filed in NDA letter 10/6/75 JWinkler 10/6/75

Acting Director
Division of Surgical-Dental Drug Products (HFD-160)

NDA 17-~~550~~ 559

At Administrative Rounds today, Dr. Marion Finkel asked about the relative attributes of Proventil when compared with Terbutyline. She wished to know if there were fewer cardiovascular effects with Proventil or if there were any other significant differences between the two drugs. Additionally, it would be useful to know which dosage forms are approved for Terbutyline and Alupent. Further, we need to know the status of the investigational work with any of the forms of these drugs which have yet to be approved.

Dr. Finkel also wanted to know where ~~Alupent~~ Proventil was marketed besides England. She particularly wanted to know about Canada as well as any other European countries.

Dr. Finkel suggested that we call either the Chairman of the Pulmonary Advisory Committee or Dr. Plummer, who is specifically assigned to assist with this drug, and ask why they feel this drug should be approved with Phase 4 studies when Terbutyline is already on the market. Specifically, what is the basis for the apparent opinion among some of the medical community that this drug is an important addition to the physician's armamentarium.

Margaret Clark, MD 9/22/75

Margaret A. Clark, M.D.

cc: NDA 17-550
HFD-160
MClark,M.D.:HFD-160:9/19/75
Final typed from tape nm 9/22/75
Doc.Rm.-160

3-1

NDA 17-559 October 2, 1975

Memorandum of Telephone Conversation

Between: Dr. Edward Neary
Schering Corporation
Bloomfield, New Jersey

and

A. Joel Arónson, CSO
HFD-160

Initiated by: A. Joel Aronson

Subject: The marketing status of Albuterol Sulfate in other parts of the world.

As requested by Dr. Winkler, I called Dr. Neary and asked him if he could tell us in which countries Albuterol Sulfate is marketed. I also requested to know what dosage forms this product is marketed in.

Dr. Neary called me back with the requested information. He stated that Albuterol,aerosol and other dosage forms as marketed by Allan and Hambury is marketed in the following countries: Argentina, Australia, Belgium, Brazil, Columbia, Finland, France, Germany, Great Britain, Italy, Mexico, Netherlands, New Zealand, Philippines, Portugal, South Africa, Sweden, and Switzerland. He also informed that this drug is also marketed in Japan as a tablet and nebulized solution. I asked Dr. Neary if the aerosol,tablet and nebulized solution are the three dosage forms that are marketed in other countries of the world and he indicated that they were.

I thanked Dr. Neary for the information and the conversation ended with the usual amenities.

A. Joel Aronson 10/16/75

A. Joel Aronson, CSO

cc: NDA 17-559 Orig.
HFD-160 (2)
HFD-108
Doc.Room(HFD-160)
R/D A.J.Aronson
finaltyped from tape pd 10/14/75

Please Circulate for Research.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE: October 6, 1975
FROM: Dr. Winkler J Winkler 10/6/75		OFFICE: NDE
TO: Dr. Clark		DIVISION: DSDDP/HFD-160

SUBJECT: NDA 17-559 -- Proventil Aerosol and your Memo dated September 19, 1975

SUMMARY

With regard to the initial question of a comparison of Proventil with terbutaline, it would be more appropriate to compare Proventil Aerosol with metaproterenol aerosol inasmuch as:

1. Terbutaline is not available as an aerosol in the United States.

2. Metaproterenol is available in the United States in aerosol form similar to the proposed product of Proventil and has labeling claims quite similar to those currently being considered for the Proventil application.

In view of this, and in line with the type of questions raised in the Memo of September 19, we have attempted to compare the efficacy and the cardiovascular effects of equivalent doses of these two aerosols, metaproterenol vs. Proventil, based on the literature available to us at this time. This includes the references most recently submitted by Schering in their submission of August 14, 1975 (see attached Medical Review).

Based on our review thus far of those studies in which a comparison was made between aerosol Alupent and aerosol Salbutamol, no significant difference was demonstrated in either efficacy or cardiovascualr effects.

With respect to the second question regarding dosage forms currently approved for terbutaline and Alupent and the IND status of the forms of these drugs which have yet to be approved the current situation is as follows:

a. Terbutaline is available as an injectable form and as oral tablets.

b. Metaproterenol (Alupent) is available as a metered aerosol, tablet, and syrup. An additional dosage form of Alupent solution 5% for I.P.P.B. and for hand nebulization has not been approved. A "not approvable" letter issued for this dosage form on June 30, 1975. A meeting was held with the sponsor on July 31, 1975, at which time they indicated they would resubmit information to satisfy the application's deficiencies. No further correspondence has been received fromthe sponsor thus far.

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

October 6, 1975

Dr. Winkler — NDE

Dr. Clark — DSDDP/HFD-160

NDA 17-559 -- Proventil Aerosol and your Memo dated September 19, 1975

With regard to the initial question of a comparison of Proventil with terbutaline, it would be more appropriate to compare Proventil Aerosol with metaproterenol aerosol inasmuch as:

1. Terbutaline is not available as an aerosol in the United States.

2. Metaproterenol is available in the United States in aerosol form similar to the proposed product of Proventil and has labeling claims quite similar to those currently being considered for the Proventil application.

In view of this, and in line with the type of questions raised in the Memo of September 19, we have attempted to compare the efficacy and the cardiovascular effects of equivalent doses of these two aerosols, metaproterenol vs. Proventil, based on the literature available to us at this time. This includes the references most recently submitted by Schering in their submission of August 14, 1975 (see attached Medical Review).

Based on our review thus far of those studies in which a comparison was made between aerosol Alupent and aerosol Salbutamol, no significant difference was demonstrated in either efficacy or cardiovascualr effects.

With respect to the second question regarding dosage forms currently approved for terbutaline and Alupent and the IND status of the forms of these drugs which have yet to be approved the current situation is as follows:

a. Terbutaline is available as an injectable form and as oral tablets.

b. Metaproterenol (Alupent) is available as a metered aerosol, tablet, and syrup. An additional dosage form of Alupent solution 5% for I.P.P.B. and for hand nebulization has not been approved. A "not approvable" letter issued for this dosage form on June 30, 1975. A meeting was held with the sponsor on July 31, 1975, at which time they indicated they would resubmit information to satisfy the application's deficiencies. No further correspondence has been received fromthe sponsor thus far.

FROM: J Winkler 10/6/75	OFFICE
TO:	DIVISION

SUBJECT: NDA 17-559 -- Proventil Aerosol Page 2

SUMMARY

c. There is an active IND for Proventil for both tablet and syrup formulations. These are currently in Phase 3 with acute effect studies in both adults and children and comparative effect studies between tablet and syrup formulations. Thus far there are no long-term well controlled studies for efficacy for either formulation. There is also an active IND for terbutaline aerosol which is in Phase 3 with a number of acute effect studies and comparative in progress.

With respect to the questions from Dr. Finkel regarding foreign marketing of Proventil, we have checked with the sponsor and have been informed that Albuterol Sulfate is marketed in one or more forms in the following countries as aerosol, tablet or nebulizer solution: Argentina, Australia, Belgium, Brazil, Canada, Columbia, Finland, France, Germany, Great Britain, Italy, Mexico, Netherlands, New Zealand, Philippines, Portugal, South Africa, Sweden and Switzerland.

With respect to the question raised regarding the basis for the opinion of our Pulmonary Advisory Committee that this drug should be marketed at this time, reference can be made to the portion of the minutes or summary of the last meeting of that committee that relates to the discussion of Proventil which has just been completed by Mr. Rachanow. I do not believe there is any information in this record that would explain the "apparent opinion among some of the medical community that this drug is an important addition to the physician's armamentarium." Any further consideration of this point should be based on the question of a need for Proventil Aerosol while metaproterenol (not terbutaline) aerosol is currently available. As noted earlier the literature reviewed thus far shows no definite advantage for Albuterol from either the safety or efficacy standpoint. It may be of interest to note that this question was touched on by a recent visiting clinical pharmacologist from Heidleburg, Dr. Gross, and to my recollection he expressed the opinion that the unavailability of Salbutamol in this country did not represent a "drug lag" and that any difference between the actions of this drug and metaproterenol were marginal at the most.

cc: NDA 17-559 Orig.
HFD-160
HFD-108
R/D Dictated by JWinkler 10/3/75
Final typed 10/6/75:jw

John Winkler, M.D 10/6/75

Attachment: Medical Review by D. Fidel MD.

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

OCT 07 1975

NDA 17-559

ADDENDUM MEDICAL REVIEW

NDA 17-559

Product Proventil Inhaler

Sponsor Schering corp.

Material Reviewed Relevant literature articles from August 14, 1975 submission pertaining to a comparison of metered dose metaproterenol and salbutamol aerosol formulations

Label usual dosages

1. Metaproterenol (0.65 mg/spray) is recommended at 2 sprays q.i.d. (total of 1.3 mg. q.i.d.)

2. Salbutamol (0.10 mg/spray) is recommended at 2 sprays q.i.d. (total of 0.20 mg, q.i.d.)

Literature studies in which comparisons are made, in part or in whole, between salbutamol and metaproterenol aerosols (studies x referred to in August 14, 1975 submission)

1. Choo-Kang et al, But. M.J. 2: 287, 1969

Design Single administration

Metaproterenol 1.5 mg and salbutamol 0.20 mg

Patients:

chronic asthma; 24 patients Isoproterenol responsive

Evaluation

"Area under the curve" - integrated FEV_1 change -- difference between salbutamol and metaproterenol not significant at 5% level. No significant change in heart rate.

CONCLUSION: "From the data available in this study it is difficult to reach a firm conclusion on the relative therepeutic merits of salbutamol and orciprenaline (metaproterenol), because the differences in the effects of thes two drugs only rarely achieved statistical significance".

NDA 17-559

2. Riding et al, Brit. J. Dis. Chest 64: 37, 1970

Design Single administration

Metaproterenol 1.5 mg and
salbutamol 0.20 mg

Patients

21 asthmatic patients
Isoproterenol responsive

Evaluation

"Area under the curve" - Integrated FEV_1 change -- difference in favor of salbutamol significant at 5% level.

No EKG changes with respect to ST-T occurred with either drug. Slight increase in heart rate (5 beats/min at 5 minutes) noted with metaproterenol.

3. Kennedy et al, Brit. J.Dis. Chest 2: 165, 1969

Design single administration,
Metaproterenol 1.5 mg and
salbutamol 0.20 mg.

Patients

12 asthmatic patients
bronchodilator responsive

Evaluation

"Analysis of variance shows that the effect of salbutamol on $FEV_{0.75}$ was significantly better ($p < 0.05$) than that of orciprenaline (metaproterenol) except at 15, 90 and 120 minutes after inhalation, when the difference between the mean values did not quite achieve significance." On the other hand, with respect to "Area Under the Curve" for $FEV_{0.75}$ salbutamol was favored at a p value less than 0.05.

In normal volunteers no effect seen at the above doses with respect to blood pressure and heart rate.

4. Racoveanu et al, Postgrad, M.J. 47: 83, Supp. March 1971.

Design Singie administration, metaproterenol 1.5 mg and salbutamol 0.20 mg

Patients 22 asthmatic patients (6 with coexistent bronchitis) bronchodilator responsive

Evaluation

Curves comparing percent increase in mean FEV_1 presented. Note the mean baseline was similar. "Variance analysis showed that the difference in the curves was not significant (even though the salbutamol curve was always greater than that for metaproterenol)."

Similar results obtained if analysis made when FEV_1 data expressed as ml changes.

"Area under curve" analysis favored salbutamol but the difference was not statistically significant.

No difference between the drugs noted over the course of the experiment with respect to blood pressure and pulse rate.

The authors note that the Kennedy et al and Riding et al studies were not double-blind. Another variable considered by the authors is the reproducibility of base-line measurements on two occasions. Thus, if a lower initial base-line value is recorded on a salbutamol day, the results may favor the salbutamol group.

5. Tala et al, Postgrav. M.J. 47: 61, supp. March 1971.

Design Single administration, metaproterenol 1.5 mg and salbutamol 0.20 mg.

Patients 12 patients with asthma

Evaluation:

" The bronchodilator effects of orciprenaline (metaproterenol) and salbutamol were very similar at all times, although salbutamol produced a slightly more prolonged effect."

" According to our data it is impossible to determine the relative clinical effects of orciprenaline and salbutamol because the differences were not statistically significant".

"No significant effect on heart rate".

Overall Comments

The following conclusions are drawn by this reviewer from the above reviews of 5 literature studies:

1. With respect to cardiovascular adverse aspects, nax at the recommended doses, there are no significant differences in blood pressure, pulse rate, and EKG.

2. With respect to efficacy aspects, from the viewpoint of statistical differences 3 of the 5 studies do not distinguish between salbutamol and metaproterenol by inhalation. Two of the 5 studies showed statistical significance favoring salbutamol aersol when the "Area Under the Curve" for FEV_1 (or $FEV_{0.75}$) was calculated.

However, it is to be noted that the two studies supporting the thesis of greater efficacy for salbutamol are not of a double-blind design. The significance of such a criticism is commented on by Williams and Kane "Finally, patients with asthma are notoriously subject to suggestion, and no study can be considered valid unless it is carried out in a double-blind fashion" (Amer. Rev. Resp. Dis. 111: 321, 1975)

Finally it is noted that a 1.5 mg dose of metaproterenol was employed in the above clinical studies, as compared to the label recommended dose of 1.3 mg.

Conclusion

Data from five reviewed literature studies comparing salbutamol and metaproterenol per aerosol inhalation do not support an inference that differences exist with respect to safety and efficacy.

David Lidd

David Lidd, M.D.

cc: NDA 17-559 ORIG.
HFD-108; HFD-160; Doc. Rm. 160
R/D by David Lidd, M.D.
R/D init. by M. Clark, M.D. 10/2/75
T/F: kd 10/6/75

Mildred D 10/7/75

See memo dated 10/6/75 attached
J Winkler 10/6/75

IND 7542
NDA 17-559

October 14, 1975

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Nelson Schimmel, M.D.
Schering Corporation
Bloomfield, New Jersey 07003
(201) 743-6000 Ext. 3248

and

Gerald M. Rachanow, CSO
DSDDP, HFD-160

Initiated by: Dr. Schimmel
Call returned by Mr. Rachanow

Subject: NDA 17-559 and IND 7542

Dr. Schimmel called regarding the status of the minutes of the September 10, 1975 Pulmonary-Allergy and Clinical Immunology Advisory Committee meeting and their relationship to the 60 day time extension on NDA 17-559, Proventil Inhaler. He stated that the 60 day extension was up on October 22. I informed him that the minutes had been completed and were being final typed and would be available to FDA medical personnel within a day or two. I told him that I could not comment on the relationship of the completion of these minutes to any final action on the pending NDA by October 22.

Dr. Schimmel also had a question about the letter dated October 10, 1975 to IND 7542 for Proventil Oral Tablets. He stated that the kinds of comments posed in this letter did not seem quite appropriate in view of the recent amendments to the IND and asked whether a "new" medical officer, unfamiliar with the history of this IND and the Proventil Inhaler NDA had been assigned to review this IND. I replied that I was unable to answer this question.

Dr. Schimmel stated that he had a conference scheduled with Dr. Clark on November 4, 1975 regarding bone cement. I suggested that he discuss any problems which he had with the October 10 letter to the IND with Dr. Clark at that meeting and that he notify her of his intentions to do so when he confirmed the November 4 meeting so that appropriate FDA personnel could attend. He replied that he would take my advice and do so, and he thanked me for my assistance. The conversation concluded with the usual amenities.

Gerald M. Rachanow 10/15/75
Gerald M. Rachanow, CSO

cc: IND 7542 Orig.
NDA 17 559 Orig.
HFD-160(2), HFD-108
cc Mr.Aronson(HFD-160)
R/D G.M.Rachanow(HFD-160)10/14/75
Dr. Clark 10/17/75
Doc.Room(HFD-160) R/D Init. C.M.Nealey10/14/75R/DInit.L.V.PascualforM.Clark 10/14/75
ft pd 10/15/75

Director, Division of Surgical-Dental Drug Products (HFD-160)

October 20, 1975

Acting Associate Director for New Drug Evaluation (HFD-100)

Proventil (albuterol).

The data submitted by the company for the Advisory Committee may be skewed somewhat to a more favorable position for albuterol with respect to cardiovascular side effects than is the case. There is, of course, no doubt that albuterol has advantages in this regard as compared with the older agents and metaproterenol but whether it is significantly different than terbutaline in this respect is open to question.

However, since albuterol is to be administered by inhalation, with its consequent more rapid onset of action than oral terbutaline, it should be made available for U.S. patients in the near future. (I suppose you know that terbutaline is available by inhalation in other countries.) Consequently, I would agree with the Advisory Committee that it should be approved with Phase IV studies to examine the tachyphylaxis issue. The protocols for such studies should be submitted and approved by your Division prior to NDA approval and, in addition, the investigators should have been designated by the firm along with a starting date. I disagree with the Committee that the drug should be labeled for acute use only until the long-term studies are completed since no one will use it in this manner. It would be preferable to simply use our standard asthma indication wording but to inform the doctor that it is not known whether tachyphylaxis will develop with long-term use since studies to answer that question are still ongoing. Please consult with Dr. Rheinstein on ways to convey that message in advertising. We may have to make the NDA conditionally approvable also on the basis that, until the long-term studies are completed, all ads will need to inform the M.D. in a prominent manner of the lack of information about tachyphylaxis.

Marion J. Finkel, M.D.

cc:
Orig. NDA 17-559
HFD-160
MJFinkel:eks 10/15/75-10/20/75

TO: HFD 160

Grader not to hold up

Approvable Letter, we should

APPROVAL ☐ REVIEW ☐ PER CONVERSATION
SIGNATURE ☐ NOTE AND SEE ME ☐ AS REQUESTED
COMMENT ☐ NOTE AND RETURN ☐ NECESSARY ACTION
FOR YOUR INFORMATION
PREPARE REPLY FOR SIGNATURE OF

REMARKS: waiver S.O.P. for "drug-by drug, viz., approvable if data from subj's a protocol in Phase IV studies, etc. etc.

(Fold here for return)

Marion J. Finkel, M.D.
Associate Director for
FROM: New Drug Evaluation HFD-100

NONE | BUILDING | ROOM

OPN NEW-30 REV. 11/74 ROUTE SLIP
U.S. GOVERNMENT PRINTING OFFICE: 1974 620-389/3503 1-3

ENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DATE: October 20, 1975

FILE IN ORIGINAL

; Evaluation (HFD-100)

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nistered by-inhalation, with its than oral terbutaline, it should be e near future. (I suppose you know ation in other countries.) Conse-ry Committee that it should be ine the tachyphylaxis issue. The ubmitted and approved by your Divi-ition, the investigators should with a starting date. I disagree with the Committee that the drug should be labeled for acute use only until the long-term studies are completed since no one will use it in this manner. It would be preferable to simply use our standard asthma indication wording but to inform the doctor that it is not known whether tachyphylaxis will develop with long-term use since studies to answer that question are still ongoing. Please consult with Dr. Rheinstein on ways to convey that message in advertising. We may have to make the NDA conditionally approvable also on the basis that, until the long-term studies are completed, all ads will need to inform the M.D. in a prominent manner of the lack of information about tachyphylaxis.

M.J.F.
Marion J. Finkel, M.D.

Margaret Clark, M.D.	NDE
TO: John Winkler, M.D.	DIVISION HFD-160

SUBJECT: NDA 17-559 Proventil Inhaler memo to Winkler advising him to approve

SUMMARY

Please note Dr. Marion Finkel's memo dated October 20, 1975 with regard to this application. On October 24, 1975 I discussed this matter with her to clarify the intent of the memo. The matter is to be handled as follows: an "approvable" letter is to be prepared which will state that final approval is contingent upon submission and approval of a protocol for Phase 4 studies to deliniate long-term usage, including information with regard to tachyphylaxis; revised labeling to inform the physician that certain information regarding the drug is lacking.

In order to accomplish this you will need to write an addendum to Dr. Miranda's review to expand and clarify what is known from the information which has been submitted. You shall also have to prepare a Summary Basis of Approval document.

I will ask Mrs. Malless to expedite all clerical work connected with this work. Further, I will ask Mr. Aronson to obtain information for the Summary Basis of Approval from Drs. Oneson and Fefer.

The necessary work on this NDA should take precedence over other matters so that the "Approvable" letter and supporting documentation may be forwarded to HFD-100 no later than October 31, 1975. If I can be of assistance in this matter please let me know.

cc: HFD-100
Mr. Joel Aronson
NDA 17-559

SIGNATURE Margaret Clark, MD.	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-~~550~~ 559 October 23, 1975

Between: Dr. Neary
Schering Corp.

and: Dr. Margaret Clark
Director HFD-160

Initiated by: Dr. Neary

Subject: NDA 17-~~550~~ 559

Dr. Neary of Schering called to ask when he might expect an approval letter for Proventil Aerosol. I told him that we were still looking at various aspects of the application and I could not give him any timetable as to our actions. I asked if he would be with the group coming in for a meeting on November 4 with regard to another drug. He said he was not planning to attend that meeting but that Dr. Schimmel would be here at that time. I said I would plan to take a few minutes to discuss the Proventil application with Dr. Schimmel at that time. Dr. Neary said that was agreeable with him and the conversation ended.

Margaret A. Clark, M.D.

cc: NDA 17-~~550~~ 559
HFD-108
HFD-160 (2)
MClark,M.D.(HFD-160)10/23/75
Final typed from tape nm 10/24/75
Doc.Rm. - 160

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE: October 20, 1975
FROM: J. Winkler, M.D. Winkler		OFFICE: NDE
TO: Director, HFD-160 Director		DIVISION: HFD-160
SUBJECT: NDA 17-559, Proventil Inhaler and your memorandum of October 20, 1975.		

SUMMARY

I have reviewed the various memoranda on this file, including your memorandum of September 16, 1975, to Dr. Finkel and her response of October 20, 1975, to you.

It is my understanding from your memorandum of October 28, 1975, and from the discussion held in a division meeting of this date that a decision has been made at the Office level to approve the New Drug Application for Proventil Aerosol under the conditions outlined in your memorandum of October 28, 1975, addressed to me.

As discussed with you previously, and today, and as reflected in the various memoranda and reviews, I am of the personal opinion that the application is not approvable at this time due to the absence of minimal requirements with respect to adequate and well-controlled studies of sufficient duration. This lack of any long-term well-controlled studies has been recognized and documented by the Medical Officer Review, by the sponsor (see their letter of August 7, 1975, and our memorandum of the meeting with them on August 7, 1975, in which the visitors acknowledged this deficiency and recognized it as a problem in the processing of their New Drug Application for Proventil Aerosol - page 2, paragraph 2), and by the members of the Pulmonary-Allergy and Clinical Immunology Advisory Committee in the meeting of September 10, 1975.

With respect to questions of the possible relative merits of Proventil Aerosol when appropriately compared with other currently available agents, I have already indicated my thoughts in this area as contained in my memorandum to you dated October 6, 1975, together with an attached Addendum Medical Review of that same date by Dr. Lidd that was attached to my memorandum. This memorandum of mine was in response to yours of September 19, 1975, relating to your discussions of this New Drug Application with Dr. Finkel at administrative rounds on that date.

Dr. Miranda's medical review of July 17, 1975, adequately describes those studies upon which the New Drug Application currently relies. I believe that this review, together with the discussions relating to these studies by the Pulmonary-Allergy and Clinical Immunology Advisory Committee, confirms the fact that there is a lack of adequate and well-controlled studies as defined in the current regulations or as ordinarily required for approval of a New Drug Application. (see summary minutes of meeting of September 10, 1975)

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

In velw of the above comments, it is my recommendation that the further processing of this New Drug Application, as requested and along the lines directed by you in your memorandum of October 28, 1975, be performed administratively by the Chief Consumer Safety Officer of this division.

J. Winkler, M.D.

cc: NDA 17-559
HFD-108
HFD-160
JWinkler,M.D.:HFD-160:10/28/75
Final typed nm 10/28/75
Doc.Rm.-160

MEMORANDUM

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

TO : Director, Division of Surgical-Dental Drug Products (HFD-160)

DATE: OCT 3 1 1975

Finkle response to Winkler memo

FROM : Acting Associate Director for New Drug Evaluation (HFD-100)

SUBJECT: Proventil (albuterol) Inhaler.

Reference is made to the memorandum of October 28, 1975 from Dr. Winkler to you which describes Dr. Winkler's belief that the NDA should not be approved because of the absence of long-term well-controlled studies. Dr. Winkler's opinion is duly noted. Nevertheless, the issue at present is that an adequate medical officer review of the data in the NDA and the IND (if the latter contains clinical trials which were not also submitted in the NDA or were cross-referenced to the NDA) needs to be written. Such a review should be our usual detailed one describing the protocols and the results with respect to both safety and effectiveness. Dr. Miranda's review cannot be considered adequate.

There would appear to be only two alternatives to this dilemma: (1) Dr. Miranda be asked to rewrite his summary according to the guideline for medical officer reviews (and he could be given a copy of one of Dr. Triantas's summaries for guidance) or (2) a full time medical reviewer in your division review the data.

M. J. F.
Marion J. Finkel, M.D.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE Nov October 3, 1975
FROM: Margaret Clark, M.D.		OFFICE NDE
TO: John Winkler, M.D.		DIVISION HFD-160
SUBJECT: NDA 17-559 Proventil Inhaler		

SUMMARY

Please see Dr. Marion Finkel's memo of October 31, 1975 which is attached.

directive to Winkler

I concur with Dr. Finkel with regard to the fact that Dr. Miranda's review cannot be considered adequate. Since Dr. Miranda is not available to re-write his review you should undertake this assignment. You have spent considerable time going over the data with Dr. Miranda and so should be familiar with the subject matter.

This NDA is 255 days old as of this date, so this review should be done promptly.

cc: NDA 17-559
HFD-1
HFD-160

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

MEMORANDUM OF MEETING

NDA 17-559

November 3, 1975

Winkler claims harassment. Says Clark

Present: J. Winkler, M.D.
Medical Officer, HFD-160

and: Dr. Margaret Clark
Director, HFD-160

In response to Dr. Finkel's memo of October 31, 1975 and my memo of November 3, 1975, Dr. John Winkler came to talk with me. He said that my memo was not clear and he did not know what I was asking him to do. I said that what I intended was that he review the clinical data submitted to the NDA. Since he felt that this was not clear I said I would write him an additional memo while he waited. I immediately typed out my second memo of November 3 to him. Dr. Winkler felt that this was a form of harassment and he was being punished for his opinion that this drug was not ready for approval at this time. He suggested that since Dr. Finkel's memo noted Dr. Irlantas' name that she should be asked to review the NDA. I said that was inappropriate as that was not her field and she was not a member of his group.

I told Dr. Winkler that it was my personal intention never to harass or punish him. I was simply interested in obtaining an adequate medical review for this NDA. Dr. Winkler stated that he thought Dr. Miranda's review was adequate and pointed out that I had countersigned this review. I reminded him that I signed that for typing purposes in preparation for the last Pulmonary Advisory meeting as we had to have something ready to present at that time. I was aware at the time that the review was not up to our usual standards and that we had discussed at that time, and on several occasions since, the areas where the review is inadequate.

Dr. Winkler also pointed out that since he is no longer in a supervisory position he does not feel that he has the responsibility for seeing that this NDA has another medical review. I responded by saying that he was the Group Leader and responsible for the pulmonary drugs. I said that it would be best for him or a member of his group to do the review. Dr. Winkler stated that he had no particular expertise in pulmonary drugs but was rather an internist and had had no specialized training in pulmonary disease. I told him that he could ask Dr. Lidd to do the review if he wished. I had not suggested this be done because I knew Dr. Lidd already had a heavy workload but I would not object if Dr. Winkler chose to do this.

Dr. Winkler also objected to memos regarding this application being transmitted without the attached documents and previous memos attached.

I suggested that he ask the Consumer Safety Officer to see that the file was put in order with all memos in sequential order. I also suggested that he and I take another look at the review done by Dr. Solymossy. I was under the impression that at the time that was done both Dr. Winkler and I had agreed that it was inadequate. However, it would not hurt to have a second look at this document.

Dr. Winkler said he would prepare a memo in response to my memo.

Margaret A. Clark, M.D.

cc: NDA 17-559
HFD-108
HFD-160(2)
MClark,M.D.:HFD_160:11/3/75
Final typed from tape rm 11/5/75
Doc.Rm-160

See my Memo of this meeting dated 11/3/75 for full details.
J Winkler

MEMORANDUM OF MEETING

NDA 17-559
Proventil Aerosol

November 3, 1975

Present: Dr. Margaret Clark
Director, HFD-160

and: Dr. J. Winkler
Medical Officer, HFD-160

At approximately 4:00 p.m. on November 3, 1975 Mr. Joel Aronson delivered to me without comment a single memo incorrectly dated October 3, 1975, but one that had just been prepared on November 3, 1975, by Dr. Clark and addressed to me, together with an attached memo from Dr. Finkel to Dr. Clark relating to NDA 17-559, Proventil Aerosol.

Dr. Clark's memo of this date to me informed me that I was to undertake the assignment to re-write the medical review of Dr. Miranda which she stated that, in concurrence with Dr. Finkel's opinion expressed in her memo of October 31, 1975, could not be considered as adequate. This was the first communication to me regarding this NDA since my memo of October 28, 1975, addressed to Dr. Clark in response to her memo to me of that same date. The memos brought to me on this date by Mr. Aronson were not attached to the appropriate NDA volume or any other material and specifically were not attached to my memo of October 28, 1975, to which Dr. Finkel's memo of October 31, 1975, was in response. It appeared from the contents of Dr. Finkel's memo that she had apparently been given my memo of October 28, 1975, as an isolated piece of paper without the necessary prior documents that would be essential to properly interpret and respond to my memo of October 28, 1975. At the very least, she should have seen the prior memo from Dr. Clark to me on that same date to which I was responding. This impression that Dr. Finkel had been given only the isolated memo of mine dated October 28, 1975, was confirmed later by Dr. Clark at our meeting today as related below.

After reading the memos delivered to me by Mr. Aronson, I went directly to Dr. Clark's office and informed her that I disagreed with the action being taken and specifically with the assignment to me to re-review the clinical material in this NDA in the face of my already stated position relating to the currently proposed action on this NDA as clearly stated in prior memos and discussions. I advised Dr. Clark I had already seen Dr. Finkel's memo when it came to the office on October 31, 1975, and in anticipation of it being forwarded to me had already prepared an initial draft memo of response and that I would complete this in final for the file. I told her that I did not agree that the issue was the adequacy of the Medical Officer Review and that in my opinion the real issue was whether or not the drug should be approved for long-term use in the absence of any adequate long-term controlled studies.

NDA 17-559

I informed Dr. Clark that in my opinion Dr. Finkel's memo of October 31, 1975, is not responsive to the issues contained in my memo of October 28, 1975. I also noted that Dr. Clark had made no response to, nor taken a position on my memo but instead gave it to Dr. Finkel as an isolated item with no supporting or pertinent documents, not even a copy of the memo of October 28, 1975 to me from Dr. Clark to which my memo of the same date was in response. Dr. Clark stated that she had left the isolated memo alone with Dr. Finkel, and agreed that it should have been given to her as a total package.

I informed Dr. Clark that many problems arise from a procedure, as described above, in which isolated memos are passed around for someone's evaluation but without being accompanied by the prior pertinent memos or other documents. I stressed the desirability to put these documents in the proper sequence and to circulate or forward them only on the appropriate current volume of the NDA. Only in this way can someone in another office be expected to properly evaluate and respond. Dr. Clark agreed with me on this point.

I informed Dr. Clark that I had already clearly stated my position on this NDA and it is in the record and she indicated that she recognized this. I further indicated that a position is needed at her level as Division Director regarding the approvability of the NDA along the lines discussed previously between Drs. Clark and Finkel. Dr. Clark responded that she could not take a position in the absence of an adequate Medical Officer Review. I responded that in my opinion the review by Dr. Miranda was adequate with respect to an evaluation of those studies upon which the NDA currently relies. I also reminded Dr. Clark that both she and I had endorsed the review without qualifications. I also stated that this medical review had been considered adequate for presentation to the Pulmonary-Allergy and Clinical Pharmacology Advisory Committee, and represents the medical evaluation upon which the Advisory Committee made their recommendation for approval that is currently being considered as the major basis for an approvable letter. If this review is now considered to be an inadequate one, it would seem to be only proper to so inform the Advisory Committee Chairman of this so that he will be aware that the recommendations of his committee were based on the presentation by us of what is now regarded by this Division and by the Office of New Drug Evaluation as an inadequate medical review.

I indicated that in my opinion the reevaluation of these studies previously referred to would be a waste of time. I also reminded Dr. Clark that this NDA has been reviewed thus far by three medical officers (Smeltzer, Solymossy, and Miranda) and all had found it not approvable as of the time of their review. I continued to stress that in my opinion such a reevaluation would be of no value in meeting the real issue at hand, that is, whether or not the application should be approved for long-term use in the absence of long-term controlled data. I indicated my

NDA 17-559

understanding from prior discussions and memos between Dr. Clark and myself that Dr. Finkel has indicated her desire for approval at this time on the premise that this drug represents a significant example of a "drug lag". I restated my previous opinion in this regard that I do not believe evidence exists to support this "drug lag" position. I reminded Dr. Clark that this question of "drug lag" had been explored in my memo to her of October 6, 1975, and in the attached Addendum Medical Review by Dr. Lidd of the same date. I then raised the question of whether or not Dr. Finkel had seen this material in view of her comments in her subsequent memo of October 20, 1975, and on it's attached buck slip of October 24, 1975. Dr. Clark could not answer this question but stated that, if I thought there was any material that should be brought to Dr. Finkel's attention, this would be done.

Dr. Clark stated that she agreed that all of the recent memos and related material should be properly filed in the open jacket and indicated that this will be done promptly for the purpose of proper evaluation of this file up to this present time.

The meeting ended at this point with no further discussion or response from Dr. Clark on the issues raised above. Earlier in this meeting I requested that, if I am to be required to re-review this material in spite of my presently stated position, I be given something in writing more clearly describing the orders. In response to this, Dr. Clark presented me with a second memo also incorrectly dated October 3,1975, instead of November 3, 1975 requesting me to "review the clinical data and related information submitted in NDA 17-559."

The meeting ended abruptly due to an interruption and it was not clear to me whether or not there was to be any further discussion or consideration of the above points.

John J. Winkler

J. Winkler, M.D.

11/7/75

cc: NDA 17-559
HFD-108
HFD-160(2)
JWinkler,M.D.:HFD-160:11/7/75
Final typed nm 11/7/75
Doc.Rm.-160

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	~~October~~ 3, 1975
FROM: Margaret Clark, M.D.		OFFICE NDE
TO: John Winkler, M.D.		DIVISION HFD-160
SUBJECT: NDA 17-559 Proventil Inhaler		

SUMMARY

In response to your request for clarification of my memo of earlier today I request that you review the clinical data and related information submitted in NDA 17-559.

In no way do I wish to influence your decisions or recommendations in this matter.

SIGNATURE	DOCUMENT NUMBER
M. Clark, MD.	

FORM FDH-2034 (11/66)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 11/4/75
FROM: J. Winkler, M.D.		OFFICE NDE
TO: Margaret Clark, M.D., Director, HFD-160		DIVISION HFD-160
SUBJECT: NDA 17-559, Proventil Inhaler, and Dr. Finkel's memorandum of October 31, 1975.		

SUMMARY

As discussed in some detail with you in our meeting on November 3, 1975, I have reviewed the memorandum from Dr. Finkel dated October 31, 1975, and forwarded to me by you on November 3, 1975, and have the following comments:

1) It is noted that as determined in our meeting of November 3, 1975, Dr. Finkel's memorandum was written following her review of a single document, my memo of October 28, 1975, without the necessary prior memos and documents that were relevant to the issues contained in my memo of October 28, 1975. This may explain why, although she states that Dr. Winkler's opinion is duly noted, she makes no comment on the several issues contained in my memo of October 28, 1975, and speaks only on the subject of the adequacy of the Medical Officer's Review.

2) In my opinion the "issue at present" is not the adequacy of the most recent Medical Officer Review. This review by Dr. Miranda was endorsed at the Division level by the Group Leader and the Division Director. It was considered adequate for presentation to the Pulmonary-Allergy and Clinical Immunology Advisory Committee at the meeting on September 10, 1975, and served as the basis for their recommendation for approval that the Office of New Drug Evaluation has indicated thus far a willingness to accept. If this review is to be declared "inadequate" at this time, I believe the Chairman of the Advisory Committee deserves to be advised of this in some detail, inasmuch as, the recommendations of this committee were based on their deliberations over this very review, as presented by Dr. Miranda.

3) I believe the real "issue at present" is whether or not this NDA should be approved providing for the recognized intended long-term repetitive use of this drug in the recognized absence of any adequate long-term controlled clinical studies. As pointed out in my memorandum of October 28, 1975, there is documentation in this NDA of unanimous agreement that such a deficiency exists.

I believe an initial definite Division position is now needed here, and a final decision is needed at the Office level and at the Bureau Director's level. I have already expressed my opinion in this regard as the Group Leader.

SIGNATURE	DOCUMENT NUMBER
J Winkler	

FORM FDH-2034 (11/65)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE
FROM:		OFFICE
TO:		DIVISION
SUBJECT:		

SUMMARY

Page 2.

4) I believe a "side issue" is whether or not this drug represents a real "drug lag" item at this time. This question had been previously considered at your request and that of Dr. Finkel, and comments in this regard are contained in my earlier memo of October 6, 1975, and in Dr. Lidd's Addendum Medical Review of that same date. In these documents we noted that there is no substantial evidence, on a controlled clinical trial basis, to support the repeated suggestions that salbutamol aerosol possesses significant clinical advantages over currently recommended doses of metaproterenol aerosol, either from the standpoint of efficacy or from that of safety, including cardiac stimulatory effects.

J. Winkler, M.D.
November 4, 1975

cc: NDA 17-559
HFD-108
HFD-160
JWinkler,M.D.:HFD-160:11/4/75
Final typed nm 11/7/75
Doc.Rm.-160

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

MEMORANDUM OF MEETING

NDA 17-559
and IND 7542

November 4, 1975

Present: Schering Corp.:
Dr. Schimmel
Dr. Iazoni

and: Dr. Margaret Clark
Director, HFD-160

Subject: NDA 17-559 and IND 7542

I met with Dr. Schimmel and Dr. Iazoni of Schering Corp. with regard to these two products. They asked what was happening with regard to the Proventil inhaler application. I said that the Advisory Committee had made some preliminary recommendations with regard to labeling revisions and protocol for Phase 4 studies. The Committee is to meet again the first week in December and we have some final questions for them and we anticipate processing the NDA as soon as is feasible. I told them that they will have to do a long-term study as there is no information available on long-term use of the drug. I indicated that this can probably be handled as a Phase 4 project. They are concerned with regard to the type of protocol the Advisory Committee might like to see as they fear it might be too extensive. I assured them that FDA staff would also have input into this matter and we would not impose any unreasonable requests that would not be made of any other company.

They asked about the possibility of ordering the printing of the package insert. I informed them that they definitely should not do this as I knew that there was going to be one or two additional recommendations for revisions and they should wait for our advice in this matter.

We reviewed the chronology of studies being done on the Proventil tablet which is IND 7542. It was agreed that they do have an adequate plan of investigation under way with this drug.

The patients who have completed the double-blind studies and are being continued on the drug are also being continually studied. They are being tested at periodic intervals and the company anticipates that they will eventually have complete information with regard to the drug when used up to three years.

I also questioned the amendment which provides for comparing the drug when used with ephedrine or with theophylline. They clarified this matter and said that these were not combination drugs but rather the patient was on two separate medications. Dr. Iazoni raised the question of whether it

it might not be useful for a company to submit periodically a "road map" of where the status of the investigations were at any given point of time. I said that I thought that this might be a very useful document as we are frequently confronted with multiple amendments coming in within a short time span and it is difficult to keep track of everything that is going on with the investigation of a drug. If we had a broad outline of the status periodically it would be useful. Theoretically the annual progress report should provide this but in fact the reports rarely are done in such a way as to be helpful in this regard. Further, if a drug is under very active investigation a report at only a one-year time period may not be sufficient. Dr. Iazoni said that they would give more thought to this idea and I encouraged him to do so.

We briefly discussed beclomethazone and I reminded them that that was in HFD-150 and I only knew some of the peripheral matters regarding this application and they would have to discuss this with Dr. Gyarfas. We talked generally about the problems seen with the trachea in dogs and the fact that additional studies will no doubt need to be done in this area.

Margaret A. Clark, M.D.

Margaret A. Clark, M.D.

cc: NDA 17-559
IND 7542
HFD-108
HFD-160(2)
MClark,M.D.:HFD-160:11/4/75
Final typed from tape rm 11/5/75
Doc.Rm.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE November 11, 1975
FROM: Margaret A. Clark, M.D., Director HFD-160		OFFICE NDE
TO: John Winkler, M.D., Medical Officer HFD-160		DIVISION HFD-160
SUBJECT: NDA 17-559 Proventil		

SUMMARY

With regard to Dr. Miranda's Medical Review dated 7/30/75, I have the following suggestions:

1. Attached is an example of what might be used for the opening statements of the Medical Review. This information need not be presented in precisely this manner but should contain this type of information at the outset of the review. See attachment 1.

2. With regard to the review of the studies done by Drs. Dwek and Stein, the duration of the study should be stated. This might go in the section labeled "objective" or possibly at some other point in the description of the studies. The conclusions the reviewer reaches with regard to the studies should be expanded. At the time that this information was presented to the Pulmonary-Allergy Advisory Committee it was my understanding that Dr. Miranda was relying upon attached tables giving the results of these studies, and that this committee of experts could reasonably be expected to draw their own conclusions from these tables. However, whatever conclusions may be drawn from the tables should be clearly stated in the review at this point. If the tables are to be attached for additional reference material, they should be clearly labeled and referred to in the text of the review so that one can correlate the conclusions reached with the appropriate table.

3. For the multi-clinic study where 92 patients were involved, the results with regard to effectiveness of the drug should be stated in the review. The information on page 4 of the NDR of 7/30/75 conveys some of this information but this requires a clearer statement of the conclusions reached by the reviewer with regard to this data. Again, any reference to tables should be clearly set forth within the text of the review.

4. The section on page 5 which is entitled Clinical Studies, I believe was part of an earlier draft review and was not intended to be part of this review. At this point the information with regard to the third study involving 16 patients should be presented. The evaluation of the effectiveness of the drug as shown in the study of these 16 patients appears to be adequately described in this review. The adverse reactions should be more adequately described as they are for the multi-clinic study.

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/66)

5. There should be a section entitle "Review of the Literature". In this section Dr. Miranda might refer to the October 7, 1975 review which was done by Dr. David Lidd.

6. There should be a review of the package insert. If the package insert as submitted on August 14, 1975 is satisfactory except for the revisions recommended by the Advisory Committee, this may be so stated. We can further state that we will await the further recommendations of Dr. Plummer who has been asked to help us with this application.

7. The conclusions should clearly state what evidence has been provided from each study to support safety and/or effectiveness of the drug. Also, whatever conclusions may be drawn from the literature articles or with regard to labeling should be stated. There should be a final section entitled Recommendations. The content of this section will depend on the content of the section entitled Conclusions.

In your memo of 11/4/75 you recommend that any revisions of this review be brought to the attention of the Chairman of the Advisory Committee. I fully concur in this opinion and if this review can be revised prior to December 5, 1975 it will be presented to the Committee at that time. Please note that this is not a response to your 11/4/75 memo but merely concurrence with one of the recommendations you made in that memo.

I shall be willing to meet with you and Dr. Miranda to discuss this further if you so desire.

Margaret A. Clark, M.D.

Margaret A. Clark, M.D.

cc: NDA 17-559
HFD-160
MClark,M.D.:HFD-160:11/11/75
Final typed from tape nm 11/11/75
Doc.Rm. - 160

Recieved 11/17/75 and discussed with Dr Clark. Per discussion, the previously requested revisions of the M.O.R. of 7/30/75 is to be done by Dr. Miranda. This supercedes Dr Clark's previous memos to me dated Nov 5, 1975.

J Whitby
11/17/75

FINAL

FOOD AND DRUG ADMINISTRATION

BUREAU OF DRUGS

PULMONARY-ALLERGY AND CLINICAL IMMUNOLOGY ADVISORY COMMITTEE

December 5, 1975

Conference Room C
Parklawn Building
Rockville, Maryland

page 6-8

2nd meeting

MEMBERS OF THE ADVISORY COMMITTEE PRESENT:

Philip A. Bromberg, M.D. - Chairman
Gildon N. Beall, M.D.
Ronald I. Carr, M.D.
David A. Dolowitz, M.D.
Helen G. Morris, M.D.
Alan L. Plummer, M.D.
Sami I. Said, M.D.

MEMBERS OF THE ADVISORY COMMITTEE ABSENT:

Herbert C. Mansmann, Jr., M.D.

BUREAU OF DRUGS PERSONNEL IN ATTENDANCE:

Gerald M. Rachanow, Executive Secretary
Margaret A. Clark, M.D., HFD-160
John Winkler, M.D., HFD-160
David Lidd, M.D., HFD-160
Armando Miranda, M.D., HFD-160
Enrique Fefer, Ph.D., HFD-160

PUBLIC ATTENDEES:

None

87

80-211 O - 76 - 15

OPEN PUBLIC HEARING:

There were no public attendees present at this portion of the meeting.

OPEN COMMITTEE DISCUSSION:

No open committee discussion was scheduled on the agenda.

CLOSED PRESENTATION OF DATA:

No closed presentation of data was scheduled on the agenda.

CLOSED COMMITTEE DELIBERATIONS:

The Committee discussed and made its final recommendations concerning:

1. pending NDA 17-573,

2. pending NDA 17-559, and

3. the proposed package insert revision for cromolyn sodium capsules.

The Bronchodilator Clinical Testing Guidelines were deferred to the next meeting, which was tentatively scheduled for late March or early April 1976.

I certify that I attended the ninth meeting of the Pulmonary-Allergy and Clinical Immunology Advisory Committee of the Food and Drug Administration on December 5, 1975, and that these minutes accurately reflect what transpired.

Chairman Philip A. Bromberg
Philip A. Bromberg, M.D.

Executive Secretary Gerald M. Rachanow
Gerald M. Rachanow

The Committee recommended that all of the numbered paragraphs on page four as well as the first paragraph on page five be placed in the WARNINGS section. The Committee also recommended that all adverse reaction information which has been reported in man be placed in the ADVERSE REACTIONS section and that the FDA use its standard pregnancy warning statement for this drug. The Committee suggested that literature references directly keyed to the DOSAGE AND ADMINISTRATION section might be useful in this insert.

The adverse reaction data from the minutes of the April 1975 meeting of the Australian Drug Evaluation Committee were briefly discussed, but felt to offer little additional assistance.

The Committee concluded that this revised insert should be forwarded to the company for negotiation and that the Committee should not be involved in this negotiation.

Regarding the Phase 4 studies, the Committee was asked whether they desired to make any additional recommendations beyond those detailed on page 19 of the minutes of the last meeting. The Committee felt that they should only state that special studies of tissue with a view of defining the possible problem associated with the trachea should be conducted and that they need not specify what types of studies or stains should be used. A suggestion was made that a tantalum study of the tracheal-bronchial tree should be part of the tracheal dynamics studies in animals. Another suggestion was made that the FDA pharmacologist should check to see if mucociliary transport studies were done in animals, and if not done, such studies might be suggested to the company.

Regarding interaction studies with beta-adrenergic drugs, the Committee had previously concluded (page 19 of the minutes of the last meeting) that such studies would be desirable but could not be required for marketing approval. The Committee reemphasized that the company should be informed that we would like to have such data, especially interaction studies with beta-adrenergic drugs for cardiac toxicity (conducted in animals).

Proventil (albuterol) Inhaler - NDA 17-559

Dr. Beall announced (for the record) that he had participated in some of the early clinical investigations of Proventil, and he neither participated in the subsequent discussions nor voted.

Dr. Morris stated (for the record) that she did not agree with the previous Committee recommendation that this drug should be approved because the only long-term studies submitted in support of marketing approval totaled 12 days. This comment initiated a reevaluation of the Committee's recommendation to approve the drug for marketing.

Comments were made that the FDA was considering approving the drug with Phase 4 studies as the Committee recommended, but that the FDA felt it was impossible to label the drug for acute use only as the Committee had recommended.

A question was asked whether there really was a drug lag (i.e., the drug is marketed in a foreign country, but there is not a suitable alternative on the market in the United States) for Proventil. The conclusion was that metaproterenol was a comparable drug, that there was little difference between these two drugs as to duration of action and safety, i.e., cardiovascular side effects. It was noted that Proventil was somewhat longer acting than metaproterenol.

The Committee commented that approval of this drug now, when it does not have minimal required studies (i.e., long-term repetitive dose studies), would be a complete departure from the Bronchodilator Clinical Testing Guidelines which are being developed by the Committee. Comments were also made that if the FDA approved this drug on the basis of its limited study, what standards would be applied to other similar drugs being studied by other companies.

It was noted that the company had conducted some long-term studies previously, but these results had to be discarded because of delivery problems with the metered dose aerosol (i.e., could not accurately ascertain the amount of drug which the patient received). It was further noted that the company knew this a long time ago, yet has not initiated the necessary studies. The Committee concluded that there was a need for a chronic study to study tachyphylaxis and long-term toxicity.

The Committee concluded that there is convincing evidence that Proventil is an effective drug for acute use and for periods up to 12 days, that the drug would be marketable if it can be show that it retains its effectiveness for more than a very brief period of time and does not develop any undue toxicity under these circumstances, but that these facts do not obviate the need for the appropriate studies and that the company should be required to do a minimum three month long-term study.

The Committee noted that its previous recommendation to approve this drug had been made with considerable hesitancy and based on appropriate labeling being worked out. Since such labeling does not appear feasible, the Committee voted (six for, none against, one abstention) to reverse its previous recommendation and to now recommend that the NDA for Proventil not be approved at the present time because the company has not satisfied the minimal requirements for efficacy and toxicity. The Committee added that the double-blind toxicity and efficacy studies for a minimum of a three month period must be conducted and the results evaluated before approval of this NDA can be considered. Comments were made that this might take 1½ years.

The Committee evaluated a protocol which had been prepared as a Committee proposal for Phase 4 study of Proventil and recommended that this protocol (comparing Proventil to metaproterenol and/or isoproterenol) would be satisfactory for the FDA to use as a starting point or working guideline in discussing the three month required long-term studies with the company. It was suggested that FDA statisticians review the protocol to ascertain whether the number of patients listed therein (150) will be adequate, especially if a three compartment study is conducted. A suggestion was made that the body plethysmography test need only be done on some of the patients.

Cromolyn Sodium Capsules - NDA 16-990 and NDA 16-991

There were two major items for the Committee's consideration:

1. the companies' request to terminate the long-term follow-up studies of cromolyn sodium, and

2. the companies' request to expand the INDICATIONS section for this drug and other proposed package insert revisions, based on the Phase 4 data presented to the Committee at the April 30, 1975 meeting.

Regarding the long-term follow-up studies, the Committee concluded that because the blood pressure data reported were inadequate (there were no conclusions in older age groups) and there had been very minimal autopsy data reported, the companies should be required to continue to follow blood pressure and to report information on deaths in patients receiving cromolyn (autopsy reports if possible), particularly in children.

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-573
and 17-559

January 7, 1976

Between: Dr. Schimmel
Schering Corp.

and: Dr. Margaret Clark
Director, HFD-ϕ60

Initiated by: Dr. Schimmel (returned by Dr. Clark)

Subject: NDA 17-573 and NDA 17-559

I returned a call from Dr. Schimmel of Schering Corporation. He had called Mr. Rachanow yesterday to find out what recommendations the Pulmonary Advisory Committee had made with regard to the dog study and malformed tracheas in the study of beclomethasone. Mr. Rachanow had referred him to me. I explained to Dr. Schimmel that we did not have available as yet the minutes of the last Pulmonary Advisory meeting but that I was certain that they had recommended that there would have to be additional animal work done to clarify this situation. He asked if this would be work that could be done post approval of the drug. I said that I was moderately certain this was true, but reminded him that this drug is still being handled in HFD-150. He asked who he might talk to in that division to ascertain the status of this application and I suggested that he call Mr. Jerry Deighton who is the Supervisory Consumer Safety Officer.

I asked Dr. Schimmel if the DMF file they had submitted for Palacos Bone Cement included some pharmacology data. He said that he was sure it did contain some but he was not certain exactly how much or what type it was.

He asked me what information I could give him with regard to the Proventil application. I told him that we were waiting for the minutes of the Advisory Committee meeting and then we would have additional work to do on that application. He said that he was quite eager to be able to give his management some information. I said that I was aware of his situation but we had concentrated more of our time on getting reviews and data together for the beclomethasone on the assumption that that was the more significant drug from the clinical aspect. Dr. Schimmel said that he would have to agree that it was the more important of the two as there are other bronchodilators available.

We briefly discussed Dr. Koenig's IND for Palacos Bone Cement and then the conversation ended.

Margaret A. Clark, M.D. 1/7/76
Margaret A. Clark, M.D.

cc: NDA 17-573 &(17-559
HFD-108, HFD-160
HFD-150

/CLARK,MD.:HFD-160:1/7/76; Final Typed from Tape NM 1/8/76
1/7/76

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-559

January 20, 1976

Between: Dr. Schimmel
Schering Corp.

and: Dr. Margaret Clark
Director HFD-160

Initiated by: Dr. Schimmel

Subject: NDA 17-559

Dr. Schimmel of Schering Corporation called with regard to Proventil. He said that he understood that the minutes of the last Pulmonary Advisory Committee meeting had now been transcribed and he wondered what this application stood. I explained that we had been recently temporarily disrupted by having the offices painted. The minutes of the last Advisory Committee meeting had just been typed the end of last week. These will now have to go to the medical review staff so that they may continue their work on the application. Dr. Schimmel said that it was his understanding that the only remaining problem was any recommendations with regard to labeling. I said that without having the minutes at hand, or knowing the recommendations of the reviewing medical officer, I was not certain of the exact status of this application at the present time. He asked if he might call in a week to see where things were and I told him that I would be out of town but that he can call Mr. Nealey or Dr. Winkler who will be acting in my stead.

We discussed briefly the Beclomethasone application and I reminded Dr. Schimmel that the Kennedy Hearings started today and that any final letters probably would not issue in the next several days due to members of the Bureau of Drugs being downtown for the hearings. He said he had forgotten about that and thanked me for reminding him.

Margaret A. Clark, M.D.

cc: NDA 17-559
HFD-108, HFD-160(2)
MClark.M.D.:HFD-160:1 /20/76
Final typed from tape on 1/20/76
Doc.Rm. - 160

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-559 February 17, 1976

Between: Dr. Schimmel
Schering

and: Dr. Margaret Clark
Director, HFD-160

Initiated by: Dr. Schimmel (returned by Dr. Clark)

Subject: NDA 17-559

I returned a call from Dr. Schimmel of Schering with regard to this pending NDA. He wanted to know the present status of the NDA. I said that there was additional work to be done and such work was in progress. He said that he could not understand what was taking so long with our processing of this application. I explained that any package which goes forward to NDE or Bureau of Drugs must be of high quality and in the acceptable format and that this requires, at times, considerable effort and polishing of the writing. He asked if I could predict a date when it would leave the division level. I said that I would prefer not to predict any time limits on any pending applications as such predictions seem to be more frequently incorrect than correct. One cannot anticipate the time that any of the individuals working on a project will require in order to turn in a first-rate job.

Dr. Schimmel asked if it would do any good for him to call people in higher authority. I told him that in my opinion I did not see what good this would do but that was his perogative. He asked if he should, or could, talk with Dr. Winkler again. I suggested that he might give Dr. Winkler a ring next week. Dr. Schimmel indicated that he knew that Dr. Miranda was the reviewing medical officer.

Dr. Schimmel said that he had difficulty explaining to the people at his place the length of time that this has taken. I assured him that work was being done on the application and that it was not being ignored.

Dr. Schimmel indicated that he would call Dr. Winkler next week.

cc: NDA 17-559
HFD-108, HFD-160(2)
MClark,M.D.:HFD 160:2/17/76
Final typed from tape nm 2/20/76
Doc.Rm.-160

Margaret A. Clark, M.D.

MEMORANDUM OF TELEPHONE CONVERSATION

NDA 17-559
NDA 17-573

March 3, 1976

Between: Dr. Schimmel
Schering Corp.

and: Dr. Margaret Clark
Director, HFD-160

Initiated by: Dr. Schimmel

Subject: Pending NDA for Proventil

Dr. Schimmel of Schering Corporation called with regard to their pending NDA for Proventil. He said that when he talked to Dr. Winkler last week thatDr. Winkler told him they would have the final drafts ready for me this week and he wondered if I had them. I told him I did not have them as yet but it was my understanding that they would be coming to my desk shortly. I then explained that from here on in I would give him no further information with regard to the location of the application as it moved through the various stages except to tell him it was "under review". I explained to him the number of pending NDAs in any one division and if one multiplies this by six for all of the divisions we cannot expose Dr. Finkel or Dr. Crout's office to phone calls with regard to all of these pending applications. The lines of communication must remain between the sponsor and the division. He asked if I thought the application would be "under review" by the end of this week. I said that I hoped it would be. He seemed to understand our situation and my reasons for not giving him specific information as to whose desk held the application at any one moment.

With regard to Beclamethasone he said that they wished to make revisions in the proposed package insert that we had sent along with the approvable letter. One aspect revolved around the format and he wished to know if he should use the proposed new format or the one that is currently in use. He said that the Anti-Infective Division had advised him with regard to an application in their division to use the proposed new format. I said that I had not encouraged anyone to use the new one since it had not been finalized and I did not know whether the Office or Bureau would sign out approval letters with the new format but that I would check and find out about this and let him know. He pointed out that there were areas in the proposed package insert that we had given them that definitely needed some revisions, such as the Indications section which failed to clearly delineate the indication for the drug. I told Dr. Schimmel that I would find out about the format and call him back.

NDA 17-559
NDA 17-573

I discussed this matter with Dr. Crout and he said they definitely should use the old format and make as few revisions as possible so as to make it easier for us to handle the application expeditiously.

I called Dr. Schimmel and gave him the information with regard to format and holding revisions to a minimum. He said he would do so and get the labeling in in the next few days. I suggested that he put in his cover letter his reasons for the revisions he makes and also ask that we communicate with him if we have any trouble accepting their proposal. He said he would do so and thanked me for the information. He said he was now concerned about the format of the revised labeling he has pending in HFD-140. I told him that I would call Dr. Murl Gibson and let him know the gist of my conversation with Dr. Crout this morning. Dr. Schimmel thanked me for my help.

Margaret A. Clark, M.D.

Margaret A. Clark, M.D.

cc: NDA 17-559
NDA 17-573
HFD-108
HFD-160 (2)
MClark,M.D.:HFD-160:3/3/76
Final typed from tape nm 3/3/76
Doc.Rm.-160

Noted - With regard to Proventil Ltr Schimmel has misquoted me. I never told him anything would be any where by a specific time. I told him that the situation remained the same, that the review was still being worked on, and that we did have other work to do including a recently higher priority work assignment (per order from Mr Crout - memo of Feb 9, 1970). I told him that we hoped to have the Proventil finished at this level within a week. JWinbush 3/5/76

NDA 17-559 Date Completed: March 4, 1976

EXPANDED MEDICAL OFFICER'S REVIEW
(SEE ORIGINAL MEDICAL OFFICER'S REVIEW OF 7/30/75)

NAME OF DRUG: Proventil Inhaler, brand name of albuterol (generic) or salbutamol (generic)

COMPANY: Schering Corporation
80 Orange Street
Bloomfield, New Jersey 07003

DOSAGE FORM: Aerosol; 100 mcg. per actuation.

ROUTE: Oral inhalation

CLINICAL STUDIES:

Four studies were submitted in support of this NDA with the following labeling claims.

Actions - Albuterol is a beta-adrenergic agent with claims for direct, selective pharmacologic action on the smooth muscle of the bronchial tree. Inhalation of albuterol is said to promptly relieve bronchospasm and associated dyspnea and improve vital capacity in patients with reversible airway obstruction. Near maximum improvement in pulmonary function is said to occur within fifteen minutes of one or two inhalations of albuterol and to continue for four to six hours. Albuterol is claimed to exert comparable bronchospasmolytic action throughout the course of long-term treatment; tachyphylaxis has not been reported according to the sponsor. However as will be pointed out, none of the studies are designed in such a way as to enable one to evaluate this aspect.

The effect of albuterol on bronchial smooth muscle is said to be selective in that it acts primarily on the beta-2 adrenergic receptors; it is claimed to have little or no effect on the beta-1 adrenergic receptors of the cardiovascular system at the dosage used by patients. Tachycardia and blood pressure alterations have been reported to be minimal and infrequent following administration of the drug.

I. The first two studies were those of Drs. Joseph Dwek and Myron Stein. These were separate studies using the same protocol:

A. OBJECTIVE:

These studies were designed to compare albuterol aerosol (100 micrograms) with isoprotererol aerosol (100 micrograms) with regard to relative effectiveness, optimum dose range, pattern of PRN dosage and safety of medication when prescribed for use on a PRN basis in patients with reversible obstructive airway disease. The study was double-blind and conducted in a non-crossover manner with half the patients receiving albuterol and half isoproterenol. The study lasted 12 weeks (Dwek) and 13 weeks (Stein) and the patients were seen every 2 weeks. A total of 47 patients completed these trials, 21 in Dr. Stein's and 26 in Dr. Dwek's study.

B. PATIENT SELECTION:

1. Before being entered into the study, patients had to demonstrate a significant reversibility of bronchospasm defined as a 15% or greater improvement in FEV_1, FVC or $FEF_{25-75\%}$ after a screening dose of 140 mcg. of isoproterenol.

2. Patients with a primary diagnosis of asthma were studied. Some patients with other bronchospastic disease (chronic bronchitis and emphysema) who met the reversibility criteria were also enrolled in the study.

3. Patients were between the ages of 18 and 65. No pregnant women were treated. The following laboratory tests had to be within normal limits or accounted for by concurrent disease: WBC, fasting blood sugar, BUN, SGOT, alkaline phosphatase, and urinalysis. Patients were allowed to use the aerosol as needed but dosage was not to exceed three inhalations every four hours. Each patient was asked to keep a daily diary on which was recorded the following information:

   (1) Amount of medication taken of both the test aerosol and concurrent therapy.

   (2) An estimate of the onset and duration of effect of the aerosol.

   (3) Severity of symptoms, especially cough, sputum production, wheezing and shortness of breath.

   (4) A weekly assessment of overall symptomatology.

C. EVALUATION OF EFFICACY:

Both albuterol and isoproterenol aerosols were found on an objective basis per pulmonary function tests to be effective in relieving the symptoms of asthma on an acute basis (at 15 minutes post-drug.).

The subjective estimate of duration of relief from a single dose showed little difference between the two preparations (Dr. Dwek), according to the sponsor, except at the last revisit when the effects of albuterol lasted longer (5.5 vs. 3.5 hours). The mean time of onset in those who used albuterol was consistently less than in those using isoproterol. Patients generally reported that relief of symptoms of asthma began within 6 minutes of administration of the drug.

On a subjective basis only the duration of relief (mean time) calculated from the patient diary data and from the investigator's data showed the mean duration of effect for albuterol was up to twice as long as isoproterenol (Dr. Stein), according to the sponsor.

The pulmonary function tests (Table IA - Dr. Stein, Table 1B - Dr. Dwek) demonstrated a mean percent improvement in the three parameters measured for albuterol and isoproterenol, representing approximately equivalent bronchodilator activity at 15 minutes, the only time measurements were made.

According to the sponsor Dr. Stein's study suggests on the basis of subjective response data only that albuterol is of longer duration of action as compared with isoproterenol; however, this was not corroborated by Dr. Dwek's study utilizing the same protocol.

The evaluation of effectiveness in these two studies was based on the patient diary which was primarily a subjective one. The patients were seen by the investigator every two weeks; at which time they were examined and interviewed including a review of their daily diaries. The following subjective measurements of efficacy in the preceding two weeks were considered and entered on their case report form: degree of dyspnea, usual onset, duration and extent of relief attributed to the aerosol, the patient's and physician's impressions of the effectiveness of the aerosol. In addition, spirometry and single breath nitrogen washout were measured before and fifteen minutes following two inhalations of the test aerosol. At each revisit the patient was asked about possible adverse reactions. The laboratory tests were obtained prior to the trial and after one and three months of therapy. Chest x-ray and EKG were done before and at the termination of the study.

Dr. Dwek started with 30 patients, 19 female and 11 males ranging in age from 19 to 62 years. All patients had a primary diagnosis of asthma and the severity and the duration of the disease was moderate to severe and over one year. Of these, 26 patients completed the study; three patients who received isoproterenol were dropped from the study because of a paradoxical response to isoproterenol, and another patient assigned to albuterol expired after being in the study for four weeks. Autopsy revealed severe plugging of the bronchi by mucus.

Dr. Myron Stein had the same protocol as Dr. Dwek. He started with 22 patients and finished with 21. One patient was lost to follow-up.

D. CONCLUSION:

The design of these studies was not adequate in that it was lacking in adequate objective data, inasmuch as pulmonary function studies and cardiovascular evaluations were determined every two weeks only at 15 minutes post drug. Therefore, tolerance, tachyphylaxis, and efficacy of the drug after prolonged or repetitive usage could not be adequately determined objectively. It was adequate for determining an acute effect at 15 minutes only and adequately demonstrates this.

II. MULTI-CLINICAL STUDY:

The third study is designed as a double-blind, randomized, crossover investigation comparing albuterol vs. isoproterenol vs placebo and involving 92 patients up to the time of the last submission on July 30, 1975. This is a multi-clinic study from different parts of the nation and 6 different investigators.

A. The criteria for admission to the study are: age between 18 and 70 years with a primary diagnosis of reversible airway disease. When screened for admission FEV_1 should be 30 to 60% of mean predicted value and reversibility of airway obstruction must be demonstrable by at least 15% improvement in FEV_1 and 20% improvement in MMEF following two inhalations of isoproterenol aerosol.

Clinical laboratory studies included CBC, urinalysis, fasting blood sugar, BUN, SGOT, alkaline phosphatase, and a 12 lead EKG. Patients receiving concurrent therapy, including steroids are to be stabilized. The patients selected are studied on three days, each for six hours duration per day. One of the three test preparations (albuterol 85 micrograms per burst, isoproterenol 75 micrograms per burst, and placebo aerosol (vehicle for albuterol aerosol)) is administered by two inhalations on each of the days studied in random order. All brochodilator therapy including aerosols are withheld for at least six hours prior to the test period (12 hours for sustained acting preparations). If the patient is on systemic steroids, the therapy dosage schedule is not interrupted. If on alternate day therapy, the testing should be done on the off day. On each study day the patient is seen and examined by the investigator and the basic pulmonary function studies and clinical evaluations are done such as FVC, FEV_1 MMEF, heart rate, blood pressure, auscualtation, shortness of breath, wheezing, chest pains and cough. Following administration of the test preparation pulmonary function studies are repeated at 15 min., 30 min., 60 min., 90 min. 2, 4, 5, and 6 hours. Heart rate and blood pressure are measured

also at those intervals. The patient also scores the severity of his symptoms of shortness of breath, wheezing, chest tightness, cough, and presence of adverse reactions. The physician auscultates the chest of the patients at 2 and 4 hours after medication.

B. ADVERSE REACTIONS:

Tachycardia was noted in 12 patients after inhaling albuterol and in 12 patients after isoproterenol; blood pressure did not change significantly. Ectopic beats were reported in one patient with albuterol. Local adverse reactions such as moderate irritation of the mucous membrane, unpleasant taste and dry mouth was reported in several patients. Headache, dizziness, or lightheadedness was reported by one patient each.

C. PULMONARY FUNCTION RESULTS: (See Tables I-IV)

Table I presents the percent of patients per investigator showing a 15% or greater increment in pulmonary function with albuterol at 5 and 6 hours.

Table II demonstrates that the mean percent change in FVC from the last baseline is less than 15% at 4, 5, and 6 hours. Improvement greater than 15% is shown at 2 hours.

D. EFFICACY OF THE DRUG:

Pulmonary function studies (employing the above 15% criteria) demonstrates this drug to be effective for periods up to four hours if we use the FEV_1 evaluation, and for up to six hours if MMEF is used. Albuterol was shown to have a longer duration of action than isoproterenol or placebo (Tables II-IV).

E. CONCLUSION:

Albuterol has been shown on a one day acute basis study to be more effective than isoproterenol inasmuch as significant improvement in pulmonary function occurred for up to four to six hours when used in a single inhalation.

The number of patients (88) was adequate and the study protocol was adequate for this limited use (acute single dose) evaluation. Adverse reactions such as tachycardia occurred in 10-12% of the albuterol patients, as well as in the Isoproterenol patients, and local reactions such as mucous membrane irritation were also reported.

III. CLINICAL STUDY by Dr. George N. Bedell, University Hospital, Iowa.

A. DESIGN:

This is a double-blind randomized crossover investigation involving 16 patients and comparing albuterol with isoproterenol. The crossover study consists of two 12 day treatment periods during each of which one of the two test preparations (albuterol 85 micrograms per burst, isoproterenol 75 micrograms per bursts) is administered at random. On the first and last day of each treatment period the effect of a single dose (2 bursts) of the test preparation is assessed over the course of six hours.

The two treatment periods are separated by at least two days of washout.

Evaluations are made at baseline and 15, 30, and 90 minutes; and 2, 4, and 6 hours following drugs and consist of:

(a) Heart rate and blood pressure.

(b) FEV_1 FVC, and MMEF.

(c) EKG, a 12 lead baseline and rhythm strips, obtained at 30 minutes and two hours following drug administration.

(d) Entries are made of volunteered symptoms and observed signs. Overall evaluation of the status of the patients' bronchial asthma is made by history and physical examination, compared to baseline, and at two, and four hours following drug administration

B. ADVERSE REACTIONS:

1. Tables 19, 20.

These tables compare the adverse reactions of albuterol and isoproterenol. The Albuterol reactions occurred in 7 of 16 patients; these can be classified as headaches, nervousness and mucous membrane irritation. In the isoproterenol group the adverse reactions rate was 9/16 and these were similar in type with the exception of an incidence of tachycardia in this group (4 out of the 9 patients).

2. Tables 21A, 21B, 22A, and 22B.

These tables show signs and symptoms occurring with the use of albuterol and isoproterenol comparing day one and day twelve (day "12" = "evaluation day 2".).

C. EFFICACY RESULTS:

Improvement in pulmonary function of 15% or more from the baseline is used as the criteria of effective bronchodilation. In this study the pulmonary functions used were FVC (Forced Vital Capacity), FEV_1 (Force Expiratory Volume in One Second), and MMEF (Mid Maximal Expiratory Flow). Results were as follows:

1. MMEF: (See Tables V A and V B.)

On the first evaluation (day 1), the improvement in MMEF is sufficient to show marked bronchodilation. Only 2/16 or 12% of the patients show less than 15% improvement at six hours post Albuterol aerosol.

On the second evaluation, i.e., on day "12", at four hours 5/15 or 33% and at six hours 7/16 or 44% of the patients show less than 15% improvement. In other words 67% and 56% of the patients show significant improvement at four hours and six hours respectively with the Albuterol aerosol.

2. FEV_1: (See Tables VI A and VI B)

On day 1 there is significant improvement with abuterol up to two hours in 81% (13/16); at four hours, and six hours, 69% and 63% of the patients show improvement respectively; that is 11/16 and 10/16.

On day 12 at two hours 56% (9/16), four hours 47% (7/15), six hours 25% (4/16) show improvement more than 15% in bronchodilation, that is, by four and six hours 53% and 75% were below the 15% increment of improvement.

3. FVC: (See Tables VII A and VII B)

On the first evaluation of bronchodilation the 15% or greater improvement in FVC occurred in 19% of patients at the fourth hour and in 25% at the sixth hour.

On the second evaluation the improvement varied from 25% to 19%, starting at two hours and going up to six hours.

Vital signs such as blood pressure and heart rate showed a tendency to decrease but not outside of physiological ranges.

Evaluation of laboratory parameters such as hemoglobin, white blood cell count, eosinophil count, bilirubin, alkaline phosphatase, transaminases (SGOT, SGPT), blood urea nitrogen (BUN), fasting blood sugar, urinalysis and platelets all were within normal limits with minor variations of no significant pattern.

D. CONCLUSION:

The pulmonary function study using MMEF shows that 67% of the patients at 4 hours and 56% of the patients at 6 hours react with a bronchodilation greater than 15% from the baseline at day twelve on albuterol.

Two of the pulmonary function parameters used (MMEF and FEV_1) show that on day twelve the percent of patients that react with good bronchodilation (more than 15% of the baseline) is less than on day one at the 6 hour measurement.

This study is not adequate as support for this New Drug Application because the period of study lasted only 12 days. It is to be noted that in this study, pulmonary function was measured only on day 1 and day 12 and the number of patients studied was only 16. Due to the intended long-term repetitive use of this drug, adequately controlled long-term studies with an adequate number of patients and with adequate serial determinations of pulmonary function will be needed in order to evaluate tolerance, adverse reactions, and efficacy of the drug under the conditions of use proposed in the draft labeling.

OVERALL EVALUATION AND CONCLUSION:

At the present time the total controlled clinical studies in support of this application may be briefly summarized as follows:

1) Two single dose acute effect studies (Dwek and Stein) measuring objective reponse per pulmonary function at 15 minutes post drug only, plus subjective evaluations per patient diaries every 2 weeks over a 12 week period.

2) A multi-clinic acute effect study measuring the effect of this drug versus that of isoproterenol and versus placebo on a single day for each test drug or placebo. Measurement of pulmonary function was made for periods up to 6 hours.

3) A double-blind crossover study comparing albuterol versus isoproterenol in 16 patients over a 12 day test period for each drug, and with pulmonary function measured on day 1 and day 12 of each period and with a 2 day washout period between groups.

The sponsor should be advised that the application is not approvable at this time and of the need for adequately designed controlled clinical studies that would support the present proposed labeling for long-term repetitive use of this drug. This would require studies with at least 3 month treatment periods with adequately spaced clinical evaluation of the patients including adequate serial determinations of pulmonary function in addition to physical examinations and evaluations of subjective response.

We should suggest that they submit at their earliest convenience a proposed protocol for such studies for our review and constructive comments. The protocol recently prepared by Dr. Alan Plummer of the Pulmonary Advisory Committee should be forwarded to the sponsor for their guidance in preparing a protocol for long-term studies.

Review of the labeling is deferred pending completion of adequate clinical studies.

RECOMMENDATION:

The application is not approvable under Section 505(b)(1) and (6) due to the above considerations, specifically , a lack of any adequate well controlled, long-term repetitive dosing studies.

MAR 05 1976

A. Miranda, M.D.

cc: NDA 17-559 Orig.
HFD-160
HFD-108
R/D AMiranda (HFD-160) 2/27/76
R/D init. by: MClark 2/27/76
JWinkler 2/27/76
R/D typed by sm - 2/4/76
Revised R/D typed 2/27/76:jw
Final R/D signed by Dr. A. Miranda 3/4/76
F/T 3/5/76:jw Doc. Room

J Winkler 3/5/76
M Clark, MD 3/5/76

March 5, 1976

NDA 17-559
Proventil (albuterol)
Schering Corporation

RECOMMENDATIONS OF DIVISION DIRECTOR

This application is not recommended for approval under Section 505(b)(1) and (6) of the Act. The supervisory staff have accepted the recommendations of the reviewing staff with regard to this recommendation.

The application is not approvable pending further investigations in animals of the teratogenetic potential of this compound. Schering Corporation conducted studies in rats which did not reveal any teratogenic potential for the drug. Their studies using very high oral doses were associated with an unusual fetal head malformation in Stride Dutch rabbits treated with the drug. Studies conducted by another firm in which albuterol was administered orally and subcutaneously to mice revealed that those treated subcutaneously had an increased incidence of cleft palates and other external anomalies.

Further, this application lacks clinical studies of the long-term repetitive dose use of this drug, for which it is recommended. It is the opinion of the reviewing staff and the members of Pulmonary-Allergy and Clinical Immunology Advisory Committee that metaproterenol aerosol, which is marketed in the United States, is a suitable, similar, alternative drug (see NOR, October 7, 1975, and Minutes of Advisory Committee, December 5, 1975). The Committee recommended that this application not be approved at this time, and that additional studies of at least three-month duration be conducted.

Appropriate labeling for the drug will depend on the results of the additional studies noted above.

Margaret A. Clark, M.D. 3/5/76

Margaret A. Clark, M.D.

cc: NYK-do
NDA 17-559
HFD-1
HFD-100
HFD-160
HFD-616
R/D by MClark (HFD-160) 3/5/76
F/T 3/10/76:jw Doc. Room

NOT APPROVABLE

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4/12/76
FROM: M. J. Fiebel HFD 100		OFFICE
TO: J. R. Crout		DIVISION
SUBJECT: NDA 17-559 Proventil (albuterol) aerosol		

SUMMARY Not approvable letter. The chief reason is lack of long-term (3 mos.) controlled studies to determine tachyphylaxis and long-term tolerance. There actually was one 3 mo. controlled study but pulmonary function was measured only at the 15 minute interval after drug admin. in wk. 12 or 13, so was C-V effect. There were 8-9 mos. studies but they were done with a faulty release mechanism so dosage is in question.

At the Sept. 1975 meeting of Pulm.-All.-Immun.-Adv. Comm., the latter voted to recommend, with reluctance, approval of the drug for acute use only with labeling which would state that there were no adequate studies bearing on tolerance and tachyphylaxis with long-term use. Such studies would be required in Phase IV as a condition for approval. My recommendation to the Division was that such labeling was not proper because use of bronchodilators is not confined to acute attacks only and Proventil would be used chronically; we had to take a stand one way or the other.

At the Dec. 1975 meeting the Comm. again discussed Proventil. Because it was told that its suggested labeling was not desirable, it voted, with relief, to advise that the drug not be approved until the 3 mos. studies were completed. It felt that this is not a "drug-lag" drug that metaproterenol is similar though somewhat shorter acting and that there were no advantages with respect to C-V side effects. The minutes of these meetings can be found behind the letter. One can predict with a reasonable degree of accuracy that some tachyphylaxis will occur and that no new C-V effects will emerge; nevertheless, in the absence of the studies it is not possible to be sure.

SIGNATURE

DOCUMENT NUMBER

FD FORM 2054 (2/72)

NDA 17-559

APR 15 1976

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Schering Corporation
Attention: Edward R. Neary, M.D.
60 Orange Street
Bloomfield, New Jersey 07003

Gentlemen:

Reference is made to your New Drug Application dated December 26, 1973, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Proventil (albuterol) Inhaler.

We also acknowledge the receipt of your additional communications dated October 10, November 26 (two letters), December 11, 1974, January 31, February 6, 10, 21, July 30, August 7 and 14, 1975.

We have completed our review and find that the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

The application is inadequate under Section 505(b)(1) of the Act as follows:

It fails to contain adequate preclinical studies in support of the safe use of this product.

Animal reproduction studies recently submitted to the FDA included Segment II studies in which albuterol was administered orally and subcutaneously to mice. The latter route was associated with an increased incidence of cleft palates and other external anomalies in treated mice. We invite your comments with regard to this finding and we recommend that you undertake reproduction studies in the mouse to further evaluate the teratological effects of albuterol in this species. The use of control groups receiving other beta-adrenergic agonists should be considered. We shall be pleased to discuss with you an appropriate protocol for such studies.

The application is inadequate under Section 505(b)(1) and (6) of the Act in that it fails to contain adequate reports of investigations which have been made to show whether or not the drug is safe and effective for use as suggested in the proposed labeling.

Clinical studies submitted thus far have demonstrated a clinical effect on the basis of short-term or acute response only. There are no adequate controlled studies of the long-term repetitive dose use of this drug under conditions recommended in the labeling. Such studies are needed in order to evaluate safety and efficacy under the proposed long-term repetitive use, and are also needed in order to properly evaluate tolerance, tachyphylaxis and other aspects of your labeling claims. In this regard the application currently relies on three controlled repetitive dosing studies, none of which can be considered adequate, as follows:

1) The two separate studies by Drs. Dwek and Stein, respectively, utilizing the same protocol, although evaluating the drug over a 12-13 week period, employed objective measurements of pulmonary function only at a single point, 15 minutes following drug administration.

2) The study by Dr. Bedell, although including adequately spaced serial measurements of pulmonary function, from 15 minutes up to 6 hours following drug administration, is deficient in that pulmonary function measurements were made on only 2 occasions (day 1 and day 12) for a treatment period of only 12 days duration.

It is noted that in addition to the above limited studies of the repetitive use of this drug the application contains some data from a multiclinic study in which the effect of this drug was evaluated on the basis of a single day, single dose only.

It is suggested that you prepare and submit to your IND for this drug a protocol for such necessary studies for our evaluation and comment. This should provide for properly controlled studies with evaluation periods for this drug of at least three months duration with adequately spaced serial evaluations of objective response including pulmonary function studies, physical examinations (including adequate determinations of cardiovascular effects), and subjective response on the part of the patient.

With respect to these controlled studies it is our recommendation that this drug be compared with both isoproterenol and with metaproterenol. Such studies should provide the type of information that would be essential to the development of the most meaningful type of labeling information for this product in comparison with other available products.

Following submission of a proposed protocol our reviewing staff will be pleased to meet with you at your convenience for a discussion of the design and extent of studies that will be necessary.

We are deferring comment on the labeling at this time in view of the need for adequate long-term repetitive dosing studies as described above.

Since the application is inadequate under Section 505(b)(1) and (6) of the Act, it may not be filed as an application provided for in Section 505(b).

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized which represents the information necessary to remove all the deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be reevaluated, and within 60 days of the date of receipt of such request (or such additional period as you and we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc: NYK-DO
NDA 17-559
HFD-100 HFD-1
HFD-160
HFD-616
R/D by AJAronson(HFD-160) 3/8/76
R/D init. by: JKInscoe 3/8/76
RAJerussi 3/8/76
JWinkler 3/8/76
CMNealey, jr. 3/9/76
MClark 3/9/76
Mag Card II 3/9/76:jw Doc. Room

NOT APPROVABLE

Senator KENNEDY. That recommendation was turned down as well; is that correct? This, in effect, upheld the earlier recommendation?

Dr. WINKLER. This expanded review restated our earlier recommendation at the working level, at the medical officer level.

Senator KENNEDY. So that supports your position, as I understand it, basically?

Dr. WINKLER. Yes; this does.

Senator KENNEDY. It took a long time to get there, did it not?

Dr. WINKLER. Yes; it did.

Senator KENNEDY. Is that the usual pattern?

Dr. WINKLER. I'm not sure if it is usual or not. In this particular instance I think it is very unusual though.

Senator KENNEDY. Next is Dr. Johnson and Dr. Dols.

Were you told to affirmatively concur with a memo you did not agree with during conversation with Dr. Houweling, who called you at home?

Dr. JOHNSON. Sir, repeat that question.

Senator KENNEDY. Were you told to affirmatively concur with a memo you did not agree with during a conversation with Van Houweling, who called you at home?

Dr. JOHNSON. I had a call from Dr. Van Houweling at home.

Senator KENNEDY. When was that?

Dr. JOHNSON. In latter May of 1973, I believe.

Dr. Van Houweling was quite concerned because I had not given him an affirmative concurrence with the review that he had made.

I told him there were inaccuracies in it, points that I was in disagreement with, and that I could not agree with the memo that had been written, and that in the time that Mr. Dols and I had to respond to it, that it was impossible to cover the lengthy memo that had been written.

Originally, my memo consisted of 32 pages, and I think the response was composed of some 76 pages.

He said he did not want that sort of in depth review, that what he had in mind was a concurrence by me in writing, and then at a later date I could clarify the disagreement for discrepancies that had been noted by Mr. Dols and myself.

Very definitely he wanted a concurrence on it because he indicated that, well, without my concurrence it might take another 6 months for this review to pass through the agency, through our own bureau and through the Bureau of Foods.

I did not agree with that, and I might add that all of this urgency took place some 6 months at least after the memorandum was written,

so I question that there was a great deal of urgent interest in it as was indicated.

Also, I did offer to return from vacation, which I had just started, to assist in any way I could in clarifying the matters that had come up.

He said, "No, that was not necessary."

Senator KENNEDY. I think you stand by your previous testimony?

Dr. JOHNSON. Absolutely.

Senator KENNEDY. And you testified about being asked to agree to something that you did not agree with?

Dr. JOHNSON. Yes, sir.

Senator KENNEDY. Mr. Dols, do you stand by your previous testimony as well?

Mr. DOLS. Yes; I do.

I believe the subcommittee has a prepared statement already that I wanted to put into the record as a response to the Commissioner and Dr. Van Houweling's report on my testimony.

Senator KENNEDY. What we are trying to do, in light of yesterday's decision and in terms of the recent critique, is important. In their analysis, the Panel should understand that the previous testimony is reaffirmed, restated. We do not have to restate the factual circumstance, since Mr. Dols and Mr. Johnson have given us a statement that did that.

I think that the reaffirmation of previous testimony is important against the background of the previous review, Panel review, and other review.

Also, I think your restatement is really significant because we have gone through the details earlier on the particular facts of the situation.

Dr. Beaulieu, can you confirm that Dr. Johnson and Mr. Dols were not participants in the preparation of the memo—

Dr. BEAULIEU. Yes, sir, this is my understanding.

In the middle of March 1973, Dr. Gundlach and I were given the responsibility to collate and summarize comments which had been made by various persons within the Division of New Animal Drugs relating to the earlier memo.

We put all of those together and presented that rough document to Dr. Van Houweling.

To my knowledge, when I had that document neither Mr. Dols nor Dr. Johnson was involved in any way in its preparation.

[Information supplied for the record follows:]

PREPARED STATEMENT

BY

THOMAS J. DOLS

BEFORE THE

SUBCOMMITTEE ON ADMINISTRATIVE

PRACTICES AND PROCEDURES

SENATE

on

July 20, 1976

This statement responds to Dr. Schmidt's May 3, 1976 Report to this Committee and Dr. Van Houweling's March 13, 1975 report to the Commissioner on my January 29, 1975 testimony before this subcommittee.

This statement is composed of a general overview followed by a principle argument and eight other clarifying comments.

GENERAL OVERVIEW

I would agree with Commissioner Schmidt's written statement that, "There were essentially no important issues of facts being contested, any controversy involved primarily differences in judgement or in interpretation of known events."

PRINCIPLE ARGUMENT

One fundamental difference in interpretaion of the known facts that is repeatedly stated in Dr. Van Houweling's report is that my numerous references in the Johnson Memorandum to the need for more specific tissue residues methods and development of confirmatory methods was a conclusional policy decision on my part, that as yet had not been established as agency policy. This issue seems to be the central point of the rebuttal to my previous testimony.

1. Misinterpretation of Confirmatory Methods as New Policy

   This is a misinterpretaion of what the Johnson Memorandum was all about. My statements on the specificity of certain residue methods were scientific judgements on the adequacy of the method for enforcement of the established drug tolerance in a court of law. These scientific judgements were never meant to establish a policy of requiring confirmatory methods.

2. Definitions of Technical Terms

   The attributes of an analytical method; such as precision, accuracy, specificity, selectivity, limit of detection and sensitivity of the analytical function have been regorously defined by chemists. The term, "confirmatory method," is a colloquial term that has not been rigorously defined by chemists.

   The term confirmatory method can be loosely defined as an analytical procedure(s) that adds the attribute of specificity to an analytical result that has been obtained by a different analytical method which is lacking in the necessary specificity. In other words, the results from a method that can give a false positive (in whole or part) for the substance in question, can be supported in a court of law if the results of an adequate confirmatory method (involving different chemistry) reduce

the uncertainty of having a false positive response. The confirmatory method might consist of a number of separate tests.

The use of a confirmatory method is certainly not the only way to give specificity to the results. Another approach is to develop a single analytical method that has all of the necessary performance characteristics of a method; such as accuracy, precision, specificity and limit of detection. In other words, there is more than one kind of chemical logic to reach a decision that the substance in question, is, in fact, present.

3. Actual Use of the Term in the Johnson Memorandum

In the Johnson Memorandum I suggested the need to develop certain confirmatory methods, as the simplest and most convenient way to make certain existing NADA tissue residue methods supportable in a court of law. I never meant that was the only way. To imply that I was making policy about confirmatory methods is to miss the real problem and issue we were trying to bring to their attention in the Johnson Memorandum: that is, due to the lack of specificity in many of the NADA drug residue methods as determined by scientific judgement, we could not support legal actions to enforce these established tolerances. As a result, there were very few methods we could suggest for inclusion in the USDA monitoring program. If the Federal Regulations concerning NADAs needed clarification (the present regulations only state that the residue method be practical and sensitive), that was a policy issue for the agency to resolve. The Johnson Memorandum did not attempt to make this policy.

4. FDA Policy on Adequacy of Methods for Legal Action

FDA has always had a policy that in a legal case the analytical work performed must be adequate to support the findings in a court of law. If in the judgement of a chemist, the analytical work performed on a tissue sample in a compliance case can be faulted because the analytical method used has not been shown to be specific for the drug residue in question (the result could be false positive), it has always been the policy of FDA's General Council not to proceed with the case. An indication of this policy can be found in item 4 of Mr. Peter Hutt's April 21, 1975 memo to Dr. S. Gardner found in the Commissioner's May 3, 1976 Report.

When I was a part of the former Division of Veterinary Medical Review, I was the main chemist assigned to review the adequacy of analytical work performed on veterinary products that were involved in legal actions. The assignment included review of USDA analytical drug residue work that was to be used in legal cases, by FDA, to enforce the established drug tolerances. I reviewed each case on its own merits. Such scientific judgements cannot be considered the creation of agency policy. I was only carrying out my assigned job of giving chemical advise on the cases presented to me for review.

5. Interpretive Consequences Reached in the Johnson Memorandum

The Johnson Memorandum was just an extension of this type of review. I would have been derelict in my duty as a chemist, if I had recommended inclusion into USDA's monitoring program, of certain NADA residue methods that I knew would be inadequate to support their findings in a court of law. This is a matter of scientific judgement and not of creating policy. My scientific judgements in general, were later confirmed by the Ann Holt Committee that reviewed the Johnson Memorandum for the Commissioner's Office.

OTHER CLARIFYING COMMENTS

The following comments are in response to other conclusions reached in Dr. Schmidt's and Dr. Van Houweling's report.

1. The Johnson Memorandum was responsive to the assignment. On the basis of a review of the analytical methods, most NADA drug residue methods could not be suggested for inclusion into USDA's monitoring program. The volume of the drugs and withdrawal times would be of secondary importance until the methods are determined to be adequate. We presented the facts of the problem for further consideration.

2. The written distribution of the Johnson Memorandum was accepted procedure for a document that was expected to be discussed in future BVM staff meetings. The distribution included all of the Division Directors, Dr. Booth (the PMS project manager for the drug residue problem at the time), and Mr. Mallos (person responsible for writing BVM's Compliance Programs).

3. The inaccuracy Dr. Van Houweling eludes to: the listing of Bacitracin in the Johnson Memorandum as a drug that is misused may leave illegal residues in foods, is not an inaccuracy but a misinterpretation of what we wrote. On page 3 and 6 of our memorandum we listed Bacitracin under the heading, "Drug Residues Possible in Cattle (swine) Tissue as Listed in the Regulations." In other words, we are listing the drug residues that have a published tolerance (the definition in law of an illegal drug residue). We made no attempt to re-evaluate the accuracy of the published tolerances. Dr. Van Houweling in his statement has re-evaluated and drawn a conclusion on the accuracy of the published tolerance.

   An obvious error in the memorandum that Dr. Van Houweling did not mention in his report is the description of the carbadox residue method. I was referring to an earlier method before approval was given. The method approved in the Federal Register only involves one TLC clean-up step.

4. In my testimony, the statement "that I was not to be involved in the drug residue review," I was referring to the fact that I was not asked to clarify my scientific judgements nor asked what criteria I used to make my scientific judgements except in the Ann Holt Committee. The Harold memo to USDA was an administrative assignment with verbal instructions on how to write it. It was not initiated by me. In review of the Harold report, I was not allowed to discuss the conclusions which involved criteria for reviewing methods.

5. If Dr. Harold personally conferred with Peter Hutt on the conclusions in his report or not, I cannot verify. But he certainly announced to me that he would at the meeting. Then, very shortly thereafter, Mr. Peter Hutt's comments were made available.

6. The evidence for the secrecy in the preparation of the Harold report would not be in the written record. The personnel involved would have to be interviewed.

7. Documentation indicating my involvement in aiding EDRO in setting up Denver District as a Veterinary drug residue and feed laboratory is attached.(A).

8. My transfer back to DVMR took place after my testimony even though I was informed and discussed it with Dr. Van Houweling before the testimony. The transfer order is attached(B). In neither transfer had I ever requested it on my initiative. I think what is interesting is the timing of each transfer. Shortly after Ann Holt's staff paper on the Johnson memorandum which did not support Dr. Van Houweling's position at that time, I am transferred to DNAD where I no longer will be reviewing the adequacy of the analytical work involved in Veterinary product compliance cases (including charges involving drug residue reports from USDA). At the time of the original transfer, the time of stay is vague and undefined. Most of the other transfers Dr. Van Houweling refers to were permanent. Then, just before my testimony on January 29, 1975, I am reminded that my first transfer was only temporary and I am to be transferred back to my old position. Previous to this time, Mr. Kovach had made it known through many channels that he wanted to be transferred back to DNAD but to no avail.

I have no other comments to offer on Dr. Schmidt's and Dr. Van Houweling's reports concerning my previous testimony.

Therefore, I stand on my previous testimony.

I respectively submit this prepared statement to this committee.

Sincerely yours,

Thomas J. Dols

Thomas J. Dols

Attachment A

SEP 10 1971

MEMORANDUM OF CONFERENCE

PRESENT: ACFC
H. P. Eiduson
P. E. Corneliussen

DVMR/BVM, VM-400
N. Ettelstein
T. J. Dols

We (Ettelstein and Dols) called the conference with Eiduson and Corneliussen to get more information on our assignment for compiling information on a survey of drug residues in foods of animal origin. Mr. Eiduson informed us that their request for lists of drug priorities was generated by orders from Mr. Paul Hile. Mr. Hile desires to have Denver District Office to begin functions as soon as possible as central for assay of drug residue.

At this point, Denver District has no prior expertise in assay of either drug residues in foods or medicated feeds. They need BVM's help in defining all of the drug residues to be expected in animal tissue and an order of priority. Along with this ranked list, they need copies of the methods of analysis. They are also interested in a list of the most pressing problems in pre mixes and medicated feeds with methods so they can start collecting the necessary apparatus and reagents. We agreed to supply methodology and to get reference standards. They will take the information in parts instead of waiting for the complete list. As to the total diet, they are only interested at this time in a report on the feasibility of including veterinary drug analysis on the present group I and II of the total diet.

It was made clear that, at this time, Denver District was not set up to do microbiological methods for antibiotic residues. They would send the samples to antibiotic certification for analysis.

T. J. Dols
Chemist, DVMR/BVM

cc: Dr. Johnson, VM-400
Dr. Cazier, VM-400
Mr. Eiduson, CF-30
Mr. Corneliussen, CF-30
DVMR, VM-400
CA-224 VM-13

VM-400: TJDols: NEttelstein: mb: 9/14/71
R/D typed: as: 9/13/71

MEMORANDUM OF CONFERENCE

October 4, 1971

CONFEREES: H. P. Eiduson, EDRO, CF-30
D. E. Root, DEN-DO

and

Nathan Ettelstein, VM-400
Thomas J. Dols, VM-400

SUBJECT: Tissue Residue Assay

We met with Mr. Eiduson and Mr. Root to discuss the nature of additional assistance that DVMR could provide to facilitate initiation of operations of the new Tissue Residue Analysis Laboratory within DEN-DO.

Mr. Eiduson and Root acknowledged an appreciation of the material that we had already supplied and asked us to send as many remaining NADA analytical methods as we could obtain. We agreed to do so. We mentioned that the methods are considered confidential in accord with regulation 135.33, and they said that they are aware of this requirement.

We discussed, briefly, the draft program for sampling tissues for residue assays. We suggested that some consideration be given for sampling and assaying tissues of animals that receive medicated feeds that have no withdrawal time requirement.

Mr. Root discussed cooperation with C&MS inspectors and asked whether there is an interdepartmental or interagency agreement in affect as a basis for cooperation. We said that we could inquire into the matter and provide DEN-DO and EDRO with our results.

We also stated that we will initiate a program to assemble a library of reference standards for the laboratory.

In closing, we briefly discussed the developing problem of illegal use of chloramphenicol in beef cattle.

cc: Dr. Johnson, VM-400
Dr. Cazier, VM-400
Mr. Eiduson, CF-30
Mr. Root, DEN-DO
Mr. Dols, VM-400
DVMR, VM-400
CA-224
VM-13

Nathan Ettelstein

Thomas J. Dols

NEttelstein:TJDols:jm: 10/7/71

Dr. C. D. Van Houweling, Director
Bureau of Veterinary Medicine, VM-1

November 11, 1971

Acting Director
Division of Veterinary Medical Review, VM-400

Drug Residue Analysis in the Market Basket Survey

We reference your comment of November 3, 1971, concerning Mr. Grant's question on feasibility of including drug residues in the market basket survey.

On September 10, 1971, the chemists from the Division of Veterinary Medical Review met with Mr. Eiduson and Mr. Corneliussen of EDRO to discuss a survey of drug residues in foods of animal origin. Subsequently, a September 17, 1971 memorandum to EDRO explored the Feasibility of Monitoring the Market Basket for Veterinary Drug Residues in Food of Animal Origin. This memorandum pointed up the need for a separate sampling and compositing scheme and a need for additional work in some analytical screening methods. However, we felt that such a survey could be practically implemented once these details could be worked out. We do recognize that such a program will involve considerable amounts of money and manpower.

On September 22, 1971, and October 19, 1971, additional memoranda concerning methodology were sent to Mr. Eiduson, EDRO. Again on November 9, 1971, EDRO personnel met with Mr. Ettelstein and Mr. Dols for the purpose of discussing methodology, not necessarily for a market basket approach, but for general input into the activities directed toward establishing Denver District Office as the center for drug residue assays.

The market basket feasibility study described in our memorandum of September 17, 1971, is now in the hands of EDRO. We have indicated to EDRO that we are available for further consultation or input as EDRO desires.

Copies of the materials cited in this memorandum are attached for your information.

P. D. Cazier, D.V.M.

Attachments

cc Mr. Ettelstein, VM-400
Dr. Johnson, VM-400
Dr. Cazier, VM-400

DVMR/VM-400
CA-224
VM-13

GBGuest:sk 11/10/71

Mr. Hyman P. Eidson, EDRO/FSC, CF-30 SEP 16 1971

Dr. K. F. Johnson, DVMR/BVM, VM-400

Veterinary Drugs Used in Food Producing Animals

Given in Appendix A, is a complete list of the veterinary drug residues potentially possible in tissues as grouped by animal species (including milk and eggs), without ranking by priority. This list may be expanded later, if necessary.

The provisional categories given below are an attempt to put the possible drug residues in a descending order of priority insofar as monitoring is concerned. The analytical methods will follow in another memorandum.

Category I: Those drugs that are heavily used and whose residues, if occurring, might pose ahhealth hazard.

a. Penicillin in milk - with the known anaphylatic reaction of penicillin in some people, knowledge of this residue is of high priority.

b. Diethylstilbestrol in beef tissue - is extensively used as a growth promotion drug for cattle and sheep only. It is given in feed or implanted but not approved for use by both routes simultaneously. Violation of these conditions might result in residues in the edible tissues.

c. Melengestrol acetate in beef tissue from heifers - same conditions and reasons for inclusion as stated for (b) except it is not approved as an implant.

d. Dienestrol diacetate in chicken and turkey tissue - same conditions and reasons for inclusion as stated for (b) except it is not approved as in implant.

e. Estradiol Benzoate in beef and lamb tissue - same conditions for inclusion as stated in (b), but, it is for subcutaneous use injection only (at the base of skull).

f. Estradiol monopalmitate on roasting chickens - subcutaneous injection (at the base of skull).

g. Furazolidone in chicken and turkey tissue - is used for growth promotion, increased egg production, prevention of coccidiosis, blackhead and typhoid. Furazolidone is also used in swine for growth promotion and prevention of bacterial enteritis. This drug has recently become a suspect carcinogen.

h. Nitrofurazone in chicken and turkey tissue - is used for prevention coccidiosis. Nitrofurazone in swine for treatment of necrotic enteritis. Same reasons for inclusion as stated for (e).

i. Nithydrazone in chicken tissue - is used for prevention of pullorum disease, fowl typhoid, coccidiosis, blackhead. Same reasons for inclusion as stated in (e).

j. Arsenicals (arsanilic acid, carbarsone, roxarsone, 4-nitrophenylarsonic acid, and sodium arsanilate) in chicken, turkey and swine tissue and measured as total arsenic. They are used for growth promotion and prevention of coccidiosis and blackhead. The extensive use of these drugs combined with potential for abuse of the withdrawal time could result in a residue in the tissue.

k. Sulfamethazine in beef and swine, (measured as Sulfonamides) - is used for prevention of weight loss due to cattle shipping fever, and swine enteritis. The extensive use of this drug combined with potential abuse of withdrawal time, could create a residue in the tissue.

Category II: Antibiotic Residues in Tissues:

a. Penicillin (in all foods)
b. Bacitracin (in all foods)
c. Streptomycin (in chicken, eggs, turkey and swine)
d. Tetracycline (in all foods)
e. Chlortetracycline (in all foods)
f. Chloramphenicol (in milk)
g. Novobiocin (in all foods)
h. Oxytetracycline (in all species of animal tissue)
i. Tylosin (in all foods)
j. Monensin (in chickens)
k. Erythromycin (in all foods except swine)
l. Hygromycin B (in chicken, egg, swine)
m. Lincomycin (in chicken, swine, and milk)
n. Nystatin (in chicken, eggs, swine)
o. Polymyxin B (in milk)
p. Spectinomycin (in chicken)
q. Oleandomycin (in chicken and turkey)
r. Neomycin (in veal and milk)
s. Sulfomyxin (in beef)
t. Ormetoprim (in chicken) (put in category III)

u. Carbomycin (in chickens)
v. Dihydrostreptomycin (in milk)

Category III: Other extensively used drugs that have a residue tolerance (like coccidiostats, blackhead treatments, anthelmintics, sulfonamides, and implants).

a. Bonnel (in milk)
b. Amprolium (in chicken and eggs)
c. Thiabendazole and phenothiazine (in beef, swine, lamb, milk) alkomide
d. Zoalene and its metabolite,
e. Clopidol (in all feeds of animal origin)
f. Buquinolate (in chicken and eggs)
g. Nequinate (in chicken)
h. Decquinate (in chicken)
i. Ethopabate (in chicken)
j. Levamisole (in beef)
k. 2-acetylamino-5-nitrothiazole (in turkey)
l. Other sulfonamide (such as sulfanitran in beef, chicken, swine)
m. Dichlorvos (in swine)
n. Haloxon (in beef)
o. Coumaphos (in beef)

Category IV: Specialized use drugs whose residues might pose possible hazards.

a. Medroxyprogesterone acetate (in beef)
b. Chlormadinone acetate (in beef)
c. 3, 5-dinitrobenzamide (in chicken)
d. Zeranol (in beef and lamb)
e. Progesterone (in milk and beef)
f. Testosterone (in beef)
g. Testosterone propionate (in beef)
h. Hydrocortisone (in milk)
i. Prednisone (in milk)
j. Prednisolone (in milk)
k. Methylprednisolone (in milk)

Category V: Minor Drugs not Classified Elsewhere.

a. Reserpine (in turkey)
b. Griseofulvin (in all species, and especially turkey and milk)
c. Promazine andoother tranquilizers

The categories above are for possible drug residues in food, but we also have a list of situations in medicated feeds that are economic in nature. The items of this list are all equal in priority.

a. Shell Chemical's Atgard C and V (dichlorvos) premix for swine. This anthelmintic has a stability problem in the presence of moisture.

b. Shell Chemical's Equigard (dichlorvos) pouches.

c. American Cyanamid's Aureo A-S 250 premix crumblesA(penicillin, CTC and sulfamethazine) the CTC is suspected to be very unstable in the crumbles process.

d. Bonnel premix

e. Coumaphos premix

f. Tylosin premix and finished feed, this antibiotic is not being checked at this time.

g. Oleandomycin in finished feed. We know that Pfizer's method is not able to achieve the approved ± 15% tolerance limits and would need over ± 35% tolerance limits, which is too large a variation for efficacy.

For your convenience, we have included Appendix B, a summation of the most common withdrawal periods.

Consumer and Marketing Service in USDA at present has continuing sampling programs for the following residues in samples that their meat inspectors randomly and selectively collect at the various slaughter houses:

a. Total arsenic in chicken and swine
b. DES in beef
c. Sulfonamides
d. Chlortetracycline
e. Oxytetracycline
f. Penicillin
g. Streptomycin
h. Neomycin
i. Erythromycin
j. Tetracycline
k. MGA (will start up again soon) in beef

The methodology they are using will be sent later.

At present time, Mr. ~~Malanoski~~ E. Dalton at C&MS and Mr. Glen George at Salsbury Co. are in the process of collaborating their separate methods for total arsenic in tissue for AOAC and are both in need of collaborating laboratories. Denver laboratory may want to be a collaborating laboratory.

cc: Dr. Johnson, VM-400 DVMR, VM-400 NEttelstein:TJDols:jm: 9/15/71
Dr. Cazier, VM-400 CA-224 VM-13
Dr. Weisenburger, VM-400
E. Dalton, VM-400

E. P. Johnson, DVMR

Appendix A

List of Drugs Used in Food Producing Animals (1)

If these drugs are misused, they may leave illegal residues in foods of animal origin.

A. Drug residues possible in cattle tissue.

1. Diethylstilbestrol
2. Bacitracin
3. Chlortetracycline *
4. Oxytetracycline
5. Tylosin
6. Chlormadinone acetate
7. Sulfamethazine
8. Progesterone
9. Testosterone propionate *
10. Estradiol benzoate *
11. Erythromycin
12. Sulfaethoxypridazine *
13. Thiabendazole
14. Medroxyprogesterone acetate
15. Testosterone
16. Malengestrol acetate
17. Clopidol
18. Levamisole hydrochloride
19. Zeranol
20. Haloxon
21. Penicillin
22. Coumaphos
23. Famphur
24. Dihydrostreptomycin **
25. Chlorhexidine **
26. Neomycin **
27. Tetracycline
28. Promazine Hydrochloride

Note (1) This list is not ranked by priority.

Note * Residue also possible in veal tissue.
Note ** Residue expected only in veal tissue.

B. Drug residues possible in poultry tissue.

1. Buquinolate *
2. Bacitracin
3. Reserpine
4. Oleandomycin
5. Zoalene
6. Chlortetracycline
7. Amprolium *
8. Hygromycin B
9. Streptomycin
10. Penicillin
11. Novobiocin
12. Oxytetracycline
13. Tylosin
14. Nystatin *
15. Nihydrazone *
16. Ethopabate *
17. Spectinomycin *
18. Total arsenic
19. Erythromycin
20. Estradiol monopalmitate *
21. 3,5-Dinitrobenzamide *
22. Sodium Sulfachloropyrazine *
23. Carbomycin *
24. Sulfadimethoxine *
25. Sulfomyxin
26. Sulfanitran *
27. Aklomide *
28. Metoserpate hydrochloride *
29. Clopidol *
30. Lincomycin *
31. Monensin *
32. Decoquinate *
33. Racephinicol *
34. Ormetoprim *
35. Dienestrol diacetate
36. Nequinate *
37. Furazolidone
38. Nitrofurazone
39. Dimetridazole **
40. 2-acetylamino-5-nitrothiazole **
41. Tetracycline
42. Promazine Hydrochloride
43. Ipronidazole **

Note * Residues expected only in chicken tissue
Note ** Residues expected only in turkey tissue or eggs

C. Drug residues possible in swine tissue.

1. Bacitracin
2. Chlortetracycline
3. Hygromycin B
4. Streptomycin
5. Penicillin
6. Novobiocin
7. Oxytetracycline
8. Tylosin
9. Nystatin
10. Sulfamethazine
11. Total arsenic
12. Sulfaethoxypridazine
13. Furazolidone
14. Thiabendazole
15. Clopidol
16. Lincomycin
17. Dichlorvos
18. Nitrofurazone
19. Tetracycline
20. Promazine Hydrochloride

D. Drug residues possible in lamb tissue.

1. Diethylstilbestrol
2. Progesterone
3. Estradiol benzoate
4. Thiabendazole
5. Medroxyprogesterone
6. Clopidol
7. Levamisole hydrochloride
8. Zeranol
9. Haloxon

E. Drug residues possible in farmed fish tissue.

1. Oxytetracycline
2. Sulfamerazine

F. Drug residues possible in milk

1. Hydrocortisone
2. Bacitracin
3. Chlortetracycline
4. Penicillin
5. Novobiocin
6. Tylosin
7. Dihydrostreptomycin
8. Ronnel
9. Furaltadone
10. Neomycin
11. Chlorobutanol
12. Salicylic acid
13. Erythromycin
14. Sulfaethoxypridazine
15. Prednisolone
16. Thiabendazole
17. Prednisone
18. Methylparaben
19. Propylparaben
20. Ethylenediamine
21. Medroxyprogesterone acetate
22. Hexachlorophene
23. Phenothiazine
24. Sulfadimethoxine
25. Clopidol
26. Lincomycin
27. Polymyxin B
28. Methylprednisolone
29. Diethylstilbestrol
30. Famphur
31. Tetracycline

G. Drug residues possible in eggs

1. Buquinolate
2. Bacitracin
3. Reserpine
4. Chlortetracycline
5. Amprolium
6. Hygromycin B
7. Streptomycin
8. Penicillin
9. Novobiocin
10. Tylosin
11. Nystatin
12. Nihydrazone
13. Total arsenic
14. Erythromycin
15. Dinetridazole
16. Furazolidone
17. Nitrofurazone
18. Tetracycline

Mr. Hyman P. Eiduson
FSC/EDRO, CF-30
Through: Dr. K. F. Johnson
DVMR/BVM, VM-400

SEP 22 1971

Chemists, DVMR/BVM, VM-400

Methodology for Veterinary Drugs in Foods of Animal Origin. (Refer to previous memorandum on Veterinary Drug Listing by categories dated September 16, 1971.)

Some of the methods given here for analysis of drug residue in foods of animal origin, will not be able to be used by Denver District in their laboratory, but they are listed here so you will be aware of the problem areas in methodology. You should be aware that FDA in June 1971 have let out research contracts on DES, MGA, nitrofurans and phenothiazine residue in tissue methodology. Dr. Mercer, VM-500, in BVM is the contact officer.

You should also be aware that C&MS/USDA Laboratory manual on residue methods is being revised and will be available after publication sometime in October.

Attached, is a complete list by categories of drug residue and feed methodology except for these methods that are in the appropriate NADA. That list of methods will follow in another memorandum.

Category I

A. Penicillin in milk - AOAC XI Ed. 16.100.

B. DES residue in cattle tissue.

1. Official method is in 21 CFR 135g.26 (quantitation by Umberger's mouse uterine weight test and qualitative identification of DES by paper chromatography). This method is sensitive to 2 ppb depending on the standard deviation in the experiment.

2. Uncollaborated quantitative methods in Food Additive Analylical Manual.

a. Method II a - (colorimetric determinative step).

b. Method II b - (fluorometric determinative step).

3. A representative of Denver District attended the Workshop on DES Methodology held at Eli Lilly & Co. in July 1971 and observed operation of Elanco's new DES residue method (Enzymatic hydrolysis of bound DES and ec-GLC determinative step). This method has not yet been submitted as a supplement to Elanco's NADA and, therefore, it has not been validated even though Consumer & Marketing Service in USDA is at present using a similar method if not the same.

C. MGA residue in cattle tissue.

1. Official method is in 21CFR 135g.56. (Organic solvent extractions; silica gel column clean-up; spotted on TLC and extracted MGA spot injected into a FID-GLC for determination.) This method has reported sensitivity to 25 ppb in tissue.

2. Upjohn has supplemented their NADA 39-402 with a new residue in tissue method (shorter clean-up steps and ec-Ni^{63}-GLC determinative step). This method has not yet been validated nor approved by FDA.

D. Total arsenic residue in chicken and swine tissues. At present, we do not have an official method. Mr. E. Dalton at C&MS/USDA is presently completing an AOAC collaborative study on their method /dry ash; and arsine evolution and Molydenum blue colorimetric or flame atomic absorption (of the arsine) determinative step./ For your information a copy of the atomic absorption method is attached. Mr. Glen George at Salsbury Laboratory, Inc. is doing an AOAC collaborative study on his method (dry ash; arsine evolution and diethyldithiocarbamate colorimetric determinative step).

E. Dienestroldiacetate residue in tissue-official method is in 21CFR 135g.46 (mouse uterine weight test).

F. Estradiol Benzoate and monopalmitate residues-official method is in 21CFR 135g.30 (mouse uterine weight test).

G. Sulfamethazine residue in tissue (measures total sulfonamides). NADA method in Food Additives Analytical Manual (Bratton-Marshall colorimetric determinative step). C&MS/USDA is presently using (in general) the same method.

H. Furazolidone residue in swine tissue. The present NADA method is in Food Additives Analytical Manual (conversion to 5-nitro-2-furfuraldehyde phenylhydrazone and colorimetric determinative step).

I. Furaltadone residue in milk. The present NADA method is in Food Additives Analytical manual (casein ppt.; adjust pH; extract with $CHCl_3$ and back extract into 0.1 NHCl for scan of color absorption.

J. Nihydrazone residue in chicken tissue and eggs.--Enclosed is the chicken tissue method in NADA 13-200 and 13-195. Method is similar to method for H. We have not been able yet to locate the residue method for eggs.

K. Nitrofurazone residue in chicken and swine tissue - use same methods as in H. and J. The four nitrofurans (H., I., J., and K.) listed above are presently suspected to product tumors. New and more sensitive milk and tissue residue methods have recently been submitted as supplements to the appropriate NADA's and are being reviewed by FDA.

Category II

A. NCAA/OPRT's report, "Antibiotic Residues in Milk, Dairy Products and animal tissues: Methods, Reports, and Protocols," October 1968, gives microbiological methods for identifying and quantitating: Penicillin, Bacitracin, Chlortetracycline, Oxytetracycline, Tetracycline, Streptomycin, Dihydrostreptomycin, Neomycin, Polymyxin, Erythromycin, and Novobiocin.

B. C&MS/USDA's Laboratory Procedures include microbiological methods for identifying, quantitation and conformation of: Penicillin, Tetracycline, Chlorotetracycline, Striptomycin, Oxytetracycline, and Neomycin. They also have a paper and thin layer Chromatographic methods for the tetracyclines in tissue. C&MS/USDA's methods are attached.

C. Other antibiotic drug residue methods are in their appropriate NADA. They will follow in another memorandum.

1. Tylosin
2. Monensin
3. Hygromycin B
4. Lincomycin
5. Nystatin
6. Spectinomycin

page 4

7. Oleandomycin

8. Sulfonmyxin

9. Carbomycin

10. Chloramphenicol

11. Griseofulvin

Categories III, IV, and V drug residue methods that are official.

1. Progesterone in cattle tissue and milk-official method is in 21 CFR 135g.23 (bioassay)

2. Testosterone propionate in cattle tissue-official method is in 21 CFR 135g.29 (bioassay)

3. Testosterone in cattle tissue-official method is in 21 CFR 135g.53 (bioassay)

4. Chlormadinone in cattle tissue-official method is in 21 CFR 135g.23 (ec-GLC method)

5. Medroxyprogesterone Acetate in cattle tissue-official method is in 21 CFR 135g.49 (paper chromographic method)

6. 3,5 - Dinitrobenzamide in chicken tissue-official method is in 21 CFR 135g.45 (colorimetric method)

7. Zeranol and AHOT in cattle and lamb tissue-official method is in 21 CFR 135g.64 (TMS derivative formation and FID-GLC method) and AOAC XI 37.001 and 37.018

8. Dpronidazole in turkey tissue-official method 21 CFR 135g.43 (FR May 13, 1971) method 21 CFR 135g.43 (Ni^{63}ec-GLC method).

The other drug residue methods for Categories III, IV, and V.

1. Ronnel (in milk) - FAAM*

2. Amprolium (in chicken tissue and eggs) - FAAM

3. Thiabendazole (in swine tissue) - FAAM

*Your copy of the FAAM should have been revised up to February 1969.

4. Phenothiazine (in tissue and milk)-method in NADA.
5. Alkonamide(in tissue and milk)-FAAM.
6. Clopidol (in tissue)-FAAM.
7. Buquinolate (in chicken tissue and eggs)-FAAM.
8. Nequinate (in chicken tissue)-method in NADA.
9. Decoquinate (in chicken tissue)-method in NADA.
10. Ethopabate (in chicken tissue)-FAAM.
11. Levamisole Hydrochloride (in cattle tissue)-method in NADA.
12. 2-Acetylamino-5-nitrothiazole (in turkey tissue)-method in NADA.
13. Sulfaethoxypridazine (in cattle tissue)-FAAM.
14. Sodium sulfachloropyrazine (in poultry tissue)-FAAM.
15. Sulfadimethoxine (in poultry tissue)-method in NADA.
16. Sulfanitran (in tissue)-method in NADA.
17. Sulfamethazine (in tissue)-FAAM.
18. Sulfamerazine (in farmed fish tissue)-method in NADA.
19. Dichlorvos (in swine tissue)-method in NADA. (attached) ~~FAAM~~
20. Haloxon (in cattle tissue)-method in NADA.
21. Coumaphas(in cattle tissue)-method in NADA.
22. Famphur (in cattle tissue)-method in NADA and PAM I.
23. Ormetoprim (in chicken tissue)-method in NADA.
24. Prednisone (in milk)-FAAM.
25. Methylprednisolone (in milk)-method in NADA.
26. Prednisolone (in milk)-method in NADA.
27. Flormethesone (in milk)-method in NADA.

page 6

28. Hydrocortisone-FAAM (method attached).
29. Chlorobutanol (in milk)-method in NADA.
30. Salicybi acid (in milk)-method in NADA.
31. Methyl Paraben (in milk)-method in NADA.
32. Propyl Paraben (in milk)-method in NADA.
33. Hexachlorophene (in milk)-method in NADA.
34. Ethylenedeamine (in milk)-method in NADA.
35. Reserpine (in poultry tissue)-method in NADA.
36. Promazine (in tissue)-method in NADA.
37. Metoserpate (in poultry tissue)-FAAM.
38. Rescphenicol (in poultry tissue)-method in NADA.
39. Chlorhexidine (in veal tissue)-method in NADA.
40. Ethoxyquin (in chicken tissue and eggs)-AOAC XI Ed. 37.009.
41. Nalidixic acid (in chicken tissue)-AOAC XI Ed. 37.014.
42. Furfanitran (in chicken tissue)-method in NADA
43. Metoserpate hydrochloride (in chicken tissue)-method in NADA.

page 7

Methodology for Animal Drug in Premix and Finished Feeds.

A. Collaborated Methodology for Non Antibiotic Drugs in Premix and Finished Feeds.

1.	Total Arsenic	AOAC XI Ed.	38.001
2.	2-Acetylamino-5-Nitrothiazole	"	38.007
3.	Aklomide	"	38.013
4.	Amprolium	"	38.022
5.	Arsanilic acid	"	38.32
6.	Buquinolate	"	38.038
7.	Decoquinate JAOAC54, 69 (1971)	"	38.044
8.	DES	"	38.048
9.	Dimetridazole	"	38.052
10.	Ethopabate	"	38.058
11.	Furazolidone and/or Nitrofurazone	"	38.064
12.	Glycarbylamide	"	38.066
13.	Nicarbazin	"	38.072
14.	Nicotine	"	38.078
15.	Nihydrazone	"	38.082
16.	Nithiazole	"	38.084
17.	Nitrodan	"	38.088
18.	Nitromide	"	38.093
19.	Nitrophenide	"	38.097
20.	4-Nitrophenylarsonic acid	"	38.100
21.	Phenothiazine	"	38.105
22.	Piperazine	"	38.107

page 8

23.	Racephenicol	AOAC XI Ed.	38.112
24.	Reserpine	"	38.121
25.	Sulfadimethoxine	"	38.135
26.	Sulfaguanidine	"	38.138
27.	Sulfaquinoxaline and arsanilic acid	"	38.140
28.	Sulfanitran	"	38.145
29.	Thiabendazole	"	38.149
30.	Zoalene	"	38.158
31.	Nifursol JAOAC54, 66 (1971)	"	38.A14
32.	Dpronidazole JAOAC54, 72 (1971)	"	38.A01
33.	3-Nitro-4-hydroxy benzenearsonic acid JAOAC54, 80 (1971)	"	38.A21
34.	Sulfamethazine	"	38.142
35.	Romnel	"	38.126
36.	Nequinate JAOAC53, 875 (1970)	"	38.A08

B. Collaborated Methodology for Antibiotic Drugs in Premix and Finished Feeds.

1.	Pencillin	AOAC XI Ed.	38.214
2.	Chlortetracycline	"	38.179
3.	Tylosin	"	38.223
4.	Oleandomycin	"	38.204
5.	Bacitracin	"	38.170
6.	Hygromycin B	"	38.183
7.	Lincomycin	"	38.188
8.	Neomycin	"	38.192

page 9

9.	Nystatin	AOAC XI Ed. 38.200
10.	Oxytetracycline	" 38.208
11.	Streptomycin	" 38.219
12.	Griseofulvin	" 38.227
13.	Erythromycin JAOAC54, 940-6 (1971).	" 38.A34

C. Non-collaborated Methodology for Non-Antibiotic Drugs in Premix and Finished Feeds.

1.	Diethylstilbestrol (GLC method)	JAOAC53, 1242 (1970)
2.	Oremtoprim	JAOAC53, 1244 (1970)
3.	Combination of sulfanitran, aklomide and Arsanilic acid	JAOAC53, 875 (1970)
4.	Menadione Dimethylpyrimdinol Bi-sulfate-	FAAM
5.	Diethyl Carbamazine-	FAAM
6.	2-Chloro-4-Nitrobenzamide-	FAAM
7.	Dienestrol Diacetate-	FAAM
8.	Ethoxyquin-	FAAM
9.	Furazolidone-	FAAM
10.	Methiotriazamine-	FAAM
11.	Nihydrazone-	FAAM
12.	Coumaphas-	Method in NADA (attached
13.	Atgard C premix (dichlorvos)-	"
14.	Clopidol-	"
15.	Metoserpate	"
16.	Famphur	"

page 10

17.	Melengestrol Acetate	Method in NADA
18.	Sulfamerazine	"
19.	Poloxalene	"
20.	Sodium Sulfachloropyrazine Monohydrate	"
21.	Sulfaethoxypridazine	"
22.	Phenothiazine	"
23.	Hexachlorophene	"
24.	Medroxyprogesterone Acetate	"
25.	3,5-dinitrobenzamide	"
26.	Estradiol Monopalmitate	"
27.	Estradiol Benzoate	"
28.	Testosterone Propionate	"
29.	Progesterone	"
30.	Chlormadinone Acetate	"
31.	Promazine Hydrochloride	"

page 11

D. Non-collaborated Methodology for Antibiotic Drugs in Premix and Finished Feeds

1. Monensin-	JAOAC53, 1244 (1970)
2. Novobiocin-	Method in NADA
3. Spectinomycin-	"
4. Sulfomyxin-	"
5. Dihydrostreptomycin	"
6. Chlortetracycline (Fluorometric method)	JAOAC54, 947 (1971)

E. Associate referees in AOAC are planning collaboration of the following methods.

1. Bacitracin	JAOAC52, 681 (1969)
2. Monensin	" 53, 49 (1970)
3. Neomycin	" 54, 121 (1971)
4. Nystatin	" 52, 675 (1969)
5. Tylosin	Given at 83rd Annual Meeting

page 12

We have also attached copies of papers that would be an aid in future development of veterinary drug residue screening methods by categories:

1. TLC of Sulfonamides

   a. J. of Chromatog. 48, 27 (1970)

   b. J. Pharm. Pharmac. 22, 845 (1970)

2. Estrogens, Ketosteroids, sulfonamides and preservatives by High Speed Liquid Chromatography. - FDA - By - Lines 1, 279-98 (May 1971).

More compiling methods in NADA's will follow.

Thomas J. Dols
DVMR/BVM

cc: Dr. Johnson, VM-400
Dr. Cazier, VM-400
N. Ettelstein, VM-400
H. Eiduson, CF-30
DVMR, VM-400
CA-224
VM-13
VM-400: TDols: mb: 9/21/71

Mr. Hyman P. Elduson
FSC/EDRO, CF-30
Through: Dr. K. F. Johnson
DVMR/BVM, VM-400

October 19, 1971

Chemists, DVMR/BVM, VM-400

Final Report of NADA Methodology for DEN-DO (See previous Memorandum of September 22, 1971).

This memorandum includes two copies each of: (1) 37 tissue residue NADA methods. (2) 28 feed and premix (or product) NADA methods. (3) Official lists of Assay Limits. (4) Address of AFCO publications. (5) CLC methods for Erythromycin and Penicillin drug substances (for ideas of method development).

Any method that DEN-DO does not have, but is needed on an immediate basis can be gotten to them by FAX.

Please add Racephenicol in poultry tissue to list in memorandum of September 22, 1971.

Thomas J. Dols

Nathan Ettlestein

cc: Johnson
Cazier
DVMR
Dols
Ettlestein
TJDols/ps/10-19-71

October 19, 1971

Mr. Hyman P. Eiduson
FSC/EDRO, CF-30
Through: Dr. K. F. Johnson
DVHR/BVM, VM-400

Chemists, DVHR/BVM, VM-400

Final Report of NADA Methodology for DEN-DO (See previous Memorandum of September 22, 1971).

This memorandum includes two copies each of: (1) 36 tissue residue NADA Methods. (2) 28 feed and premix (or product) NADA methods. (3) Official lists of Assay Limits. (4) Address of AFCO publications. (5) GLC methods for Erythromycin and Penicillin drug substances (for ideas of method development). (6) High pressure liquid Chrom method for nicotinic acid (drug substance of some capture guns).

The following tissue residue methods as listed in Sept. 22, 1971 memorandum are not included in this report:

1. Phenothiazine) - use method for Sulfachloropyrrazine and
2. Sulfamerazine) TLC for identification.
3. Griseofulvin - put in Category V.
4. Coumaphas - use PAMI.
5. Methylprednisolone) use method for Prednisone
6. Prednisolone) " " " "
7. Flumethosone) " " " "
8. Chlorobutanol)
9. Salicylic acid)
10. Methyl and Propyl Paraben) put in category V
11. Hexachlorophene)
12. Ethylenediamine)
13. Chlorhexidine)
14. Furfanitran - omit from category list.
15. USDA/C&MS total arsenic method - 6 collaborators failed to validate method (85th annual ADAC meeting).

The following feed and premix methods as listed in Sept. 22, 1971 memorandum are not included in this report:

1. Hedroxyprogesterone acetate
2. Hexachlorophene
3. Estradiol Implant - NF
4. Testosterone Propionate Implant - USP
5. Progesterone
6. Novobiocin
7. Dihydrostreptomycin
8. New MGA method (ec-GLC) - given at 85th Annual ADAC Meeting.
9. Dichlorophen - given at 85th Annual ADAC Meeting.

Any method that DEN-DO does not have, but is needed on an immediate basis can be gotten to them by FAX.

Please add Racephenicol in poultry tissue to list in memorandum of September 22, 1971.

Thomas J. Dols

Nathan Ettlestein

cc: Dr. Johnson
Dr. Cazier
T. Dols
N. Ettlestein
DEN-DO
TDols/ps/10-19-71

Standard Form 52—Rev. July 1968
U.S. Civil Service Commission
FPM Ch. 295

REQUEST FOR PERSONNEL ACTION

attachment B V-2661

PART I. REQUESTING OFFICE: Unless otherwise instructed, fill in all items in this part *except those inside the heavy lines.* If applicable, obtain resignation and separation data on reverse side.

1. NAME (CAPS) LAST—FIRST—MIDDLE — MR—MISS—MRS.	2. (For agency use)	3. BIRTH DATE (Mo., Day, Year)	4. SOCIAL SECURITY NO
DOLS, THOMAS J. MR.		07-08-38	XXXX

A. KIND OF ACTION REQUESTED (1) PERSONNEL (Specify appointment, reassignment, resignation, etc.)	B. REQUEST NUMBER	C. DATE OF REQUEST
Reassignment	MED-156-5	01-24-75
(2) POSITION (Specify establish, review, abolish, etc.)	D. PROPOSED EFFECTIVE DATE	E. POSITION SENSITIVITY
	ASAP	NTS

5. VETERAN PREFERENCE 2—NO 3—10 PT. DISAB 5—10 PT. OTHER 2—5 PT. 4—10 PT. COMP	6. TENURE GROUP 1	7. SERVICE COMP. DATE 11-28-61	8. HANDICAP CODE 00
9. FEGLI 4 1—COVERED (REGULAR ONLY—DECLINED OPTIONAL) 2—INELIGIBLE 3—WAIVED 4—COVERED (REG. & OPT.)	10. RETIREMENT 1 1—CS 2—FICA 3—FS 4—NONE 5—OTHER		11. (For CSC use)
12. NATURE OF ACTION CODE 721 Reassignment	13. EFFECTIVE DATE (Mo., Day, Year) 02-16-75	14. CIVIL SERVICE OR OTHER LEGAL AUTHORITY Reg 335.102	

15. FROM: POSITION TITLE AND NUMBER	16. PAY PLAN AND OCCUPATION CODE	17. (a) GRADE OR LEVEL (b) STEP OR RATE	18. SALARY
~~Chemist~~ P73F206	~~GS-01320(42)~~	~~13~~	pa $

19. NAME AND LOCATION OF EMPLOYING OFFICE ~~PHS~~
~~Food and Drug Administration~~
~~Bureau of Veterinary Medicine~~
Division of New Animal Drugs/Large Animal Drugs Branch 6A120350000

20. TO: POSITION TITLE AND NUMBER	21. PAY PLAN AND OCCUPATION CODE	22. (a) GRADE OR LEVEL (b) STEP OR RATE	23. SALARY
Chemist P72F457	GS-01320(42)	13 3	2327000 pa $

24. NAME AND LOCATION OF EMPLOYING OFFICE PHS
Food and Drug Administration, Rockville, Maryland
Bureau of Veterinary Medicine
Division of Veterinary Medical Review/Surveillance Branch 6A120230000

25. DUTY STATION (City—county—State)	26. LOCATION CODE
Rockville, Maryland	241360031

27. APPROPRIATION	28. POSITION OCCUPIED 1—COMPETITIVE SERVICE 2—EXCEPTED SERVICE	29. APPORTIONED POSITION FROM: 1—PROVED-I 2—WAIVED-2 TO: STATE
TK #09460 PR #5-6993022	1	

F. REMARKS BY REQUESTING OFFICE (Continue in item F on reverse side, if necessary)

G. REQUESTED BY (Signature and title) (Leave blank on resignations)

I. REQUEST APPROVED BY: SIGNATURE for Pearlie McKeogh TITLE: Asst. Director for Mgmt/BVM

H. FOR ADDITIONAL INFORMATION—CALL (Name and telephone number)
Pearlie McKeogh 31573

PART II. TO BE COMPLETED BY PERSONNEL OFFICE (Items inside heavy lines in Part I above also to be completed)

J. POSITION CLASSIFICATION ACTION ☐ IDENTICAL ADDITIONAL ☐ NEW ☐ VICE ☐ REGRADED

K. CLEARANCES	Initials or Signature	Date	(7) REMARKS (Note: Use item 30 on reverse for Standard Form 52 remarks)
(1)	[illegible]	1-31-75	
(2) CEIL. OR POS. CONTROL			
(3) CLASSIFICATION			QUALIFICATION STANDARD
(4) PLACEMENT OR EMPL.			
(5)			
(6) APPROVED BY:			

1-27-75

Dr. K. F. Johnson
The Willows
Box 611
Moorefield, W.Va. 26836

August 8, 1976

Hon. Edward M. Kennedy
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

This is a follow-up to testimony presented on Tuesday, July 20, 1976 at the FDA oversight hearings before the Senate Subcommittees on Health and Administrative Practice and Procedure. As Chairman of the hearings you requested that the witnesses submit in writing any suggestions that might be useful in improving the Food, Drug & Cosmetic (FD&C) Act incident to its possible revision.

Because my employment prior to reitrement in January of this year was with the Bureau of Veterinary Medicine, I will limit my recommendations to the area of drugs. It is my impression that the existing law in some respects gives undue attention to satisfying industry needs at the expense of the consumer. With this in mind I offer two suggestions and my rationale for each.

Suggestion #1: Amend the FD&C Act to require that FDA review both pre- and post-clearance drug reports (human as well as animal) within a specified time interval. As presently written, the law imposes review requirements within stated time intervals on pre-clearance drugs only.

Suggestion #2: Amend the FD&C Act as necessary to limit the influence of industry on FDA's decision and policy making.

Discussion on Suggestion #1:

Sections 505(c) and 512(c) of the Act require that new drug applications submitted by the sponsor be processed and acted upon within 180 days of receipt by FDA. While this does not necessary result in an immediate drug approval, it does guarantee positive action by FDA in reviewing the new human or animal drug application and this does require FDA manpower.

Sections 505(j)(1) and 512 (1)(1) of the Act require the submission of Clinical Experience Reports for marketed drugs at prescribed intervals. This requirement is beneficial in detecting many adverse drug reactions, faults in labelling, improper advertising, etc. However, the gross weakness of this requirement is that no time limit is placed on FDA for processing, reviewing, analyzing and recommending corrective action. Thus action that should be taken may be long delayed and potentially harmful or improperly labelled drugs remain on the market for the consuming public to purchase.

Because of this weakness and because of the law-imposed time requirement for review of new drug applications, the Agency places great emphasis and disproportionate manpower allocations on New Drug Application review. This is most certainly discrimination in favor the drug industry.

During my service as Director of the Division of Veterinary Medical Review in the Bureau of Veterinary Medicine, it was common to have great backlogs of industry-submitted Drug Experience Reports with far fewer than adequate staff members to review them. Some portions of the reports were filed without review. In some instances a percentage of those previously unreviewed portions were later retrieved and analyzed. This was done with the full knowledge and approval of the Bureau Director.

It should also be noted that every time a new drug is approved and marketed, the drug sponsor is obliged to meet Clinical Experience Reporting requirements--annual or semiannual submissions depending on the type of drug or the age of its approval. This is a never-ending responsibility so long as the drug approval remains in effect. The net result is an ever-mounting volume of clinical reports needing review and action by FDA.

It was also my experience that as manpower allocations became available, without exception the Drug Pre-Clearance Groups received 80-90% of the assigned personnel. Written pleas to the Bureau Director with supporting data and justification for increased manpower in the Drug Experience Review Group failed to bring satisfactory results.

I believe the only way to provide a semblance of equality between industry and consumer insofar as drugs are concerned is to impose the same or similarly-appropriate restrictions on pre- and post-clearance drugs.

Discussion on Suggestion #2:

Frequent and close association with industry organizations and executives of drug firms is exercised by some agency administrators. While communication between the two entities is desireable and necessary, the extent to which it takes place and the informal and social aspect it often assumes could place regulatory groups in a compromising position. This may be entirely unintentional, but it is neither proper nor conducive to a fair administration of the law.

I appreciate the opportunity to express my views of these subjects and wish you well in your endeavors.

Very truly yours,

Klemens F. Johnson, DVM

Senator KENNEDY. Did you work on an IND of an injectable product to determine bioequivalence last summer?

Dr. BEAULIEU. Yes, sir.

Senator KENNEDY. As I understand it, you recommended disapproval of that drug?

Dr. BEAULIEU. That is right.

Senator KENNEDY. Why?

Dr. BEAULIEU. Well, in my opinion, the firm was trying to establish that their product was bioequivalent to a product which had never been established to be effective.

Senator KENNEDY. You were asked to establish bioequivalence of a drug that was not even effective?

Dr. BEAULIEU. That is right.

Senator KENNEDY. How could you do that?

Dr. BEAULIEU. Well, I could not, obviously.

Maybe if I go into a little more detail.

Senator KENNEDY. Yes; I would like to hear it, just briefly.

Dr. BEAULIEU. First of all, I was detailed to the Division of New Animal Drugs.

Senator KENNEDY. Bring the mike up a little closer.

Dr. BEAULIEU. I was detailed to the Division of New Animal Drugs for 60 days to help them decrease the backlog of NADA's.

The first NADA I was given was for an injectable antibiotic product.

On perusal of the file I realized it was going to be very difficult to review it because there were a number of policy issues involved.

I discussed this—there is not time to go into it here—I discussed those in my medical summary.

My final conclusions were that I could not conscientiously recommend approval of that product because it depended for its efficacy on the establishment of its bioequivalence to a product which was not supported by substantial evidence of efficacy.

Senator KENNEDY. That product is on the market, is it not?

Dr. BEAULIEU. Yes; it is.

Senator KENNEDY. It is not effective?

Dr. BEAULIEU. I do not know that it is not effective.

In my opinion, it has not been proven to be effective.

Senator KENNEDY. Well, did you ever look at the proof that shows that it was effective?

Dr. BEAULIEU. There is not proof in the file derived from well-controlled studies.

Senator KENNEDY. Why not? Do you know why not?

Do you know why there is not proof in the files from well-controlled studies?

Dr. BEAULIEU. No. The issue is somewhat complicated because the product was the subject of an NASNRC review, and it was found probably effective on NASNRC review.

Senator KENNEDY. Were you asked to revise your review?

Dr. BEAULIEU. Yes.

There were other reasons why I recommended that the application be disapproved.

I was asked to revise my review in a meeting August 27, I believe, of last year, with Drs. Mark, Holt, and Haines.

Senator KENNEDY. Did you revise your review?

Dr. BEAULIEU. Some of the points they raised were well taken, I thought.

I agree that where I could conscientiously do so, I would revise my summary to reflect those points.

Senator KENNEDY. There is nothing improper about that?

Dr. BEAULIEU. Not that I see.

I think they were performing——

Senator KENNEDY. Did you change your position?

Dr. BEAULIEU. No.

In fact, my conclusions were not materially affected, the revisions were mainly editorial.

Senator KENNEDY. Were any of your final reviews removed from the files?

Dr. BEAULIEU. Well, in late May of this year I had occasion to review that file in connection with some adverse reactions which had been reported out in the field.

I discovered at that time that neither my original summary nor my revised summary nor any memo of the conference in which I was told to revise my summary were in the application.

Senator KENNEDY. This was the file that you were reexamining for the purpose of adverse reaction?

Dr. BEAULIEU. That is right.

Senator KENNEDY. In view of that, you could not find any of your previous recommendations or work products——

Dr. BEAULIEU. That is right.

Senator KENNEDY. Should it not be there?

Dr. BEAULIEU. In my opinion it should be, yes.

Senator KENNEDY. Would it not normally be expected to be there?

Dr. BEAULIEU. Yes, sir.

Senator KENNEDY. But it was not?

Dr. BEAULIEU. It was not.

Senator KENNEDY. You do not know where it went?

Dr. BEAULIEU. No; I only know it was not there.

Senator KENNEDY. Do you feel that there is undue industry influence in your Bureau?

Dr. BEAULIEU. There is definitely industry pressure.

I am not sure how I would define undue industry pressure.

I expect pressure from industry. The nature of our organization, of our responsibility, determines that there will always be conflict between industry and the people regulating it.

What disappoints me is the fact that, in my opinion, our administration does not lend the support to the reviewing personnel which they deserve when confronted with this kind of pressure.

Senator KENNEDY. I think that that is a very fair and candid opinion and one which has been stated by many others.

Dr. Frazier, you stand by your previous testimony?

Dr. FRAZIER. Yes.

I have given you a prepared statement in rebuttal——

Senator KENNEDY. We will take that and put it in its entirety in the record.

Just tell us very briefly in your own words what the main point of it is.

I'll obviously include it in its entirety.

[The document referred to follows:]

MEMORANDUM

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

TO : Mr. Walter Sheridan

DATE: June 4, 1976

SHD 6/4/76

FROM : S. H. Frazier, D.V.M.
Division of Toxicology (HFF-152)

SUBJECT: Reply to Dr. Van Houweling's Responses Item 18

CAMERA COPY—PLEASE SHOOT AND SUPPLY 2 SETS DYLUX (Hand Page Numbers Thereon)

In reply to your instructions I am submitting a critique of Dr. Van Houweling's response, under Item 18, concerning Ronidazole and its sensitivity of the analytical method. His response is a rebuttal to the testimony given by me to the Senate Subcommittee on Administrative Policies and Procedures in February 1975, chaired by Senator Kennedy.

Reply to Dr. Van Houweling's Responses Item 18

(1) (Tab 18-1) The first toxicology review written by Dr. S. I. Shibko was for 90-day oral studies (memo dated May 7, 1968, NADA 39-247). The comments in item 18 of Dr. Van Houweling's response are accurate.

(2) (Tab 18-2) The response made by Dr. Van Houweling is accurate. However, Dr. R. L. Gillespie's review, memo dated 11/14/68, VID. 77, stated a level of sensitivity of 2-5 ppb must be developed. A 21-day withdrawal period was assigned for marketing experimental turkeys. This conclusion was based on preliminary data we received from the firm, which indicated that ronidazole produced tumors.

(3) A third toxicology review was made by Dr. J. V. Sladek of the Bureau of Foods, Division of Pharmacology and Toxicology (DPT), memo dated 11/22/68, VID No. 456. This was a request from the firm for authorization to market some experimental turkeys treated with ronidazole. It was concluded that the petitioner should hold up the experiments in VID 456 until the tumor question is solved.

On November 26, 1968 a telephone conversation was held between Mr. Young (Merck) and Dr. Blumenthal (DPT). This conversation dealt with birds which had been slaughtered following a 15-16 day withdrawal period. Analytical data showed that radioactivity levels in plasma at 5 days were below 10 ppb. Based on that information it was considered the slaughtered birds did not pose a problem to humans. The firm was requested to submit more recent analytical data for our examination.

(4) (Tab 18-3) This response refers to the conference held 11/27/68 with representatives of the firm and FDA personnel. The firm's representatives were told that a method sensitive to 2-3 ppb would be

(4) needed to market the drug. We also authorized the release of 7,200 turkeys for slaughter, based on the advice from our chemist, Mr. Prochazka.

(5) (Tab 18-4) The memo of March 7, 1969, from our chemist (Mr. Prochazka) to Dr. Ducharme (BVM) requested a 2 ppb level of sensitivity for Ronidazole. I agree with Dr. Van Howeling's statement.

(6) (Tab 18-5) I agree in part with Dr. Van Houweling 's statement in this exhibit. Our records show that a draft letter was sent to Dr. Blumenthal from Dr. Mark, under a memo dated March 11, 1969. This draft letter was forwarded following Mr. Prochazka's memo of March 7, 1969.

The third paragraph of the draft letter from BVM requested a "better sensitivity (preferably 2 ppb.) be developed, or the submission of the data to demonstrate the lack of carcinogenic properties of this drug". The response to the draft letter from Dr. Blumenthal was dated 4/4/69, and was not a concurrence. The Bureau of Veterinary Medicine was provided with our scientific thinking when it comes to carcinogenesis testing and types of protocols necessary. It is noted in Dr. Blumenthal's reply, he stated "we have no desire to be specific as to what studies will be required to demonstrate lack of carcinogenic properties". It was further pointed out, that if "they (the petitioner) elects to persue this matter further I am sure they will have suggestions which we will be in a position to respond to." In no instance was there a concurrence in the draft letter as proposed by BVM. Rather, the reply was given as a guide for rephrasing the proposed letter to reflect the scientific thinking of the, then, Bureau of Science. Exhibit Tab 18-6 is self-explanatory concerning this subject.

It is noted that the letter to the firm dated April 28, 1969, does not reflect the comments which Dr. Blumenthal submitted in reply to the draft letter. Compare exhibit Tab 18-6 and 18-8.

(7) Following BVM's letter, April 28, 1969, to the firm, the chemist reviewed residue data for the 10 ppb level of sensitivity. The comments are found in a memo dated July 8, 1969.

(8) Tab 18-19, Our review memo dated September 3, 1969 contains the comments and conclusion for a two-year dog and rat study. This is a review of the complete data, and we concluded that the drug was tumorigenic and probably carcinogenic. We stated that the level sensitivity 0.05 ppm was inadequate.

Dr. Van Houweling states that I did not review the New Animal Drug Application until September 3, 1969, and that I failed to mention the error. Our records indicate that the application was received by the Division of Pharmacology and Toxicology (DPT)

on March 17, 1969. Therefore, the letter, dated 4/28/69, sent to the firm by BVM could not have been available at the time we reviewed the petition.

The Division of Pharmacology and Toxicology (DPT) has never received an official copy of the 2/28/69 letter BVM sent to the firm. In July 1971, we became aware of the requirements the firm was following. The firm provided us with a copy of BVM's letter when we asked them why they were submitting data for an additional two-year study and validating the method at 10 ppb.

Dr. Van Houweling in his response failed to mention that an additional letter drafted 10/2/69 signed by Dr. Kingma also requested a 10 ppb level of sensitivity. Therefore, the firm received two letters with the same request.

(9) Memo dated January 14, 1970, Mr. Prochazka (SC-470) to Dr. Ducharme, BVM (VM-110) states we would need a level of sensitivity of 2-3 ppb. This document was not included in Dr. Van Houweling's response.

(10) Memorandum of conference dated February 3, 1970, showed a meeting was held between Merck representatives and FDA (BVM and DFCT). Dr. Ducharme was in charge of the meeting. Dr. Ducharme told the firm that the 10 ppb level of sensitivity was acceptable at that time, but a lower sensitivity might be needed upon review of the toxicity data from the second rat study.

No representative from DPT was present at this conference. Dr. Ducharme's advice to the firm was inaccurate. We were not waiting for the additional toxicology data. As shown by previous evidence the 2 ppb sensitivity was the requirement. Also, during this conference BVM failed to acknowledge the chemist's statement in his January 14, 1970 memo.

(11) The firm persisted to validate the method at 10 ppb, based on the requirements given them by BVM in the letters dated April 28, 1969 and October 2, 1969 and in the conference of February 3, 1970.

(12) Review memo of DPT dated March 5, 1971 concerning the second two-year rat study was sent to BVM on March 9, 1971. The DPT concluded that the new study was inadequate to show the lack of carcinogenic properties of MK-930. Also, we stated the reason for not accepting the study and that the validated method of 10 ppb is inadequate. Again, we requested a 2 ppb level of sensitivity.

This study was conducted according to the 4/28/69 BVM letter to the firm, which was designed to show a "no-effect" level. Additional conferences were held between Merck and BVM on March 11, and

April 26, 1971. The firm was told then the required level of sensitivity was 2 ppb. They insisted that they were following the requirements as stated in the letters dated April 28, 1969 and October 2, 1969 which requested a 10 ppb level of sensitivity.

In the May 26, 1971 conference Dr. Ducharme again stated that we were waiting on the results of the second two-year rat study, before deciding on a level of sensitivity. This statement was incorrect. No representative from DPT was present at the March 11 and April 26, 1971 conferences.

(13) On July 1, 1971 a conference was held between the firm, DPT personnel, with Dr. Mark and Dr. Gabuten representing B.V.M. We discussed the reason for requring the 2 ppb sensitivity of the method. This was the point in time when DPT became aware of the two letters BVM sent to the firm requesting the 10 ppb level of sensitivity. Until this time we had no knowledge why the firm persisted to validate the method at 10 ppb. Also, we discovered the reason why the firm conducted the second two-year rat study in a manner to demonstrate a "no-effect" level.

(14) The Bureau of Veterinary Medicine finally transmitted a letter dated August 3, 1971, drafted by Dr. Mark, to the firm which expressed DPT's requirements. It was over 2 years of review before we were able to get the situation in order. As of this date this product has not been approved.

SUMMARY:

Dr. Van Houweling stated that I had not checked the files before giving testimony. Also, he implied that my remarks were a deliberate attempt to be derogatory. The sequence of events speaks for thmself. My testimony at the 1975 hearing was accurate. The primary error in this entire procedure was made by BVM in April 1969, when they failed to acknowledge Dr. Blumenthal's reply of April 4, 1969 concerning the proposed draft letter to the firm and other reviews which stated that a 2 ppb level of sensitivity was needed for ronidazole.

BVM failed to provide us with copies of correspondence which they sent to the firm. Therefore, it was extremely difficult for us to be sure our recommendations were being transmitted properly,or at all.

We still cannot document at what point in time the firm proceeded to conduct the second rat study. The Bureau of Foods did not receive a protocol or give advice concerning the study. Also, it was suggested by Dr. Blumenthal (memo 4/4/69) that the firm be invited to discuss the matter of the conduct of a study to show the lack of carcinogenesis.

Dr. Van Houweling's statement that the 10 ppb not 2 ppb was clearly a typographical error is questionable, taking into consideration all of the reviews made prior to the 4/28/69 letter to the firm. Also, BVM continued to advise the firm about the 10 ppb sensitivity and a second rat study as late as February 3, 1970.

Dr. W. A. Rader
Division of Veterinary New Drugs (VM-110)

November 14, 1968

Dr. E. L. Gillespie
Division of Pharmacology and Toxicology
Petitions Review Branch (BC-970)

Ronidazole for Turkeys

VETERINARY INVESTIGATIONAL DRUG NO. 77
NEW DRUG APPLICATION NO. P39-247V

Merck and Company
Rahway, New Jersey
(AF 4-715)

Data submitted today by the petitioner indicates definitely a tumorigenic effect. The metabolism of the drug as indicated by their analytical method (sensitive to 0.05 ppm is rather rapid). Tissue levels of 3 ppm at zero withdrawal decreased below the sensitivity of the method 0.05 ppm at 3 days. C_{14} studies indicate all metabolites are destroyed within 21 days.

We propose that birds currently on test be marketed following a 21-day withdrawal.

For future use of the drug, a much more sensitive analytical method getting down in the area of 2 to 5 parts per billion must be developed.

EXIT: Ultimately

cc: BC-970
BC-440
VID No. 77
NDA No. P39-247V

ELGillespie:gr 11-14-68

Orig + 5 cy VM-100 11-21-68

Dr. K. A. Hader
Division of Veterinary New Drugs (VM-120)

November 22, 1968

Dr. J. V. Sladek
Division of Pharmacology and Toxicology
Petitions Review Branch (SC-970)

Ronidazole Tablets (1-methyl-2-carbamoyloxymethyl-5-nitroimidazole)

VETERINARY INVESTIGATIONAL DRUG NO. 456

Merck, Sharp and Dohme
Rahway, New Jersey 07065
(AF 4-715)

The petitioner with a letter of Sept. 11, 1968 submits a Veterinary Investigational New Drug (VIND) recorded under VID 456V, dealing with Ronidazole Tablets to be shipped to various investigators for treatment of outbreaks of blackhead in turkeys. The petitioner asks for authorization to market the treated birds for food, the request based on the attached information as well as on that submitted with VID 77 for Ronidazole (HK-930) Medicated Feed and Drinking Water.

The label, according to the presented text for experimental Ronidazole Tablets, contains the following information:

> Each tablet contains 20 mg Ronidazole for the treatment of histomoniasis in turkeys. The label mentions further that turkeys drinking insufficient water for proper medication with Ronidazole powder should be returned to unmedicated water. They then should be given one 20 mg tablet for each 10 lb of body weight for 5 to 7 days or until normal water consumption is resumed. To facilitate swallowing, each tablet should be placed well back in the mouth.
>
> Caution: Do not slaughter birds in less than 5 days of the last treatment. Contains a new drug for use in investigational animals in clinical trials only. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S.F.D.A. or by the U.S. Dept. of Agric.

Approximately 10,000 turkeys are to be treated in various sections of the United States.

Maximum daily dose: ca 2 mg/lb orally. Size or age of animal: 2 or 3 weeks to 2 years. Maximum duration of administration: 7 days. Withdrawal time: 5 days.

Our note: The size, weight of the animals should have been given to facilitate calculations for comparison with the amounts already used in turkey's feed and drinking water (VID 77).

Orig & 2 Cys BVM 11-29-68

BVM should comment on the weight of turkeys 2 or 3 weeks of age (these may weigh about 1/2-1 lb) and older and on the form and weight of dosage, which would be about 2 mg for these as compared with those 2 years old.

In VID 77, the petitioner proposed (letter of Dec. 2, 1966) the maximum daily dose in drinking water 0.0015 to 0.004% for turkeys from 2 or 3 weeks to 2 years of age, duration of administration 14 days; in the feed 0.003 to 0.006 or 0.008% for 3-4 days. In both cases a withdrawal time of 21 days.

According to DFCT/SC-440 (Prochazka of Jan. 19, 1967) tables (IV-4 and IV-5) the tissue residues of turkey poults fed for 3 days MK-930-C^{14} at 0.008% showed less than 0.1 ppm at 21 days withdrawal; this (0.008%) is said to be equivalent to MK-930 in drinking water at 0.004% administered for 14 days. DFCT/SC-440 concurs with petitioner's request at all the proposed levels on 21-day withdrawal (see also the BVM summary document of Jan. 27, 1967).

In authorization letters of June 28, 1967 to April 26, 1968 issued by BVM to Merck, Sharp and Dohme was concluded that edible products derived from turkeys under trials described can be utilized in a manner that is consistent with public health.

On March 27, 1968, the petitioner submitted to FDA an NDA No.P39-247 for Ronidazole (Ritzol) medicated feed containing data on the physiological disposition and tissue residues. These data indicate that a 5-day withdrawal period is satisfactory to deplete tissues of Ronidazole; in the letter of April 16, 1968, the petitioner proposes therefore to revise the withdrawal period in VID 77 from 21 to 5 days, based on data contained in the above petition evaluated by this office (Dr. Shibko) in the memo of May 7, 1968.

For the quantitative determination of tissue residues in this NDA P39-247 was used the polarographic method which was found by EAB/SC-510, (Prochazka, April 8, 1968) adequate. Sensitivity in muscle and liver was validated at 0.05 ppm and in kidney, skin, and fat at 0.2 ppm after 3 days of withdrawal. Residues found down to control values at 5 days withdrawal even when the drug was fed at 0.012-0.024-0.04% and in the drinking water at 0.012% (Prochazka, April 8, 1968, June 14, 1968). Control tissue readings are negligible and not used.

DFCT (Prochazka, July 3, 1968) concurs with the petitioner's request to use Ronidazole in turkeys' feed at levels of 0.006-0.02% and in the drinking water at 0.01% with a 5-day withdrawal.

DFT (NDA 39-247 evaluated by Dr. Shibko) finds Ronidazole safe (when turkeys are fed as directed) and 5-days withdrawal period adequate. However, Ronidazole should not be used in breeding turkeys unless the hatchability tests are performed.

Tissue residues have been revieued by Mr. Prochazka (DFCT/SC-440). Turkeys fed for 3-5-6 weeks at 0.012% Ronidazole feed at zero withdrawal time, showed 8.4 ppm in muscle, 0.1 ppm in liver, zero in kidney, 3.1 ppm in skin and 3.0 ppm in fat. At 3 days withdrawal, all tissue residues were less than 0.05 ppm (sensitivity of the method) except for plasma; at 5 days withdrawal residues in all tissues were less than 0.05 ppm.

DISCUSSION:

Explanation for 21-days withdrawal period (asked for in VID 77), for the birds fed Ronidazole-C^{14} would be, that in the tests for R-C^{14} determined was also the radioactivity of tissue constituents derived from labeled breakdown products of the drug (e.g. as lipid-like materials, proteins, nucleic acids).

The polarographic examination by direct measurement (used in NDA No. P39-247V) estimated only the residues of the not excreted Ronidazole (in the urine and feces, as the metabolic studies show) which residues could not have been any more found after 5 days, being present in amounts below the method's sensitivity of 0.05 ppm.

The amount of the administered 20 mg Ronidazole Tablets for each 10 lb body weight of the bird, in the light of toxicity studies reported in the NDA P39-247V, as compared by calculation with its consumption in feed is not excessive and therefore, safe to the birds. "No-effect" level, in dogs, (the most sensitive species to R.) based on short-term studies is 25 mg/kg/day.

The only question would be, if these 20 mg Ronidazole Tablets will be also administered to birds below 2 weeks of age.

At high dosages of 100 and 200 mg/kg/day in dogs, which did not survive 5-15 days, there were found at autopsy many pathological changes among them a marked effect of the drug on the testicular tissues (also in rats). Therefore, this drug should be used only in meat producing turkeys; hatchability tests also should be required before it can be used for breeder turkeys.

Additional Discussion:

According to report of the representatives of Merck, Sharp and Dohme, Research Laboratories, at the meeting on November 1, 1968, with Dr. H. Blumenthal and members of FBB, 2-year chronic toxicity studies with Ronidazole were conducted by International Research and Development Corp. (IRDC) in Kalamazoo, Michigan.

Studies in rats and dogs showed high incidence of mortality in both the control and treated animals. Because the critical 18 months period passed, the animals were sacrificed with Dr. Blumenthal's consent.

Telephone conversation between IRDC and Dr. Mattis of Merck, Sharp and Dohme indicated that there may have been an increase in the incidence of mammary tumors in the treated rats. Dogs sacrificed at about the same time at autopsies revealed no grose lesions of the mammary glands.

While the data were inconclusive in view of the sensitive nature of the field, it was decided temporarily to suspend testing activities in this drug until the firm could make further scientific inquiries regarding IRDC results. Merck, Sharp and Dohme are notifying their clinical investigators not to treat additional animals with the compound until further notice. This may also refer to 10,000 turkeys to be treated with Ronidazole Tablets, asked for authorization to use these for food purposes in this VID 456V.

CONCLUSION:

1. The drug is safe when fed to turkeys as directed.
2. Because of the marked effect of the drug on the testicular tissues of dogs and rats, the drug should be used only in meat producing turkeys.

   A Hatchability test will be required before the drug can be used for breeder turkeys.
3. BVM should comment on point 2 and on dosage and its form (whether it should be used in smaller amount than 20 mg Ronidazole Tablet) for birds younger than 2 weeks.

Additional CONCLUSION:

This office suggests that the petitioner holds up these VID 456 experiments until the question of tumor production is solved.

INIT: HBlumenthal

cc: SC-970
SC-440
VID No. 456
NDA No. 139-247

JVBladek:gr 11-22-68

MEMORANDUM OF TELEPHONE CONVERSATION
November 26, 1968

BETWEEN:

Dr. J. Young - Merck, Sharp & Dohme
Rahway, New Jersey
(AF 4-715)

and

Dr. H. Blumenthal - Division of Pharmacology
and Toxicology (SC-970)

SUBJECT: Ronidazole (VID No. 77)

Dr. Young's call followed shortly after one from W. Rader (BVM). Both were related to the fact that some ronidazole-treated birds had gone to slaughter after 15-16 day withdrawal.

Previously, we had evaluated some chronic rat data and concluded the material was a potential tumorogen. Based on a radioactive study we concluded that birds slaughtered after 21 days withdrawal would be free of residues.

While Dr. Rader had estimated an involvement of 5,000 birds, Dr. Young informed me that these were mixed-up in 5 truck loads of fresh killed turkeys. Thus, the numbers of birds was considerable. Also, since they were for the fresh-kill market it was likely, since slaughter dates were November 22 and 23, that they were already in homes of buyers.

It is fortunate that Dr. Young has evidence that levels in plasma at 5 days are below 10 ppb, the sensitivity of their new assay method. Since the radioactive study, which had been sensitive to 50 ppb, showed plasma to be the most persistent site, it would appear that danger to the consumer from these birds was nil. However, I requested of Dr. Young that he submit their recent analytical data for our examination. Dr. Young agreed to meet with us tomorrow at which time we will review the complete picture.

H. Blumenthal, Ph.D.

cc: SC-970
SC-440
VID No. 77
VID No. 456

HBlumenthal:gr 12/5/68

MEMORANDUM OF CONFERENCE
November 27, 1968

PRESENT:

Mr. Jack Young	-	Merck, Sharp and Dohme Rahway, New Jersey (AF 4-715)
Mr. Milo Prochazka	-	Division of Food Chemistry and Technology
Dr.W. A. Rader	-	Bureau of Veterinary Medicine
Dr. H. Blumenthal	-	Division of Pharmacology and Toxicology
Dr. R. L. Gillespie	-	
Dr. S. H. Frazier, Jr.	-	

SUBJECT: Ronidazole, MK 930 - Veterinary Investigational Drug No. 456

The purpose of the conference was to discuss the problem of treated turkeys slaughtered with less than 21-day withdrawal time. Also, the firm wanted to discuss a revised analytical method for this drug. Ronidazole is suspected of having tumorgenic properties.

Mr. Young stated that approximately 4,000 treated turkeys, owned by the Goldsboro Milling Company, Goldsboro, N. C., and raised by Mr. W. Jones, LaGrange, N. C., were slaughtered on November 22/23, 1968. The birds were scheduled for slaughter November 29, 1968. The earlier date allowed only a 15-16 day withdrawal period instead of 21 days for the later date. The 4,000 treated birds were mixed with approximately 4,000 control birds in the slaughter house. The number of turkeys in question is 7,200. The birds were retained until a decision could be made on residue to assure safety for human consumption.

The discussion was concerned with an analytical method to assure safety. The old method of sensitivity was not adequate, since the drug is suspected of having tumorgenic properties. Mr. Young stated they now have a method sensitive to less than 0.01 ppm for 5 days in plasma, at dietary levels of 0.24% of Ronidazole. This new data, showing the slope of the curves, was discussed. Dr. Blumenthal stated, based on the 0.24% dietary level fed, the 15-16 day withdrawal time of slaughtered birds and the new method of sensitivity of 0.01 ppm for 5 days in plasma, it is felt there would be no residue problems in the slaughtered birds.

Mr. Procheska stated, based on the data submitted, within 15 days the residue levels would probably be down to 2-3 ppb. He requested Merck to submit raw chemical data for evaluation.

Mr. Young asked what method of sensitivity would be necessary to market the drug? He was advised that 2-3 ppb is needed at the withdrawal time.

It was concluded that the approximately 7,200 birds could be released for slaughter. Dr. Rader would contact the appropriate officials in the USDA to arrange the release.

S. H. Frazier, Jr., DVM

INIT:HSBlumenthal

cc: SC-970
SC-440
VM-120 (Dr. Rader)
VIP No. 456

SHFrazier:dps 12-5-68

Dr. Ducharme, BVM (VM-110)

March 7, 1969

NDA P-39-247V, Ronidazole - Merck & Company

Mr. Prochaska, BFCI/PEB (BC-470)

Additional evaluation of NDA P-39-247V,
Ronidazole in feed for turkeys - Merck & Company

Kansas City District and AIB have completed their study of the method for the determination of Ronidazole residues in turkey tissues.

Kansas City spiked tissues (muscle and liver) at 1.0 ppm on two different days. They obtained recoveries in muscle of 75-102% (average 88%) in liver 61-113% (average 85%). The standard was also run at 1.0 ppm and recoveries calculated as outlined in calculations by petitioner rather than from a true reference standard curve.

The analyst attempted to assay muscle and liver spiked at 0.05 ppm but no Ronidazole could be detected.

No other level was attempted. The analyst questions the meaning of a tissue recovery study in which the drug is added just prior to the extraction step. We do not understand this statement as the drug is equally added to the tissue prior to the extraction step.

Also no data was submitted to show how they (KC) arrived at the recoveries on the standards run through the procedure.

AIB spiked tissues (muscle and liver) at 0.5 and 1.0 ppm of the drug. No drug residue was detectable when tissues were spiked at 0.05 ppm. They state that at 0.5 ppm the limit of detection is being rapidly approached using the Sargent XXI with a maximum sensitivity of 0.003 Ma/mm.

Recoveries (at 0.5 ppm) using the calculations by petitioner were 92% for liver and 80% for muscle (1 st.run) and 98% for liver and 80% for muscle (2 nd. run). Recoveries in table 1, using the standard curve, would be 48% for liver and 43% for muscle.

Kansas City District is of the opinion that they can detect residues in tissues at 0.5 ppm but they only validated at 1.0 ppm. AIB validated recoveries at 0.5 ppm. See Table I attached.

Conclusion

1. Petitioner claims that the method has a sensitivity of 0.05 ppm for muscle liver and kidney and 0.08 ppm for skin/fat tissues. Neither Kan-DO nor AIB was able to detect residues at 0.05 ppm.

2. The best that Kan-Do or AIB was able to obtain was a sensitivity of 0.5 ppm in tissues.

3. The method uses a procedure carrying the standard through the whole procedure. We usually request that the standard not be carried through the clean-up steps as some loss may occur and this is not a true reference curve.

4. DFT now states that they need a method sensitivity of 2 ppb so the petitioner needs to submit new methodology.

cc:
SC- 1
SC-12
SC-403
SC-970
SC-470

MProchaska:br:3-7-69
RD init. VEM 3-4-69

TABLE I

NDA P-39-417V, Ronidazole

Kansas City District				A I B			
Tissue	ppm Drug added	ppm Drug found	Recovery %	Tissue	ppm Drug added	ppm Drug found	Recovery %
Liver	1.0	1.13	113	Liver	0.5	0.46	92
Liver	1.0	.73	73 > 93%	Liver	0.5	0.52	104 > 98%
Muscle	1.0	1.02	102	Muscle	0.5	0.39	78
Muscle	1.0	.90	90 > 96%	Muscle	0.5	0.41	82 > 80%
				Muscle	0.5	0.40	80
Liver	1.0	.94	94	Liver	1.0	0.74	74
Liver	1.0	.61	61 > 78%	Liver	1.0	0.85	85 > 80%
Muscle	1.0	.83	83	Muscle	1.0	0.84	84 - 84%
Muscle	1.0	.75	75 > 80%				

The above results are obtained by using calculations submitted by petitioner.

Memorandum

Food and Drug Administration

TO : Dr. H. Blumenthal, SC-970
Division of Pharmacology and Toxicology

DATE: March 11, 1969

FROM : Dr. James H. Mark, VM-100
Director, Division of Veterinary New Drugs

Merck and Company, Inc.
Rahway, New Jersey
AF 4-715

SUBJECT: Incomplete Letter to Merck and Company on Possible Carcinogenic Properties of Ronidazole

Attached please find rough draft of a letter we propose to send to the firm in regards to their new drug application.

Please indicate if you concur with the language or indicate suggested changes.

We would also appreciate an indication of just what studies will be required to demonstrate the lack of carcinogenic properties of a drug.

Attachment

AF 4-715

Merck, Sharp & Dohme
Research Laboratories
Division of Merck and Company, Inc.
Rahway, New Jersey 07065

Attention: Mr. R. R. Buck NDA P-39-247V

Gentlemen:

Reference is made to your new drug application dated March 27, 1968, for the preparation Ridzol (ronidazole) for use in medicated turkey feed.

We also acknowledge your correspondence of October 2, 1968, and November 4, 1968.

We have completed our study of this application as submitted and find we are unable to act favorably on it due to the absence of an analytical method with acceptable sensitivity. On this basis, we cannot accept the use of ronidazole as safe until an acceptable method with better sensitivity (preferably 2 ppb) is developed, or the submission of data to demonstrate the lack of carinogenic propertie of this drug.

In the event data can be generated to demonstrate the lack of carinogenic properties of ronidazole, further work will have to be done on your present method, as we are unable to validate it at the claimed sensitivity of 0.05 ppm.

In view of the above, you may wish to withdraw your new drug applicatic without prejudice to a future resubmission. If so, the corresponding food additive petition will be withdrawn by notice in the FEDERAL REGIS but it too may be refiled when appropriate.

The alternative options would be of necessity the publication of a Notice of Opportunity for a Hearing on the matter of denying the application, or if waived, the publication of a scheduling of hearing.

We would appreciate being advised of your intentions within the next 30 days.

Sincerely yours,

Director, Bureau of
Veterinary Medicine

cc: Dup NDA
Trip NDA
NYK-DO
DPDucharme:lh 3/11/69

Withdrawal

4-4-69

Draft ltr to Merck, Sharp & Dohme re, ronidazole (NDA P39-247V) your memo 3-11-69

VM-100 Dr. J. H. Mark:

In response to your question "do we concur with the language" of the draft letter, Yes, we do. In our evaluation of this question we have been purposefully vague because the data as presented is not absolute.

In the company's internal memo (Mattis to Peck, 11-7-68), mammary tumor incidence has been summarized. This data indicates first, that in females there is a dose response to fibroadenoma and that adenocarcinoma in females are recorded for the highest dose group only. Since detailed write-up of these tumors are lacking we can only conjecture at the diagnostic's involved in this differentiation. However, since there is no mention of metastasis one can assume that the differential in diagnosis is probably based on invasive characteristics of the "adenocarcinomata." If this is so then such differentiation is largely subjective on the part of the pathologist and it is certain that no two pathologists would be wholly in agreement about these conclusions. More disturbing is the incidence of tumors in the males. Although we've had little experience with the Manor Farm Strain of rat, such tumors in males are not usual and again suggest the presence of a carcinogen. However, tumors were again responsive to dose and the malignancy of the one adenocarcinoma may also be a

subject for interpretation. Thus, our conclusion at the moment is that tumorigenesis has been definitely established while carcinogenesis is only suggested.

Your second question deals with "just what studies will be required to demonstrate lack of carcinogenic properties of the drug." Here again we have no desire to be specific. As you know, even people in the field of carcinogenesis, are not in universal agreement as to what constitutes a valid study. At the moment our ad hoc committee for protocols is in the process of devising a "carcinogenesis protocol." At this time we are in a poor position to present a recipe for a carcinogenic protocol. The petitioners have some very competent people and if they elect to persue this matter further I am sure they will have suggestions which we will be in a position to respond to.

In summary, then the letter as proposed reflects our thinking and its vagueness as desirable at this time.

H. Blumenthal, Ph.D.
Chief, Petitions Review Branch

cc: SC-970
SC-440

HBlumenthal:dps 4-4-69

FF 4-715

[illegible], Chas & Pfizer
Research Laboratories
Division of Pfizer & Company, Inc.
Pfizer, New Jersey 07001

APR 28 1969

Attention: Mr. H. R. Buck

NDA 8-59-2.7V

Gentlemen:

Reference is made to your new drug application dated March 17, 1969, for the preparation Diosol (tonidazole) for use in enriched turkey feed.

We also acknowledge your correspondence of October 2, 1968 and November 4, 1968.

We have completed our study of this application as submitted and find we are unable to act favorably on it due to the absence of an analytical method with acceptable sensitivity. On this basis, we cannot accept the use of tonidazole as safe until an acceptable method with better sensitivity (preferably 10 ppb) is developed, or the submission of data to demonstrate the lack of carcinogenic properties of this drug.

In the event data can be presented to demonstrate the lack of carcinogenic properties of tonidazole, further work will have to be done on your present method, as we are unable to validate it at the claimed sensitivity of 0.05 ppm.

Since we are unable to recommend favorable action on your submission we suggest you withdraw your new drug application and the overage petition [illegible] petition without prejudice to a future filing of the necessary data cannot be furnished promptly. Within 30 days of the date of this letter please let us know whether you wish to withdraw your submission or indicate when all of the necessary data will be furnished.

Sincerely yours,

Director, Bureau of
Veterinary Medicine

cc: Dup NDA
Vet Lab
[illegible]
[illegible]
[illegible]
[illegible]

COPY

Dr. Weidner, BVM (VM-110) July 18, 1969

M. Prechazka, DFCT (FAPEB) (SC-470)

NDA P 39-247V - Vol. 3 & 4 - Ronidazole
Merck & Co. (AF 12-611)

Additional evaluation of NDA p 39-247V, Vol 3 & 4, Ronidazole in feed for turkeys - Merck & Co.

DFT has stated that they now need a method which is sensitive to 2 ppb so Merck has presented a modified method (letter dated 7/1/69). The previous method had a claimed sensitivity of 30 ppb but the best that Kan DO and DFCT were able to obtain was a sensitivity of 500 ppb (0.5 ppm). See DFCT memo dated 3/7/69.

This modified method has a claimed sensitivity of 10 ppb. It is very similar to the previous method except that it mainly differs in instrumentation. It utilizes pulse polarography instead of conventional polarography. The Heineb Pulse Polarograph or, the Davis Polarotrace may be used.

The ronidazole is extracted from the tissue into ethyl acetate, the ethyl acetate is evaporated and the residue taken up in 1M HCl. Separation of most of the interfering tissue components is accomplished by washing the acid layer with petroleum benzin and/or benzene, followed by an extraction of the ronidazole at alkaline pH back into ethyl acetate. For final separation, of interferences, the concentrated ethyl acetate is streaked beside a 5 µg marker spot of ronidazole on TLC plate which is then developed with acetonitrile. The silica in area adjacent to marker spot is scraped from the plate and slurried with 1 ml. cold pH 11.0 buffer; the slurry is filtered and then polarographed in a micro-cell. A standard is separately carried through the assay procedure and ronidazole concentration in the tissue is determined from comparison of response of standard to that of sample.

Conclusions

1) The lowest standard run was 30 ppb. A standard should be run at 10 ppb to calculate recoveries at that level.

2) The readings from non-medicated controls are subtracted from the readings of the standard. This should not be done. The controls should be subtracted from the spiked samples when calculating recoveries.

3) Recoveries at 0.1 ppm level of drug in tissues (Table V-1) should be reported as 64% for muscle, 86% for liver, 92.7% for kidney and 68.4% for skin/fat.

4) The previous data showed that residues in tissues were down to < 0.05 ppm at 5 day withdrawal. We need data to show that residues will be less than 0.01 ppm (10 ppb) at 5 days. Better still, data to show that feeding exaggerated levels will result in residues of less than 0.01 ppm at 5 days unless DFT will accept 10 ppb residue as safe. If DFT needs residues of 2 ppb how can this be enforced with a method sensitivity of 10 ppb unless we can be assured that in actual practice turkeys would not be slaughtered until 8-10 days after treatment?

5) Instead of running the standard through the whole procedure, we would prefer to see the instrument calibrated by using the standard in buffer solution and run at 3 different concentrations. Petitioner should run standard as suggested above and compare recoveries with those using standard carried through the whole procedure at 10 ppb level.

We would prefer to have petitioner use a standard addition technique for the procedure.

cc: SC-1
SC-12
SC-401
SC-470
SC 970

MProchazka:mcs 7/18/69
D/Init: VKHumsey 7/18/69

Dr. R. F. Seidner
Division of Veterinary New Drugs (VM-110)

September 3, 1969

Dr. S. H. Frazier, Jr.
Division of Pharmacology and Toxicology
Petitions Review Branch (BC-470)

Ronidazole (Ridzol, MK-930)

NEW DRUG APPLICATION NO. 39-247

Merck, Sharp & Dohme
(Div. of Merck & Co.)
Rahway, New Jersey 07065
(AF 4-715)

The petitioner has submitted for review the following reports: (1) the complete two-year chronic study in dogs and rats, (2) an interim report of a 3-generation rat reproduction study, and (3) an evaluation of the estrogenic activity of MK-930.

Ronidazole has been satisfactorily identified in a previous evaluation (see Dr. Shibko's memo, dated May 7, 1968). The firm was requested to complete the chronic studies and conduct a demyelination study in chickens. Also, data from acute and subacute studies (17 weeks) in dogs and rats have been evaluated.

Two-year Toxicity Study: (dogs)

Twenty male and 20 female purebred beagles, approximately 6 months of age were used in this study. These animals were administered MK-930 orally in gelatin capsules once each day, seven days a week for two years. The initial dosage levels were 10, 20, and 40 mg/kg/day. After 34 days of continuous medication the high dosage level was reduced to 30 mg/kg/day for the duration of the study. The 20 animals were equally divided into a control, and three treatment groups consisting of an equal number per sex.

After one year of compound administration, two male and two female dogs in each group were sacrificed and necropsied for histopathology.

Laboratory tests performed were as follows:

a. Hematology - total and differential leucocyte counts, hematocrits, hemoglobin concentrations, erythrocyte sedimentation rates, and reticulocyte counts.

b. Biochemical Studies - plasma test for glucose, total protein, total albumen, urea nitrogen.

Orig + 2 cys BVM 9-10-69

c. Liver function - bromsulphalein retention, plasma alkaline phosphatase activity, prothrombin time, SGOT and SGPT transaminase activity.

d. Urine - gross appearance for color, bilirubin, occult blood, albumin and glucose.

Results:

1. Behavior, appearance and mortality:

a. Control: The control group of dogs remained essentially normal in behavior and appearance.

b. 10 mg/kg/day: Dogs at this dosage level exhibited occasional fine tremors and from time to time appeared to be slightly dehydrated.

c. 20 mg/kg/day: As the study progressed, dogs in this group developed nervous behavior and became hyperactive. Seven of the 10 dogs developed fine tremors which persisted throughout the 24 hours observation period and remained a few days to several months. Three dogs at this dosage level (2 males, 1 female) failed to survive the duration of the study.

d. 30 mg/kg/day: Dogs at this dosage level exhibited signs similar to dogs at the mid-dose level except the signs were more intense and of longer duration. Also, the dogs in this group showed anorexia, weight loss, ataxia, spastic stiff legged walk and humpbacked stance.

All groups of dogs showed pigmentation of the sclera. In control dogs and dogs in the 10 mg/kg/day group the areas of pigmentation were one to three millimeters in width, and appeared in the inner corners of the eye. At the 20 mg/kg level, the areas were larger in dimension than dogs at the 30 mg/kg level, the entire visible sclera was pigmented.

2. Physical examinations:

In addition to the other changes mentioned, the following physical signs were noted after 24 months of medication: One male control showed atrophy of right testicle, two males at the low level had enlarged prescapular and popliteal lymph nodes. One male at the low level had the right testicles smaller than the left. One dog at the 20 mg/kg level developed bilateral lens opacity and both testes appeared undeveloped.

3. Body weight:

All of the control dogs and treated dogs at the 10 mg/kg level maintained normal weight. At the 30 mg/kg level, three dogs gained and six dogs showed a marked decrease in weight. Food consumption was normal for both controls and the low dose groups. Most of the dogs at the high level showed signs of anorexia.

4. Laboratory tests:

Examinations of parameters in this test was made at 2, 6, 12, 18, and 24 months of the study. Hematological results demonstrated at two months interval an elevated RBC sedimentation rate at the low level. Two dogs at the mid level and four dogs at the high level exhibited a leucocytopenia.

After six months of treatment the leucocytopenia persisted at the 20 and 30 mg/kg/day levels. One dog at the high level exhibited an elevation in polymorphonuclear leucocytes and a decrease in total lymphocytes.

After 12 months of therapy, dogs at both the mid and high dose level showed leucocytopenia, lymphocytopenia, elevation in polymorphonuclear leucocytes and extremely reduced hemoglobin and hematocrit values.

After 18 months of dosing, leucocytopenia was marked in 2 female dogs at the mid dose level. The two surviving dogs at the high dose level exhibited marked leucocytopenia. The hemoglobin and hematocrit values were reduced in one female at the 20 mg/kg/day dosage level.

Twenty-four months of continuous treatment, leucocytopenia was no longer in evidence, however, one control, two treated dogs at the low level (10 mg/kg/day) and one male at the mid level exhibited low WBC counts. One female dog (10 mg/kg/day) exhibited an elevated RBC sedimentation rate.

Plasma examination revealed at the six-month interval a slightly elevated BUN value in one control male dog, one male at the 10 mg/kg level and one male at the 20 mg/kg level. After one year the one male control dog continued to show an elevated BUN, whereas, the other animals showed normal values. At 18 months, the previous mentioned control dog had normal

values and one control male and treated female (20 mg/kg) showed elevated values. After 24 months only one male (10 mg/kg/day) showed an elevation in BUN, no other alterations in plasma chemistry were seen.

Liver function at the two month interval in one female (20 mg/kg) and one male at the high level exhibited an elevation in serum transaminase (SGOT and a very slight elevation in bromsulphalein retention (30 minutes) and SGPT).

After six months of testing two animals at the mid dose level exhibited elevation in prothrombin time in addition to elevated bromsulphalein retention. No other changes were observed.

Liver function tests applied at one year and 18 months did not reveal any other changes other than those previously mentioned.

At the two year interval, two control dogs and one male dog (10 mg/kg) exhibited elevated SGOT and SGPT values. All other animals had essentially normal values.

Urinalysis results at two months exhibited an elevation at the mid and high dosage levels. After one year of treatment the number of dogs exhibiting these signs diminished (specific gravity).

The other findings included a 2-plus occult blood in one control and two dogs at the mid level. These findings were considered incidental.

Pathological Results: (gross)

Gross lesions which were considered compound related were found in the brain of two male dogs at 30 mg/kg/day level. Bilateral yellowish, irregular areas were seen in the ventral internal capsule at the level of the optic chasma of a dog that died during the 14th week of the study. One dog which was sacrificed at 16 weeks exhibited a slightly yellowish area near the globus pallidus of the cerebrum.

No gross brain lesions were seen in 8 dogs at 30 mg/kg level which died or were sacrificed. Dogs at the 20 mg/kg/day level exhibited slight hydrocephalus at 91 weeks; a pale yellow brain and subdural hemorrhage was seen in two dogs at the 71st and 91st weeks. No other gross brain lesion were seen in the study.

Hemorrhages in various areas of the heart were found in 4 of 7 dogs of the high dose during the first year and 1 of 3 dogs at the same level during the second year. Three of six dogs at the mid level exhibited the same lesions.

Absolute testes weights of treated dogs at all dosage levels were decreased when compared with testes weight of control dogs. This decrease was at the $p < 0.05$ level in dogs from the 10 mg/kg/day group after one year, at the $p < 0.01$ level in dogs from 20 and 30 mg/kg at one year and the 10 and 20 mg/kg/day group sacrificed at 2 years.

Histopathology Data:

Microscopic lesions seen in the brains consisted of focal leucomalacia in the cerebrum and cerebellum. There were focal areas of vascularization with endothelial proliferation within the gray matter. Neuronophagia was occurring in most of these areas with a varying number of foamy phagocytes. All of these lesions were confined to the 30 mg/kg/day dosage level.

Other incidental brain lesions included a glial nodule in the cerebrum of one control dog; a subepedymal mononuclear cell nodule third ventricle of a control and treated dog at the low level. The other lesions were confined to the mid and high dose levels.

A coarse granular dark pigment was seen in lymph nodes in varying amounts in 14 dogs; one control, five-10 mg/kg, six-20 mg/kg, and two-30 mg/kg/day level. A moderate amount was seen at the low and mid dose levels. This was considered to be melanin.

The spleen exhibited a moderate to large amount of hemosiderin in 2 dogs at the 10 and 20 mg/kg levels and three dogs at the high level. Lesser amounts were seen in most other dogs on the study.

Aspermatogenesis was found in both testes of one male dog each at the 10, 20, and 30 mg/kg/day levels. Oligospermia was seen in two dogs at the 10 mg/kg and one male each at the mid and high levels. These testicular lesions were considered to be compound related.

Chronic Toxicity - Rats:

One hundred and sixty-eight males (weighing 65-145 grams), and one hundred and sixty-eight females (weighing 66-132 grams), approximately 5 to 6 weeks old, albino rats of the Manor Farms strain were used in this study.

MK-930 was mixed into the diet at initial concentrations of 100, 200, or 400 ppm. These concentrations were equivalent to 10, 20, or 40 mg/kg/day. These animals were divided into one control and three treated groups of 42 male and 42 female rats each and were selected and grouped in such a manner that the group body weight means were similar for each sex.

Laboratory tests were conducted consisting of the following parameters: hematology (total and differential leucocyte counts, hematocrits, hemoglobin concentrations and RBC sedimentation rates), biochemistry (SGOT, SGPT, glucose and urea nitrogen), urinalyses (color and appearance, pH, volume and specific gravity, albumin, glucose, bilirubin and occult blood).

Results:

There were no pharmacodynamic signs or changes in behavior which were considered drug related. Some occasional incidental signs, not unusual for albino rats included respiratory congestion, ocular or nasal discharge and alopecia. The respiratory condition was noted the first 6 months; it increased in all control and treated animals for the duration of the study. A few rats exhibited behavior characteristics of middle ear infection. Several rats in the control or treated group exhibited corneal opacity or destruction of the right eye. Some rats of both sexes, in all groups, developed cachexia, loss in body weight and died.

In the second year of the study, nodules, cysts and/or masses developed in rats in all groups. The total incidence of "masses", not including nodules or cysts were as follows:

	Males	Females
control	1/42	6/42
10 mg/kg/day	3/42	12/42
20 mg/kg/day	5/42	23/42
40 mg/kg/day	14/42	23/42

Most of the masses were located in the region of the abdomen, flank, or thorax.

Nodules and cysts also were observed in both sexes of rats in all groups. The number found was equal for all groups. Some of the smaller growth appeared and disappeared spontaneously. A few developed into larger masses.

Mortalities occurred with slightly greater frequency in the males of the control and treated groups than in the female control and treated groups.

The percentage of mean body weight was higher among treated males than control males. The 10 mg/kg ranged from 5% to 13% greater during the first 63 weeks of treatment.

Female rats from the 44th week exhibited a 6-24% less body weight than the controls at the 40 mg/kg/day dosage level. The 10 mg/kg/day dosage level did not exceed 10% at any time during the study and the 20 mg/kg levels were similar in body weight.

Hematological values were checked at 18 and 22 month intervals. At 18 months two male rats at the 20 mg/kg/day dosage level exhibited an elevation in RBC sedimentation rate and an elevation in neutrophil count and a decrease in lymphocyte count.

At the 22 month interval of examination the alterations were as follows: 1 male control elevated leucocyte count, 1 female 10 mg/kg elevated hematocrit and hemoglobin values, 3 female and 1 male 20 mg/kg decreased hematocrit and hemoglobin values and an elevated leucocyte count, and 2 males and 2 females at the 40 mg/kg level showed the same signs. Rats in all groups exhibited variable reticulocyte counts. The changes at term which disclosed variable counts in controls and treated groups would indicate dose relationship.

Biochemical and urinalysis studies showed no alterations that were considered compound related.

Pathological Results:

Gross Pathology

Bilateral testicular atrophy from male rats in the 20 and 40 mg/kg/day group was found. Rats from the treated groups which died after the first year or were sacrificed after 22 months had a greater incidence of skin masses (mammary neoplasms) when compared with the controls, which is considered compound related.

Histopathology

Compound related liver lesions were seen in rats from the 40, 20, and 10 mg/kg/day groups examined after 22 months. Livers of most rats from the high and mid dose levels had changes in the hepatocyte nuclei which were considered drug related.

Neoplasia was experienced at all levels of treatment. The most frequently found neoplasms were benign and malignant mammary tumors in female rats from the 10, 20, and 40 mg/kg/day groups and in males from the 40 mg/kg/day group.

The numbers of female rats in the control, 10, 20, and 40 mg/kg/day groups which had mammary adenomas or fibroadenomas were 7, 13, 21, and 19 respectively. Mammary adenocarcinomas were observed in two female rats from the 10 mg/kg/day group; no tumor of this type was observed in the control or 20 mg/kg/day group. Five male rats from the 40 mg/kg/day group had mammary adenomas or fibroadenomas, and one male had a mammary adenocarcinoma. No lesions were observed in male rats from the control, 10, or 20 mg/kg groups.

The mortality rates for the 22 month study are as follows.

Control				10 mg/kg/day			
1st year		2nd year		1st year		2nd year	
Male	Female	Male	Female	Male	Female	Male	Female
8	3	18	12	2	1	18	11
Total deaths - 41				Total deaths - 42			
% mortality - 48.8				% mortality - 50			

20 mg/kg/day				40 mg/kg/day			
1st year		2nd year		1st year		2nd year	
Male	Female	Male	Female	Male	Female	Male	Female
2	3	18	15	9	1	17	13
Total deaths - 38				Total deaths - 45			
% mortality - 45				% mortality - 53.6			

The following tables gives the incidence of neoplasia in all rats.

NDA No. 39-247 - 9 -

MK-930 Twenty-Two Month Feeding Study in the Albino Rat

TABLE 45 Incidence of Neoplasia, All Rats

Location Neoplasm	Control		10 mg/kg/day		20 mg/kg day		40 mg/kg/day	
	M	F	M	F	M	F	M	F
SKIN								
Mammary adenoma, fibroadenoma		7		13		21	5	19
Mammary adenocarcinoma				2			1	5
Fibroma	1		2		2	1	1	1
Fibrosarcoma						1		
Hemangioma							2	
Hemangioendothelioma				1				
Lipoma							2	
Papilloma		1						
Squamous cell carcinoma		1			1			
Basal cell carcinoma	1							
Osteosarcoma					1			
Adenocarcinoma, salivery gland							1	
Adenocarcinoma, origin undetermined								1
Adnexal tumor, benign							1	
PITUITARY								
Adenoma	5	9	4	7	4	7	3	8
Adenocarcinoma	1	2			1			1
THYROID/PARATHYROID								
Light cell adenoma, thyroid	1	1					1	
Adenocarcinoma, thyroid	1				1			
Adenoma, parathyroid	1							
PANCREAS								
Islet cell adenoma	1						1	
Adenocarcinoma, ductal					1			
ADRENAL								
Pheochromocytoma								2
OVARY								
Granulosa cell tumor						1		
UTERUS								
Endometrial polyp		1		2		3		2
Adenocarcinoma		1						1
Leiomyoma						1		

NDA No. 39-247 - 10 -

BK-930 Twenty-Two Month Feeding Study in the Albino Rat

TABLE 43 Incidence of Neoplasia, All Rats

Location (Continued) Neoplasm	Control M	Control F	10 mg/kg/day M	10 mg/kg/day F	20 mg/kg/day M	20 mg/kg/day F	40 mg/kg/day M	40 mg/kg/day F
STOMACH								
Adenocarcinoma			1					
SMALL INTESTINE								
Adenocarcinoma				1				
SPLEEN								
Hemangioma					1			
LIVER								
Hepatoma			1					
KIDNEY								
Leiomyosarcoma								1
URINARY BLADDER								
Polyp			1					
ABDOMINAL CAVITY								
Mesothelioma					1			
Adenocarcinoma, origin undetermined						1	1	
MEDIASTINUM								
Lipoma			1				1	
Chondrosarcoma					1			
BRAIN								
Oligodendroglioma								1
GENERALIZED								
Lymphosarcoma			1		1			

NDA No. 39-247 - 11 -

MK-930 Twenty-Two Month Feeding Study in the Albino Rat

TABLE 48 Incidence of Neoplasia. All Rats

Location Neoplasm	Control M	Control F	10 mg/kg/day M	10 mg/kg/day F	20 mg/kg/day M	20 mg/kg/day F	40 mg/kg/day M	40 mg/kg/day F
TOTALS								
ALL NEOPLASMS:								
Neoplasms*	12	24	11	41	16	52	28	64
Benign Neoplasms*	9	20	8	37	8	49	26	54
Malignant Neoplasms*	3	4	3	4	8	3	2	10
Rats with Neoplasms	6	17	10	19	13	25	15	24
Rats with Malignant Neoplasms	2	3	3	4	8	3	2	9
Rats with Multiple Neoplasms*	3	6	1	9	2	15	6	16
MAMMARY NEOPLASMS**								
Mammary Neoplasms*	0/34	8/39	0/40	30/41	0/40	37/41	14/32	46/41
Benign Mammary Neoplasms*	0/34	8/39	0/40	28/41	0/40	37/41	13/32	41/41
Malignant Mammary Neoplasms*	0/34	0/39	0/40	2/41	0/40	0/41	1/32	5/41
Rats with Mammary Neoplasms	0/34	7/39	0/40	14/41	0/40	21/41	6/32	20/41
Rats with Benign Mammary Neoplasms	0/34	7/39	0/40	13/41	0/40	21/41	5/32	19/41
Rats with Malignant Mammary Neoplasms	0/34	0/39	0/40	2/41	0/40	0/41	1/32	5/41
Rats with Multiple Mammary Neoplasms	0/34	1/39	0/40	6/41	0/40	11/41	3/32	13/41

* Each benign tumor counted as a separate tumor; primary and metastatic malignant tumors of same type counted as a single tumor.

** Denominator is population at end of 52 weeks which was the time the first mammary tumor was observed at necropsy.

Three-Generation Reproduction Study in Albino Rats (Interim Report)

Forty male and 80 female albino rats of the Charles River CD strain were used for this study. The rats were approximately 35 days old at the time this study started. This report concerns the data obtained in the first one-half of this study.

The rats were divided into one control and three test groups of 10 males and 20 females each. They were fed continuously a diet containing MK-930 at levels of 200, 400, and 800 ppm for a period of approximately 48 weeks.

First Generation - P_1

The control and test groups of rats were maintained on their diets for 70 days prior to the first mating. After 70 days of feeding the control and test rats were mated for 21 days.

Three weeks were allowed for gestation and an additional three weeks for nursing of the pups prior to weaning. Following a five-day period of rest after weaning the pups, the parental rats were again mated. Again, three weeks were allowed for mating, three weeks for gestation and three weeks for nursing the pups.

Pups from the first mating (F_{1a}) were examined for external abnormalities and sacrificed at the end of the 21-day nursing period. Pups from the second litter (F_{1b}) and the parenteral (P_1) rats were sacrificed and discarded.

Twenty female and 10 male rats from each group of the F_{1b} litter were selected for the second generation (P_2) parental rats. The remainder of the pups were examined and discarded.

Second Generation - P_2

After weaning the F_{1b} pups which were selected for the P_2 generation were continued on the MK-930 for 70 days and mated. The offspring from the mating (F_{2a}) were examined and sacrificed.

This generation is not complete; one litter has been born. Other females are near delivery. The F_{2b} offspring will be nursed for 21 days and then weaned. The P_2 parental rats will be sacrificed and offspring from this generation will be selected as the third (P_3) generation parents. The remainder of the progeny will be examined for external abnormalities, sacrificed, and discarded.

Third Generation - F_3

Rats composing this generation will be handled the same way as the first two generations.

Results:

No unusual alterations in behavior and appearance have been observed in either the F_1 or F_2 parental rats in this study. The incidence that appeared was respiratory congestion equally dispersed in the control and treated groups of rats. In addition, nodules and masses at various sites on the body surface was observed in both treated and control rats.

The body weights of all three test groups of both F_1 and F_2 generations, compared favorably with the controls. There were no adverse findings in the survival rates of females in both generations. There was a slight variation in group food consumption averages in all groups, male and female, control and treated from one week to another. However, at this point no noteworthy differences are noted.

Breeding Cycles:

1. Reproduction

Data obtained from both breeding cycles of the F_1 generation and from the first breeding cycle of the F_2 generation have not revealed abnormalities, development of the embryo and fetus, delivery, live births, viability of the newborn, survival of the pups to weaning or growth of the pups. When compared to the controls, fertility, gestation, viability and lactation indices are similar.

The average number of pups per litter were noticeably lower among the female rats at 800 ppm level than female rats at lower dietary levels or among females in the control group. This finding was observed in both litters of the F_1 generation parents as well as in the first litter of the F_2 generation parents.

2. Teratology

Teratologic changes which were considered to have been spontaneous, have been seen in one pup from the control group, one pup from the 200 ppm group and two pups from 400 ppm group.

A control pup from the first generation, second litter, had hydrocephalus and bilateral anopthalmia; the pup from the 200 ppm group, first generation, second litter had hydrocephalus; one pup from the 400 ppm group had hydrocephalus and unilateral anophthalmia; another pup from the 400 ppm group had anodontia.

Another study was conducted to determine if MK-930 possessed any estrogenic activity. Using three methods for detection, no evidence was found for significant estrogenicity of MK-930.

DISCUSSION:

The data from the two-year study in dogs revealed many changes that are drug related. The dosage levels used were 10, 20, and 40 mg/kg/day. Thirty-four days after the study commenced the high dose level was reduced to 30 mg/kg/day for the duration of the study.

All treated dogs exhibited signs of tremors, hyperactivity, and nervous behavior. This behavior pattern was more pronounced at the higher levels. Also, physical examination revealed testicular atrophy at all levels. These changes were prominent after 24 months of dosing.

Laboratory test results revealed leucocytopenia and elevated RBC sedimentation rates at all levels. However, the number of animals exhibiting these changes at 24 months was reduced. The BUN, SGOT, and SGPT values were elevated. Pathological changes found were gross lesions in the brains of dog at the mid and high dose levels. The weights of the testes were decreased at all dosage levels when compared to controls. Microscopic examination of the testes demonstrated aspermatogenesis at all treated levels and oligospermia at the low level. These changes are drug related.

Based on the results of this two-year study, the firm has not established a no-effect level in dogs. The two-year rat study did not reveal any serious changes in the behavior which were considered drug related. Hematological values demonstrated an elevation of RBC sedimentation rates and decrease in lymphocyte counts. Changes that were revealed and considered serious was the development of tumorous masses. Also, testicular atrophy was noted at the 20 and 40 mg/kg levels.

Neoplasia was experienced at all levels of treatment; the most frequently found neoplasms were benign and malignant mammary tumors. Mammary adenomas or fibroadenomas were found at all levels with a larger perponderance in the treated groups. Adenocarcinomas were observed at the low levels but not in the controls and mid dose levels.

A review of the data on incidence of tumors in all rats at 22 months shows the following:

	No. Rats Survived	No. Rats With Tumors	Percentage of Incidence
Control	43	23	53%
10 mg/kg/day	42	29	69%
20 mg/kg/day	46	38	82%
40 mg/kg/day	39	39	100%

Based on this data we can see the occurrence of neoplasia in rats is dose and drug related. A review of the tables included in this evaluation will reveal additional results.

The reproduction study is an interim report. It has thus far been carried through the F_1 and F_2 generation. No adverse effects were recorded. In addition, no evidence of estrogenic activity was reported for MK-930.

Mr. Prochazka's memo dated July 18, 1969 states that "residues in tissues were down to < 0.05 ppm at 5-day withdrawal."

CONCLUSION:

Based on the results of hematological changes, liver function test, brain lesions, and testicular atrophy at the low dose level, there is no no-effect level for the two-year dog study.

Due to the incidences of neoplasia in the two-year rat study at all dose levels, we can conclude that MK-930 is a tumorigen and probably a carcinogen.

The present residue levels are inadequate to assure human safety.

INIT: ERlumenthal

cc: SC-970
SC-470
NDA No. 39-247

EHFrazier:gr 9/3/69

This document verifies receipt of NADA 37-247. See front of 1st sheet and back of second sheet date lined with check.

This comes from our log file.

This is in reference to item #8 of my response.

Frazer

NDA #P89-247v

Merck, Sharp and Dohme
RIDZOL (RONIDAZOLE)
medicated turkey feed
5-days withdrawal before slaughter
x-ref. VID 77, 273, 348

ESA cert 7-3-68
+ FCT 7-25-68
DFCT-12-9-68
rec'd 3-7-69 ✓
DFCT-7-18-69
Brm-10-3-69
DFCT-1-14-70
DFCT-2-9-70 GR (WD 5-16-70
DFCT-10-9-70
rec'd 12-29-70
Prochnik's memo-1-12-71
President's memo-2-22-71
EHB memo-3-5-71 (brm 3-9-71)
Brm 8-5-71
Cafritz memo 5-17-72

OCT 2, 1969

Merck, Sharp & Dohme
Research Laboratories
Division of Merck & Company, Inc.
Rahway, New Jersey 07065

NADA 139-247V

Attention: Mr. J. H. Young

Gentlemen:

Reference is made to your submission dated July 1, 1969, submitted with respect to your new animal drug application dated March 27, 1968, for the preparation Ridnol (Ronidazole) for use in medicated turkey feed.

We have completed our study of the submitted data and have the following comments:

Tissue residue method -

1. The lowest standard run was 30 ppb. A standard should be run at 10 ppb to calculate recoveries at that level.

2. The readings from non-medicated controls are subtracted from the readings of the standard. This should not be done. The controls should be subtracted from the spiked samples when calculating recoveries.

3. Recoveries at 0.1 ppm level of the drug in tissues (table V-1) should be reported as 64% for muscle, 66% for liver, 92.7% for kidney and 68.4% for skin/fat.

4. We need data to show that residues will be less than 0.01 ppm (10 ppb) at 5 days. Better still, data to show that feeding exaggerated levels will result in residues of less than 0.01 ppm at 5 days.

5. Instead of running the standard through the whole procedure, we would prefer to see the instrument calibrated by using the standard in buffer solution and run at 3 different concentrations. Petitioner should run standard as suggested above and compare recoveries with those using standard carried through the whole procedure at 10 ppb level. We would prefer to have firm use a standard addition technique for the procedure.

Toxicity report -

1. Based on the results of hematological changes, liver function test, brain lesions, and testicular atrophy at the low dose level, there is no no-effect level for the two-year dog study.

2. Due to the incidence of neoplasia in the two-year rat study at all dose levels, we can conclude that MK-930 is a tumorigen and probably a carcinogen.

Since we are unable to recommend favorable action on your submission we suggest you withdraw your new animal drug application and the corresponding food additive petition without prejudice to a future filing. If the necessary data cannot be furnished promptly, within 30 days of the date of this letter, please let us know, in writing, whether you wish to withdraw your submission or indicate when all of the necessary data will be furnished.

Sincerely yours,

Director, Bureau of
Veterinary Medicine

cc:
Dup. NDA
Trip. NDA
CH-227
HH-11
HDucharme/cmo 9-25-69

SC-47[illegible]

January 14, 1970

FAPES/DFCI, SC-470

Additional evaluation of MDA 39-247V, Ronidazole in feed for turkeys - Merck, Sharp + Dohme.
Dr. Ducharme, BVM (VM-110)

A review of the data on the two year study (Re: Dr. Frazier letter dated Sept. 3, 1969 to Dr. Weidner, BVM) concludes that Ronidazole is tumorigenic and likely carcinogenic and that a no-effect dose has not been established.

It would then appear that a method of analysis is required to show, virtually, the absence of Ronidazole in tissues from treated animals (turkeys).

A review of the MK-930 modified polarographic method July 1, 1969 shows the method to be reliable at 20 ppb, but there is some question on the reliability at 10 ppb. The sensitivity at the 10 ppb level would most certainly require validation, if DPT concurred on safety at this level. It appears however that we would need validation at sensitivity of 2-3 ppb. However, the method would be unacceptable at the 2 ppb sensitivity since the reagent blank alone is of the order of 4 ppb.

It appears that the pulse polarographic method has been extended to the limit of its sensitivity and an entirely new method, perhaps GLC, could possibly achieve the 2 ppb sensitivity requirement.

cc: SC-1
SC-12
SC-401
SC-470 (2)
SC-970

MProchazka:mcs 1/14/70

Merck Sharp & Dohme
Rahway, New Jersey
February 3, 1970

MEMORANDUM OF A CONFERENCE

BETWEEN:

J. M. Young
George V. Downing
James J. Dittick
P. I. Pollak
Merck Sharp & Dohme

and

George D. Lakata- DFCT
Milo Prochazka - DFCT
D. P. Ducharme- DVMD, DVH

SUBJECT: NADA 39-247V - Ronidazole

The firm requested the conference to discuss the tissue residue assay method data they submitted under cover letter dated December 18, 1969. The submitted information was in response to our letter of October 2, 1969. The data was discussed and it was decided that DFCT would review the data in depth and we would correspond with the firm at a later date.

The proposed method has a sensitivity of 10 ppb. The firm was informed that as indicated earlier this sensitivity is acceptable at this point in time, but that upon review of the toxicity data, a lower sensitivity might be needed.

The firm next asked about our letter dated January 26, 1970. I indicated that since the toxicity data requested in our letter of October 2, 1969, could not be submitted until after May 1970, we would have to insist on the withdrawal of the application. The firm indicated they would submit a request that the application be withdrawn.

D. P. Ducharme, D.V.M.

cc:
CA-227
VM-11
Dup. NDA
Trip. NDA
DPDucharme/cms 2-4-70

BF 1148

March 5, 1971

MK-930 Ronidazole

Dr. A. R. Cabuten
Division of Veterinary New Drugs (VM-113)

NEW ANIMAL DRUG APPLICATION No. 39-247 Merck, Sharp and Dohme
Rahway, New Jersey 07065
(AF 4-715)

The petitioner has submitted another two-year oral chronic toxicity study in rats. These data are for the purpose of demonstrating the lack of carcinogenic properties of Ronidazole. A similar study reviewed on September 3, 1969, indicated that MK-930 was a tumorigen and probably a carcinogen. Based on these facts the sponsor was given an option of developing a more sensitive method or presenting data to show the lack of carcinogenic properties.

The earlier study was conducted using Manor Farm rats (Wistar strain), dosed at drug levels of 10, 20 and 40 mg/kg/day to groups of 42 male and 42 females each. Rats used in the present study are Charles River (CD) dosed at drug levels of 0.0, 0.5, and 5.0 mg/kg/day to groups of 30 males and 30 females each.

Tumor incidence demonstrated in the first study show a drug- and dose-related effect as follows:

	Control		10 mg/kg/day		20 mg/kg/day		40 mg/kg	
	M	F	M	F	M	F	M	F
All neoplasms	12	24	11	41	16	52	28	64
Benign neoplasms	9	20	8	37	8	49	26	54
Malignant neoplasms	3	4	3	4	8	3	2	10
Mammary neoplasms								
Benign mammary neoplasms	0/34	8/39	0/40	28/41	0/40	37/41	13/32	41/41
Malignant mammary neoplasms	0/34	0/39	0/40	2/41	0/40	0/41	1/32	5/41

Note: Neoplastic lesions also were found in other organs.

The tumor incidence of the second study which was conducted at dose levels of 0.5 and 5.0 mg/kg/day did not reveal a dose-related effect. There was no appreciable difference between the control and treated rats. The terminal results showed a higher incidence of total and confirmed neoplasms in the control than treated rats.

Based on the facts that the present study was conducted at dose levels (0.5, 5.0 mg/kg) lower than the previous study (10, 20, 40 mg/kg) and the difference in the strain of rats, our conclusions remain the same. The sponsor has not demonstrated that MK-930 lacks carcinogenic properties. Therefore, a more sensitive method for residue is needed (2 ppb or less). The present validated method of 10 ppb is inadequate.

The present results of the two-year dog study conducted at 0.5 and 5.0 mg/kg demonstrate no drug-related effects at these levels. Results obtained from the first study conducted at dose levels of 10, 20 and 40 mg/kg/day, demonstrated dose- and drug-related lesions in the brain and testes of treated dogs. These results are adequate for the dogs only, but they do not alter our previous conclusions for MK-930 as a possible carcinogen.

Three-Generation Reproduction Study in Rats:

The previous data reviewed was an interim report for the first one-half of that study. Results obtained from this report are final data for the three-generation study. MK-930 was incorporated in the diet of male and female albino rats at levels of 200, 400 and 800 ppm.

RESULTS:

No unusual alterations in behavior and appearance were observed in the mean body weights or weekly group mean food consumption values.

Teratological examinations did reveal some changes, but they were not considered compound-related. The lesions were comparable between the control and treated animals.

Reproduction data included observations for fertility, litter size, numbers of male and female pups, average pup weight at birth, viability, survival of pups to weaning and growth of pups. The fertility index was significantly lower for the 800 ppm group and slightly lower at the 400 ppm dietary level. The F_3 generation at the 200 ppm level was equal to the controls.

The total number of females born and weaned showed a dose-related decrease for all dietary levels, however, the 200 and 400 ppm groups showed no statistically significant differences. The 800 ppm group demonstrated a significant decrease when compared to the controls. The 200 and 400 ppm groups did not show a statistically significant decrease, whereas, the 800 ppm group was significantly decreased.

The total rats born and weaned again demonstrates a dose-related decrease. The 200 ppm groups showed no significant differences compared with the controls. The total pups born in the F_{2B} were significantly higher than the controls and the total weaned in the F_{2B} and F_{3A} generations were higher than the controls. Although the 400 ppm group demonstrates no significant differences in total born, the difference is slight and does suggests a trend to an effect. The total weaned at this level was significantly lower in F_{1B} generation, all other generations and litters were not lower than the controls based on statistical analysis. The 800 ppm group showed a statistically significant decrease in both total born and weaned.

Pathological examination of the F_{3B} weanlings did not reveal any compound-related gross or microscopic lesions in the controls or treated pups.

SUMMARY:

Results obtained from the three-generation rat reproduction study demonstrate that the 800 ppm dietary group exhibited drug-related effects.

Reproduction data for the 200 and 400 ppm groups revealed scattered differences when compared to the controls. The 400 ppm showed more of a trend toward an effect than the lower level. I conclude that a 200 ppm is the no-effect level on reproduction.

DISCUSSION:

It was previously concluded that MK-930 was a tumorigen and probably a carcinogen, based on results from an earlier two-year rat study. Results obtained from the present two-year rat study are not adequate to change this conclusion.

Results obtained from the first study conducted at dose levels of 10, 20 and 40 mg/kg/day using Manor Farm (Wistar strain) rats, demonstrate a dose-related effect in tumor incidence. Data obtained from the present study conducted at 0.5 and 5.0 mg/kg/day, using Charles Rivers CD rats demonstrate that the tumor incidence was not drug- or dose-related. In fact the tumor incidence was higher in the control rats when compared to the treated rats. However, based on the low levels used in the present study, the difference in the strain or rats, and positive findings of tumors in the first study run at higher test levels, the sponsor has failed to demonstrate a lack of carcinogenic properties of MK-930. Therefore, the present validated method of 10 ppb is inadequate. A more sensitive method (2 ppb or less) is needed.

Results of the present two-year dog study demonstrate a no-effect level (5.0 mg/kg) for brain and testicular lesions. Since we are dealing with

a potential carcinogen, these results have no bearing on the overall conclusions for MK-930.

The rat reproduction data are adequate to demonstrate a no-effect level of 200 ppm. The 400 ppm level showed some scattered effects and a slight trend toward an effect. The 800 ppm level showed significant adverse effects when compared to the control.

CONCLUSION:

The results of the present two-year rat study are inadequate to show the lack of carcinogenic properties of MK-930. When compared to the results of the previous two-year rat study, the dose levels were too low and there was a difference in the strain of rats used. The validated method of 10 ppb is inadequate to assure human safety. A more sensitive method is needed (2 ppb or less). MK-930 is a tumorigen and probably a carcinogen.

Dr. S. H. Frazier, Jr.
Division of Toxicology
Petitions Review Branch (BF-148)

Attachment

INIT:CJKokoski

cc:
BF-148
BF-140
BF-117
NADA No. 39-247

SHFrazier:mmt 3/8/71

NADA 39-247V
AF 4-715

March 11, 1971

MEMORANDUM OF CONFERENCE

Present: Mr. Buck
Dr. Siegmund
Merck Sharp & Dohme
Rahway, New Jersey

and

Dr. A.R. Gabuten
DMAD/VM 340

Subject: Ronidazole

1. Mr. Buck and Dr. Siegmund were in to discuss the above NADA. When Mr. Buck called to make the appointment, I did not have the comments of Dr. Frazier dated March 5, 1971. I told him that I would not be in a position to tell him anything about the two-year chronic study in rats. He insisted to drop by anyway, so I agreed. In the meantime, I got the memo from Dr. Frazier a day before the meeting.

2. In the conference, I informed them that the results of the present two-year rat study are inadequate to show the lack of carcinogenic properties of MK-930. When compared to the results of the previous two-year rat study, the dose levels were too low and there was a difference in the strain of rats used. The method is already validated by Mr. Prochazka's group with a sensitivity of 10 ppb but DT would like a more sensitive method of 2 ppb or less.

3. Mr. Buck argued that on April 28, 1969, they were given two alternatives by BVM, either to develop a method with better sensitivity (preferably 10 ppb) or the submission of data to demonstrate the lack of carcinogenic properties of this drug. He claimed that they did both and now both (method sensitive to 10 ppb and two-year chronic study) are unacceptable. Mr. Buck indicated that he did not want any letter at this time that will indicate our conclusions because they want to resolve this with BVM and the Bureau of Foods.

Adriano R. Gabuten

Adriano R. Gabuten, D.V.M.

cc:
NADA dup, VM 11
NADA trip, VM 11
CA-226
Dr. Gabuten, VM 340 ARGabuten/dsk/3-30-71

AP 4-715
NADA 39-247V

April 26, 1971

MEMORANDUM OF CONFERENCE

Between: J. M. Young
R. R. Buck
Merck Sharp & Dohme
Rahway, New Jersey

and

Dr. F. J. Kingma, VM 2
Dr. J. H. Mark, DNAD, VM 300
Dr. A. R. Gabuten, DNAD, VM 340

Subject: Ronidazole

The firm representatives requested the conference to discuss the sensitivity of the tissue assay method for ronidazole.

In an earlier conference, Mr. Buck and Dr. Siegmund were informed that the results of the second two-year rat study are inadequate to show the lack of carcinogenic properties of Ronidazole and therefore the validated method of 10 ppb is not adequate to assure human safety. We gave them the reasons why the results of this study were not adequate and Mr. Young showed us a copy of the conference memo between him and Dr. Blumenthal to prove that the use of the Charles River - SD strain of rats was acceptable with DT.

It was decided in the conference that the problem should be resolved with the Bureau of Foods since they have the responsibility of determining the adequacy of the sensitivity of the assay method. Dr. Mark told Mr. Young and Mr. Buck that he will contact Dr. Blumenthal and set up the conference. The representatives were quite concerned on why we are now requiring a method sensitive to 2 ppb since we have indicated in our previous letters that 10 ppb was adequate.

Adriano R. Gabuten

Adriano R. Gabuten, D.V.M.

cc:
NADA dup, VM 11
NADA trip, VM 11
CA-226
Dr. Kingma, VM 2
Dr. Mark, VM 300
Dr. Gabuten, VM 340
ARGabuten/dsk/4-29-71

AF 4-715
NADA 39-287V
NADA 9-476V

May 26, 1971

MEMORANDUM OF CONFERENCE

Present: Mr. J.M. Young
Mr. R.R. Buck
Dr. A. Donald Rankin
Merck Sharp & Dohme
Rahway, New Jersey

and

Dr. C.D. VanHouweling, VM 1
Dr. F.J. Kingma, VM 2
Dr. J.H. Mark, VM 300
Dr. D.P. Ducharme, VM 100
Dr. A.R. Gabuten, VM 340

Subject: Ronidazole

The firm representatives requested the conference to find out the status of their new animal drug application.

Mr. Young started the discussion by saying that they have met all the requirements for approval, i.e., validated tissue assay method sensitive to 10 ppb and the 2nd two year rat study.

In previous conferences (March 11, and April 26, 1971) Mr. Buck and Mr. Young were informed that we would need a method of tissue assay sensitive to 2 ppb since the second rat chronic study was not adequate to show the lack of carcinogenic properties of Ronidazole.

Mr. Young insisted that in two of our letters, April 28, 1968 and Oct. 2, 1969, we have indicated that we need a method sensitive to 10 ppb.

Dr. Ducharme argued that these two letters were written prior to the review of the second two-year rat data and in a conference with representatives of the firm on Feb. 3, 1970, they were definitely told that this sensitivity is acceptable at this point in time, but that upon review of the toxicity data, a lower sensitivity might be needed.

Dr. Mark has suggested that their chemists should consult with Mr. Prochazka and Mr. Lakata and see if the Ipronidazole assay method can be used with their product. Mr. Young indicated that Ronidazole is not soluble in benzene. They were told that the Ipronidazole method is sensitive to 2 ppb and that this method was acceptable with Consumer and Marketing Service, U.S.D.A.

Dr. VanHouweling stated that FDA has an agreement with C & MS for their chemists to validate the method of tissue assay for brand new drugs specially if it requires a withdrawal period. They were also told that we require some evidence to show that the withdrawal period will be adherred to when the product is approved and used by turkey growers. BVM would require a written committment on what steps, the firm will follow to obtain such evidence.

Since the problems involve the sensitivity of the method and toxicity data, Dr. VanHouweling, suggested that Dr. Mark should arrange a conference between the firm representatives, Dr. Blumenthal's group and BVM and try to find a solution to the problems.

The nicarbazin NADA was also discussed. Dr. VanHouweling wanted to know what is being done about it. I indicated that the toxicity data have been reviewed by DT and were considered adequate for granting a tolerance in tissues for the 2 metabolites. Firm was informed by letter of April 26, 1971, that we still needed a practical method of assay for the 2 metabolites.

Dr. VanHouweling suggested that we also discuss this with Bureau of Foods.

Adriano R. Gabuten

Adriano R. Gabuten, D.V.M.

cc:
NADA dup, VM 11(2)
CA-226
Dr. VanHouweling, VM 1
Dr. Kingma, VM 2
Dr. Mark, VM 300
Dr. Ducharme, VM 100
Dr. Gabuten, VM 340
Dr. Raines, VM 340
ARGabuten/dsk/6-2-71

Dr. Reichert, 7B37

BF-152

MEMORANDUM OF CONFERENCE

July 1, 1971

NDA39-247

PRESENT:

Mr. J. Young Dr. Rankin Dr. H. Peck	-	Merck Sharp & Dohme Rahway, New Jersey (AF 4-715)
Dr. J. Mark Dr. A. Gabuten	-	Bureau of Veterinary Medicine (VM-300)
Dr. J. Howard Mr. G. Lakata	-	Organic & Additive Chemistry Br. (BF-144)
Dr. H. Blumenthal Dr. C. J. Kobuski Dr. R. L. Gillespie Dr. A. J. Kowalk Dr. S. H. Frazier, Jr.	-	Division of Toxicology (BF-152)

SUBJECT: Ronidazole - NADA No. 39-247

Mr. Young opened the conference by citing a letter from Dr. VanHouweling, which gave the requirements for getting Ronidazole cleared (see Dr. VanHouweling's letter dated April 28, 1969) for NADA approval. He stated that a method sensitive to 10 ppb was requested in that letter. In response to the representative's statement, Dr. Blumenthal summarized the history of the evaluation of this product and giving DT's position on this matter as to why we requested a more sensitive method of 2 ppb.

Dr. Peck inquired about the possibility of an additional study to offset the results of the first study which was positive. This idea was discussed. Dr. Blumenthal stated that it would be pretty difficult to forget the results of the first study, and that the problem perhaps can best be resolved by developing a more sensitive analytical method to show no residues. It was re-emphasized that a method sensitive to 2 ppb would be needed for final approval.

Nicarbazin - NADA No. 9476

The product was discussed briefly. Dr. Blumenthal informed the representatives that DT was satisfied with the toxicology results. This product will not likely be called GRAS and would therefore be considered a new drug. The problem lies with developing a satisfactory analytical method. Dr. Howard (BF-144) discussed the deficiencies he found in the residue data submitted by the firm. He stated, "in the absence of recoveries to establish the sensitivity and reliability of the procedure for the analysis of the drug

in tissues, it was concluded that we could not come to any definitive conclusions concerning the residue data." The problem now rests between the chemist and the firm.

S. E. Frazier, Jr., D.V.M.

EMIT:CJKokoski

cc:
BF-152
BF-150
BF-144
VM-300
NADA No. 39-247
NADA No. 9476

SEFrazier:smt 7/19/71

AF 4-715

NADA #39-247

AUG 5 1971

Merck, Sharp & Dohme
Research Laboratories
Division of Merck & Co., Inc.
Rahway, New Jersey 07065

Attention: Mr. J.M. Young

Gentlemen:

This refers to your new animal drug application on ronidazole. It provides for the continuous use of ronidazole in turkey feed as an aid in the prevention of histomoniasis (blackhead).

Your submissions of December 11, December 15, 1970, February 8, and February 26, 1971, are also acknowledged.

We have completed our review of all the data submitted and find we are unable to recommend favorable action on your application.

Based on the facts that the most recent rat study was conducted at dose levels (0.5 and 5.0 mg./Kg.) lower than the first study (10, 20 and 40 mg./Kg.) and the difference in the strain of rats used, our previous conclusion that ronidazole is tumorigen in rats and probably a carcinogen is not altered. Because of these findings, the present validated method with a sensitivity of 10 ppb is inadequate to assure human safety. We indicated to you in a conference on February 3, 1970, that a method sensitive to 2 ppb or less might be needed pending our review of the data on the second rat study.

We are writing to you at this time to inform you that the validated method with a sensitivity of 10 ppb is unacceptable and that this agency will require a method with a sensitivity of 2 ppb.

Please advise us of your intentions with regards to this new animal drug application within 30 days of the date of this letter.

Sincerely yours,

James H. Mark, V.M.D.
Director, Division of
New Animal Drugs
Bureau of Veterinary Medicine

7-30-71

cc:
NADA dup, VM 13
NADA trip, VM 13
CA-226
Dr. Gabuten, VM 340
Dr. Blumenthal, BF 151
ARGabuten/dsk/7-29-71

Dr. FRAZIER. This refers to item 18, Ronidazole, and Dr. Van Houweling's reply to you.

He stated that I had not checked the files before giving my testimony in 1975, which was true. I think that was admitted during my testimony in 1975.

He also implied that my remarks were a deliberate attempt to be derogatory. That is something I didn't see him say about any other persons that testified during the 1975 hearing.

I think the sequence of events, as I have stated in the memorandum, speak for themselves.

I think the primary error in that whole transaction was his unwillingness and failure to follow recommendations from the Bureau of Foods in review of that petition.

Subsequent to the last hearing I requested the original documents from the Bureau of Veterinary Medicine file to recheck my facts.

I cannot find all of the memorandums that are supposed to be in the files.

I find that he omitted some of those in his reply to you that were pertinent to those whole sequence of events that I testified to in 1975.

Senator KENNEDY. You have those now?

Dr. FRAZIER. Yes.

Senator KENNEDY. You will make those a part of the record?

Dr. FRAZIER. Yes; I have.

Senator KENNEDY. What was the effect of the omission of those?

Dr. FRAZIER. The initial memorandum of April 28, 1969, was omitted.

Senator KENNEDY. What was the effect of it?

What was the import of the parts that were omitted?

Dr. FRAZIER. The important area—well, Dr. Van Houweling stated that the instructions he gave to the firm on specific recommendations was a typographical error, but that error was transposed not once, twice, but three or four times, and it was not corrected until about 2 or 3 years later.

And since that time the firm has not been able to have their product approved, up until this date.

Senator KENNEDY. These documents refute Dr. Van Houweling's comments, in your opinion?

Dr. FRAZIER. Yes, sir.

I am very displeased with his statement that I was attempting to be derogatory in the last hearing.

Senator KENNEDY. I will move on to Drs. Gable, Condon, Baldwin and Rollins.

You all stand by your previous testimony?

Dr. GABLE. Yes.

Senator KENNEDY. Do you have any comments on the Commissioner's report, the process by which it was prepared?

Do you have any copies of it?

Dr. BALDWIN. I will speak on the drug with which I was involved.

The report was made available at the Director's office, Dr. Van Houweling's office, and also the hearing clerk's office.

There are, in the one I was involved with, inaccuracies and omissions in that report, and it has been a real disappointment to me, that

the Commissioner or the Commissioner's staff failed to check back on the accuracy of the report; the one to him that came to this committee.

I think it is poor staff work.

I think it is sad commentary when a Senate committee has to take its time to check back on what the Office of the Commissioner should have done.

Dr. CONDON. I think Dr. Baldwin has summarized it very well as far as the aspect I was involved with.

I do welcome the opportunity of the committee to investigate these charges, to get a good resolution of the facts.

Senator KENNEDY. As I understand it, none of you were ever talked to personally?

Dr. GABLE. I did not even see the report.

Senator KENNEDY. Pardon?

Dr. GABLE. I did not even see Dr. Van Houweling's report.

The only time I saw the Commissioner's summary was when Mr. Sheridan let me sort of peruse through it for about 5 minutes.

Senator KENNEDY. Dr. Rollins, have you been involved with animal antibiotic transfers work?

Dr. ROLLINS. Yes.

Senator KENNEDY. Could you briefly describe what the study is, why its subject is important?

Dr. ROLLINS. The use of antibiotics in feeds results in resistant organisms developing in the GI tract, and you subsequently wind up with a large pool of organisms which have transferrable drug resistance, which can be transferred to pathogins which may subsquently wind up in people, or in animals.

Senator KENNEDY. Did not England confront this situation years ago?

Dr. ROLLINS. Yes, 1969.

Senator KENNEDY. How long has the FDA been working on it?

Dr. ROLLINS. The FDA started in 1970 and they are still working on it.

Senator KENNEDY. Excuse me?

Dr. ROLLINS. The FDA started in 1970 and they are still working on it.

Senator KENNEDY. What did the 1972 task force report recommend?

Dr. ROLLINS. That the companies be allowed to submit data to further substantiate the safety of their products and efficacy, and they were given a specific amount of time to do this.

Senator KENNEDY. Why is this so important in this area?

Would you tell us a little bit about it?

Dr. GABLE. By continuing the subtherapeutic use of antibiotics, this selects a resistant microbial population in animals which is not amenable to treatment and results in a subsequent reservoir of organisms which is transferable to man; and they are not treatable either, because we have resistant mechanisms to the drugs; and what the British report did was tend to limit the antibiotic uses for subtherapeutic purposes to those drugs not used for treatment in man or animal.

Senator KENNEDY. Well, as I understand it, England has made a decision, back in 1969, that has confronted that particular issue and has taken action.

We have been studying it for 7 years, is that correct, and it is still there and is—and there has not been any final resolution or decision on it.

Dr. GABLE. No final decision, sir, no.

Senator KENNEDY. Do we know anymore today, do we have anymore information than we did, say, in 1972?

Dr. GABLE. There have been studies conducted, and I do not think we have come out with any great discovery or new information. I think they reaffirm some things we did know about it in 1972 when we issued our initial report.

However, at least as far as the Bureau is concerned, and as far as the penicillins and tetracyclines are concerned, the Bureau feels that there is a need now to take a restrictive action similar to what was taken by Great Britain.

Senator KENNEDY. It poses or can pose an important health hazard to consumers?

Dr. GABLE. Yes, it can, sir.

Senator KENNEDY. Do you think that we could take action, do you think action is warranted?

Dr. GABLE. Yes, I do, Senator.

In fact, a reading of the report of the task force in 1972 shows that the task force said "probable human health hazard."

The Human Health Subcommittee in their appendix said it met the criteria established by the agency for an imminent health hazard at that time. The Human Health Subcommittee was the only committee that contained physicians.

Senator KENNEDY. What about it, Dr. Rollins; do you agree with this?

Dr. ROLLINS. Yes, I do.

Senator KENNEDY. Still no action has been taken yet.

There have been studies and studies and those that have reviewed the material, most involved have recommended action taken and still no action taken.

Dr. Knox and Mrs. Pogue, you testified previously before the committee.

Do you reaffirm your previous testimony?

Dr. KNOX. Yes, I do.

Senator KENNEDY. Do you have any comments about the process followed by the Commissioner, the second panel, in your evaluation efforts?

I understand you provided additional information to the Panel on your review of anoretic studies.

Dr. KNOX. I read through the Commissioner's report and the Panel's assessment.

I agree with Professor Hamilton and Dr. Gyarfas that the Commissioner's report was inadequate.

As far as the Panel's assessment was concerned, I read through the section pertaining to me, and I feel that they are correct in some respects, for which I thank them, but in certain respects, perhaps not their fault, I believe there are errors in their conclusions.

Senator KENNEDY. What was the quality of these studies?

Dr. KNOX. Well, it was decided that the way to handle this was to do a computer analysis.

Apparently it was felt that a computer analysis would be more impressive, and consequently some 206 studies were selected.

These were described in an action memorandum as being screened thoroughly by a panel of six physicians.

I have identified five of them;

I am not sure of the sixth.

They were to pass on the worthiness of the studies for validity.

Apparently, however, there was—their assessments were not heeded. They found that approximately half of the studies were not worthy of analysis. Yet, the statisticians were instructed to ignore this and put them all into the study.

During the panel's discussions, most of which I attended, the impression was given to the panel members that the outside group of consultants had disagreed with me when I said the drugs were not effective.

What they [the consultants] said was that the drugs had "clinically trivial" impact.

This was used as a basis for declairing the drugs effective, however.

For example, in the case of 1 drug, out of 23 studies only 4 showed significant weight loss according to the statisticians. And there are similar situations.

There are a number of other points.

I do not know if we have time for them today.

Senator KENNEDY. Do you, Mrs. Pogue, agree with Dr. Knox's interpreation of the studies?

Mrs. POGUE. Yes, I do.

I was very much surprised at certain statements concerning the fact that if one or two studies are effective, that is sufficient.

Statistics is based on mathematics and logic.

Logically, one would not go to a store and buy a bag of potatoes of which half or more than half were not good.

Therefore, I thought from our report, which said only 4 out of 23 studies showed a significant difference, that you consider the whole amount, and it could be by chance these 4 showed significance. We must consider the remaining 19 that did not show a significant difference.

It is simple logic which is the basis of statistics.

I felt this was sufficient to show that efficacy had not been proven.

Senator KENNEDY. You are a statistician?

Mrs. POGUE. Yes.

Senator KENNEDY. Even though only 4 out of the 23 showed some benefit, approval was made?

Mrs. POGUE. Yes, evidently.

I was not in at the end, and I do not know when and how approval was made.

I worked on the project and was mostly at the beginning part and helped write some of the summaries.

Senator KENNEDY. All right.

We would like to also ask this panel for any brief written comments or suggestions that they have about how the agency itself would be approved.

We want to thank you very much for your appearance here this morning.

The next panel consists of Dr. J. Marion Bryant, Dr. Carol Kennedy; Dr. Jerry Kennedy; Dr. John O. Nestor, Dr. Robert Gillespie,

Dr. Arthur Kowalk, Dr. David Scarr, Dr. Howard Mayers, Dr. Stanley Cortell, Dr. Roger Freeman, Dr. Julia Apter, and Mrs. Frances Dacosta.

Dr. Freeman, I know you have to depart shortly.

Do you stand by your previous testimony?

STATEMENT OF DR. J. MARION BRYANT, DR. CAROL KENNEDY, DR. JERRY KENNEDY, DR. JOHN O. NESTOR, DR. ROBERT GILLESPIE, DR. ARTHUR KOWALK, DR. DAVID SCARR, DR. HOWARD MEYERS, DR. STANLEY CORTELL, DR. ROGER FREEMAN, DR. JULIA T. APTER, AND MRS. FRANCES DACOSTA, A PANEL

Dr. FREEMAN. Yes; I do, Senator, with the exception of a point that was made about the July 7 with the drug companies.

I was unaware at the time I testified of a memo from Dr. Scoville, which apparently put the blame for confusion on Abbott, one of the sponsors.

As a consequence, since I was not aware of this, it was my feeling when I testified that the fault was probably primarily with the agency.

Senator KENNEDY. You are all advisory committee members—just Dr. Freeman?

Dr. FREEMAN. I am the only one from those three consultants—I am sorry, Dr. Apter is here as well.

Senator KENNEDY. Do you have any comments to make on the review process?

Dr. FREEMAN. I have many comments to make, but I am afraid there may not be time for them.

Senator KENNEDY. Just briefly, if you can highlight them.

Dr. FREEMAN. Do you mean the review of drugs, or the Commissioner's report?

Senator KENNEDY. Well, the process by which your testimony was evaluated by the Commission.

Dr. FREEMAN. I never responded to the Commissioner because the Commissioner's report and his request for comment arrived after the date that he gave me to respond.

Senator KENNEDY. I do not quite get that.

He asked you to respond and then his conclusions were already stated prior to the time that you were able to respond?

Dr. FREEMAN. That is essentially correct.

When I received it, he asked for a response.

I do not remember the exact dates, but it was prior to the date on which I received it.

Since it was a very large report, as you know, and I thought it would take considerable effort, I decided at that point to ignore it.

But that did not indicate lack of interest on my part or I would not be here today.

Senator KENNEDY. What about it, Dr. Apter?

Do you stand by your previous testimony?

Dr. APTER. Yes, indeed.

Senator KENNEDY. Do you have any comments on the review processes by the Commissioner and——

Dr. APTER. Before I make a comment, I would like to make sure there has not been any errata list that came with this assessment. [Indicating.]

Does anybody say that there is one page in this assessment that should not be in it?

If not, I want to make some comment.

I was a member of the Advisory Committee on Cardiovascular and Renal Drugs with FDA, from July 1972, through June 1976.

On August 14 and 15, 1974, in response to questions from you, Senator Kennedy, I made public disclosure of many things.

One was that representatives of the Parke-Davis Pharmaceutical Co. had sought me out at lunchtime on June 20, 1974, when my Advisory Committee was meeting, to tell me that they had "heard that this was my last meeting with this Cardiovascular and Renal Drug Advisory Committee."

However, I knew that my term as a member of the Advisory Committee was actually scheduled to continue 2 more years, that is, until June 30, 1976.

Therefore, I took this gratuituous remark from one of the Parke-Davis representatives, that was made within the hearing of other representatives, to be a notice that he had information that my term was to be stopped summarily or at least that he wanted me to think that there was such a likelihood.

During this review process by the Commissioner, by the Review Panel, and by the Chairman of the Review Panel, everyone has acted as though that incident never took place, and simply because I could not name the speaker. All I knew was the place that the event had occurred, the date, the time, the drug company affiliation and the fact that the speaker was a white-haired male.

I did not know his name and had no way of finding his name.

Both Chairman Chalmers and the Review Panel say together in unison "it is unreasonable to expect the Commissioner to attempt to

obtain details of this charge—note they call it a charge—"without input from Dr. Apter, since she may be the only person who knew the relevant information."

They say that on page 37 of the Review Panel's report, and on pages 2 and 3 of Chalmers' report.

Now, what do they mean by saying that I was the only one who knew the relevant information?

I can assure the review panel and Chairman Chalmers and Commissioner Schmidt that the persons about whom I testified were both a speaker and listeners, who had registered with FDA on June 20, 1974, and they knew what they had said to me.

Those men were never sought out or questioned.

The FDA source of the misinformation was never tracked down.

I understand that some FDA source gave similar information to "FDC Reports" publication.

Now, I, specifically, however, want to have your help with something. It is a dilemma of mine.

Chairman Chalmers of the Review Panel has asserted that he personally included in the "Assessment of the Commissioner's Report of 1975," only analyses which differ from analyses of the Review Panel.

He has a special section entitled "Chairman's Analyses of the Commissioner's Treatment of Individual Allegations when Different from Panel's Allegations."

However, this section, rather than including only what differed, Chairman Chalmers, with respect to this particular allegation of mine, repeats verbatim on pages 2 and 3 the analysis that also appears on page 37 of the Review Panel's section.

I am going to be turning in those pages to help you see what appears to be entirely inconsistent with the title of the chairman's section.

[See enclosed insert on those pages from the Assessment of Commissioner's Report, October 1975.]

[The information referred to follows:]

[Excerpts from "Assessment of the Commissioner's Report of October 1975."]

JULIA T. APTER, M.D.

Allegation 5: Analysis

I. Dr. Apter did not provide sufficient information to enable the Commissioner to investigate this allegation of bias toward industry in the review of Dilantin for arrhythmias.

Dr. Apter should have been able to identify the persons about whom she complains from the minutes of the meeting which are sent to each participant. If she did not have a copy of the minutes, she could have asked FDA to provide her with one. It is unreasonable to expect the Commissioner to attempt to obtain the details of this charge without input from Dr. Apter since she may be the only person who knew the relevant information.

II. The Commissioner is correct in noting that advisors' being personal acquaintances of sponsors or investigators does not necessarily constitute bias. The Commissioner should consider methods to reduce bias that may occur or appear to be present when advisors are personal acquaintances of sponsors or investigators.

Although the Commissioner's concludes that friendship does not constitute conflict-of-interest, he acknowledges that sometimes advisors are biased by this factor. FDA could minimize the effect of such bias by asking advisors to publicly disclose it.

III. The Commissioner could have concluded that the fact that the Advisory Committee did not recommend Dilantin for arrhythmias negates any inference of strong bias in favor of the sponsor.

JULIA T. APTER, M.D.

Allegation No. 5: Members of Cardiovascular and Renal Advisory Committee in their review of Dilantin for arrhythmias showed their bias toward industry. (CR 757)

Chairman's Analysis

I. Dr. Apter did not provide sufficient information to enable the Commissioner to investigate this allegation of bias toward industry in the review of Dilantin for arrhythmias.

Dr. Apter should have been able to identify the persons about whom she complains from the minutes of the meeting which are sent to each participant. If she did not have a copy of the minutes, she could have asked FDA to provide her with one. It is unreasonable to expect the Commissioner to attempt to obtain the details of this chapter without input from Dr. Apter since she may be the only person who knew the relevant information.

II. The Commissioner is correct in noting that advisors' being personal acquaintances of sponsors or investigators, or having used drugs under discussion for non-approval purposes, does not necessarily constitute bias. The Commissioner should consider methods to reduce bias that may occur or appear to be present when advisors are personal acquaintances of sponsors or investigators.

Although the Commissioner concludes that friendship does not constitute conflict-of-interest, he acknowledges that sometimes advisors are biased by this factor. FDA could minimize the effect of such bias by asking advisors to publicly disclose it.

III. The Commissioner could have concluded that the fact that the Advisory Committee did not recommend Dilantin for arrhythmias negates any inference of strong bias in favor of the sponsor.

Dr. APTER. I feel that I need some help in discovering whether this analysis of my report of the Parke-Davis remarks actually emanated from the entire Review Panel, where they say that she should supply the name, otherwise we are not going to look into it; or whether it came in from Chairman Chalmers alone and then somehow appeared in the Review Panel's section. I think we ought to discover why it was included twice; who recommended it be included twice, when really once certainly should have been enough.

I also strongly object to one of the things that I think, here, has been called, in a subtle way, that witnesses have been intimidated.

One of those subtle ways is that they keep calling us complainants.

I'm continually being accused of having complained about something.

The fact is, you stated very clearly at the beginning of your hearings in August 1974, that you had sought us out; that we had not come to you.

We were witnesses, subpenaed witnesses.

Senator KENNEDY. That is right.

Dr. APTER. I did not give my testimony in order to gain any advantage, and I have not gotten any advantage from it.

But there is this undertone that we are, as you know, dissidents or complainants.

During the handling by the review panel, the executive Secretary Bernstein asked me some questions about the Commissioner's report before I had gotten the Commissioner's report.

I wrote to tell him I'd not gotten it yet, or did not even know what he was talking about, not having seen it, and I would not have known what he meant. But those letters were not answered.

I finally had to send a telegram; and that put my request in the public domain and that request he could not ignore.

Senator KENNEDY. We will be glad to work with you in this earlier question, in trying to figure out these inconsistencies, and would welcome this opportunity to work with you.

[Recommendations from Dr. Apter follow:]

FROM JULIA T. APTER, 1976

RECOMMENDATIONS FOR NEW DRUG REGULATIONS AND LEGISLATION:

If the FDA is to continue to use Advisory Committees and Consultants for assistance in the evaluation of drugs, those used should be restricted to people sufficiently certain of the factual bases for their deliberations and advice to be willing to have their meeting records made fully public. Any "briefings" or directives from FDA officials to advisors or consultants should be a matter of record, without exception, since, otherwise, the significance of advisors recommendations would be misinterpreted, often to the disadvantage of the public.

> I have observed officials of the FDA "brief" their Advisory Committees with a specific order to be "off the record" during the briefing. Such an official should be considered incompetent and/or acting contrary to law.

Current legislation which requires demonstration of safety and efficacy should be reiterated with additional provisions that would make it impossible for an FDA official or employee to take any other position.

> I have observed FDA officials speak as though the burden of proof lies with those who claim that a drug is toxic when, in fact, current legislation requires that the burden of proof lies with those who say that a drug is safe. If an FDA official cannot accept this safeguard to public health, then that official should not be permitted to remain in a position of authority.

Approval of drugs should be "provisional" in each and every instance to permit easy and ready withdrawal if long-term animal studies

or clinical trials or actual clinical experience should show toxicity (such as cataracts) or carcinogenicity.

> I have observed drugs put on the market before long-term toxicity or carcinogenic studies. When those studies revealed carcinogenicity, we advisors were told by FDA officials that a recommendation of removal of a drug, once approved, could be virtually useless if the manufacturer appealed the FDA withdrawal since the drug would remain on the market for several years during the appeal (Aldactazide).

Newly released drugs should be accompanied by mandatory report documents to be used by the practicing physician for keeping the FDA advised of efficacy and safety problems.

The FDA could and should work more closely with manufacturers in the design of all investigations of safety and efficacy. At present, apparently, officials of the FDA recommend one series of tests which, however, do not satisfy the judgement or criteria of other reviewers for the FDA. This inconsistency contributes largely to the so-called "drug-lag", forcing manufacturers to perform two or more sets of tests when one appropriate test would have sufficed. A model for the procedures to be followed could be the NIH-sponsored study of the safety and efficacy of tolbutamide in diabetes. This study shows that the kinds of studies currently being demanded by FDA medical officers are not "impractical", as many physicians and drug manufacturers claim. Rather, this kind of study is the most economical sort that protects the public from dangerous drugs while permitting the use of effective and safe ones.

Senator KENNEDY. Dr. Freeman, is there anything in 5 minutes you would like to say before you have to depart?

Dr. FREEMAN. Yes.

There are just one or two things.

One has to do with the question of publication, publications about drugs prior to approval.

I do not know if this subcommittee can do anything about that. As you will note, if you check the record, we were concerned about misleading or incorrect information which had been published in reputable journals.

We had some rather unusual experiences with this, which are not in the record and which I think perhaps I would like the opportunity to place in the record.

But I think to save you time I would just like to mention one thing which has not come up, that you might be interested in. That is, in October 1974, and this is on the matter of Cylert, the drug company itself, not the investigators, published in the Journal of Learning Disabilities, an article about the multiclinic study.

There were two studies on Cylert.

The multiclinic study was objected to by our group, and the group they appointed above us, the group chaired by Dr. Daniel Freeman, he determined it uninterpretable as a controlled study.

In spite of this, the drug company published this, and this Journal is widely distributed to parents, to teachers and other professionals.

I was quite concerned when this was brought to my attention by someone since it made the study look quite good.

I was afraid if I wrote a letter to the editor, the drug company would cite criticisms of our task force, and I called Dr. Freeman and explained this to him and said it would be much more effective if both of us would write a letter of explanation simply indicating there were questions about this study.

Dr. Freeman agreed with me that this was perhaps an improper or misleading publication.

But he said he was not prepared to sign his name to any such letter, I suppose from his explanation, because of his contacts with Government and industry, I am not sure.

But in any event, he left it to me to draft the letter and then said he might write something to the Journal but he did not want his name mentioned.

I simply wanted to mention this as the kind of situation which can develop and over which we have no control.

Senator KENNEDY. How do you recommend we deal with that kind of situation?

Dr. FREEMAN. That is out of my area of expertise.

I am just generally concerned about publications which lead to great interest in a drug prior to its approval.

I think unless the agency, supervisory echelons, are better able to support the reviewers, then it simply increases pressure, which you have heard about this morning.

I will not presume to suggest how this be dealt with.

But we are not permitted, when we are working for the agency, as I understand it, to correct any of these misleading publications.

That is one of my concerns.

The other concern is that if raw data is no longer reviewed, or if it is put into a computer, whose raw data sheets can no longer check back, that any reviewing team that comes along later is not going to be able to find out whether these publications about drugs are misleading or not.

Senator KENNEDY. I think that is very helpful comment and suggestion.

I know you have to leave, Doctor.

Dr. FREEMAN. Is it permissible for me to submit something for the record?

Senator KENNEDY. Yes; we would welcome it.

Dr. FREEMAN. I would appreciate doing it.

Senator KENNEDY. For the other members of the Panel, we are really interested in asking you all, as I mentioned to the other panels, to submit any comments that you might have that would be helpful to us in dealing with some of the particular questions and difficulties facing us. Also, we welcome any recommendations and suggestions you have that would strengthen the department you have been associated with.

Would I be safe, with the exception of Dr. Meyers, who has not appeared before us, in assuming that all of you stand by your previous testimony?

[Show of hands.]

Senator KENNEDY. The record will show that everyone does do this.

Then I might perhaps ask each of you to make a brief comment on the major kind of problem that you have been faced with or confronted with and that you would like to see corrected.

Dr. Bryant, first.

Dr. BRYANT. As you know, I am no longer with the Food and Drug Administration.

One of the complaints, and this is the first complaint that I have ever made about the Food and Drug Administration, is that when Commissioner Schmidt promised us help in obtaining documentation to substantiate our charges that we made 2 years ago, we not only did not—I'm only speaking for myself—did not receive the aid that he had promised, but it appeared that I was harassed and the documents that I needed were not available.

I would like to make some other comments in writing at a later date, if possible.

Senator KENNEDY. How long did you work in the agency?

Dr. BRYANT. Almost 8 years.

Senator KENNEDY. You were head of cardiology prior to——

Dr. BRYANT. I was previously at Bellevue, fourth medical division, and also at Knickerbocker Hospital.

Senator KENNEDY. We would welcome whatever additional written comments you would make.

Dr. BRYANT. I want to apologize for not being able to communicate as effectively as I did 2 years ago.

Senator KENNEDY. I think you have made a very strong case.

We remember the case you made 2 years ago. We think your presence here is helpful to us and know that the reason you are here is because you feel strongly about strengthening the agency and about improving it.

So, we welcome that.

I think you've helped us very much. We want you to understand that.

Dr. BRYANT. Thank you.

Senator KENNEDY. Dr. Carol Kennedy.

Dr. CAROL KENNEDY. Senator Kennedy, I, first of all, would like for the record to say I prepared a written statement and have submitted it.

I assume it will be placed in the record.

Senator KENNEDY. Yes.

Dr. CAROL KENNEDY. The second thing I would like to say is not only do I affirm my prior testimony, but subsequent to that testimony I prepared an extensive report which was submitted to the Panel which was accompanied by 180 documents in support of that testimony.

Third, I understand you want us to address the problems which we felt should be corrected at this point, is that correct?

Senator KENNEDY. Yes.

Dr. CAROL KENNEDY. First and foremost, I believe that the secrecy under which the agency operates should be removed.

I believe the FDA officials and staff who make decisions should be held publicly accountable for those decisions.

I believe that evaluation of raw data should be mandatory and that clinical safety and efficacy data can no longer be justifiably withheld from the public while scientific investigators and drug firms are allowed to publish material under the guise of scientific literature, which contain omissions, inaccuracies, distortions, and unwarranted interpretations.

I believe the industry contact should be for substantive purposes and they should all be formally documented.

I believe adequate animal testing should be completed prior to extensive clinical testing.

I do not believe there should be any meetings between industry and division or higher officials without the reviewing team.

I think there should be some sort of restrictions placed on the shuffling between industry and FDA positions.

I think that one of the most important things is that the quality of scientific research needs upgrading.

This can only be done by appropriate clinical studies, by appropriate execution, by appropriate monitoring, not only by drug firms, but by FDA, to assure that investigators are doing the appropriate studies.

I think, finally, that procedure should be instituted to protect professional staff from unjustifiably being removed from their areas of expertise and exposed to harassment or other punitive measures.

Thank you.

[The prepared statement of Dr. Kennedy and other information supplied follows:]

STATEMENT

BY

CAROL S. KENNEDY, M. D.

FOR

SUBCOMMITTEE ON HEALTH

OF

THE COMMITTEE OF LABOR AND PUBLIC WELFARE

AND

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICES AND PROCEDURE

OF

THE COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

STATEMENT

On August 15, 1974 a Joint Hearing was held before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, United States Senate. Under subpoena, fourteen (14) current and former Food and Drug Administration professional staff and Consultants appeared and gave sworn testimony concerning management practices and regulatory decisions in the Bureau of Drugs. Major concerns were expressed on various issues including inadequate animal testing prior to extensive clinical trials, inadequate clinical testing and monitoring, inappropriate use of Agency Advisory Committees, undue industry influence in FDA management decisions, alteration of records, and harassment and punitive removal of reviewers from their areas of experience and specialty training.

The August 15, 1974 Hearing was unique in that, to my knowledge, this was the first time staff reviewers were encouraged to express their concerns about the failure of FDA Officials to carry out crucial regulatory responsibilities. In the following months additional testimony by FDA professionals appearing before the same Subcommittees provided similar accounts.

Eight of the fourteen (14) witnesses, including myself, provided information specifically involving the Division of Neuropharmacological Drug Products which evaluates and continues oversight of some of the most frequently prescribed and financially profitable drug entities. Although I am a psychiatrist and had functioned as a psychiatric reviewer in this Division for three (3) years, I was removed from the review of all psychotropic drug applications. Initially I was detailed to the Division of Surgical-Dental Drug Products to review applications for soft contact lenses. At the time of my return, the Supervisory Medical Officer in the Psychopharmacology Section was a non-psychiatrist. The Acting Division Director was also a non-psychiatrist. I was reassigned to another Section within the Division and my first assignment was to review a drug to be used for nausea and vomiting associated with anesthesia and surgery. This assignment was made despite the fact that there were two trained anesthesiologists within the Division. A second trained psychiatrist was also removed from the Psychopharmacology Section. A non-psychiatrically trained physician continued to be assigned psychotropic drug applications. More importantly, non-medically trained reviewers were recruited to review drugs used in clinical psychiatric practice. Drug applications were also referred outside the Agency to Consultants with long-standing industry ties. FDA Officials informed me that the removal from my area of specialty training was the

result of a "responsible management decision." Since FDA management policy did not consider Details or reassignments within a Division as an "adverse" personnel action, I was left with no recourse through established Personnel Procedures.

My testimony at the August 15, 1974 Hearing concerned both general issues and specific drug entities including Cylert, a drug to be used in children diagnosed as having Minimal Brain Dysfunction. A significant portion of the testimony by the three (3) current and former FDA Consultants also concerned Cylert. A detailed Report clarifying, amplifying and documenting support for my testimony was submitted to the Review Panel on New Drug Regulation created by the Secretary of HEW as a result of the August 15, 1974 Hearing. I not only affirm my prior testimony but I believe the extensive documentary evidence accompanying that Report serves to strengthen it and justifies my current concerns that relevant issues remain unresolved and totally uninvestigated.

Following the August 1974 Hearing, those who testified were exposed to derisive remarks by the trade press, by clinical investigators who were staunch industry supporters and even by FDA colleagues who felt we were "disloyal" to the Agency. Most of us believed that such reactions were tolerable if our testimony resulted in necessary and effective changes which would assure that the Agency no longer evaded its public responsibility.

The Commissioner of the Food and Drug Administration, Dr. Alexander Schmidt, promised a full investigation of the issues raised during the August 15, 1974 Hearing and initially indicated the need for independent investigation. The end result was a reversal of that position and insistence on a self-investigation. We found that assurances made by the Commissioner were violated, numerous technical obstacles were encountered, unreasonable demands, often received after the deadline for compliance, were persistently made upon those who testified. Effective right to Counsel was impaired because of restrictions placed upon the information we could discuss with him. All of these impediments served to further dampen our original optimism.

From the outset it was clear that only an investigation independent from HEW domination could satisfactorily and non-prejudicially resolve the issues under assessment. Because of our reservations about the self-investigation, and under advice of Counsel, I declined to submit additional information to the Commissioner of the Food and Drug Administration. When the Review Panel on New Drug Regulation was established, I believed that it was, as reported, an independent Panel and was given the impression that an independent investigation of the issues would be accomplished. Upon request and in good faith, I submitted a detailed Report to the Panel Members and provided specific supporting documentation which would allow

responsible conclusions. However, my Report was summarized but not analyzed.

The Commissioner's Final Report dated October, 1975 numbered over 900 pages and cost almost $200,000.00. Only the testimony of the August 15, 1974 Hearing was considered. No attempts were made to correlate possible patterns of Agency action described by subsequent witnesses before these Subcommittees. Heavy reliance was placed on information provided by the FDA Bureau of Drugs Officials who were responsible for the original improprieties which resulted in the original Hearings. Contrary information contained in Official FDA Records was either ignored, discounted or not addressed. The Commissioner's Report omitted any consideration of one former employee's testimony. Except for an incomplete investigation of information submitted by Drs. Freeman and Solomans relevant to the Cylert testimony, none of the issues raised in my statements before these Subcommittees in 1974 was investigated or included. The Commissioner commented that my not having provided specific evidence prevented his making any definitive conclusions. The fact is that the documentation that I submitted to the Panel was available in FDA files readily accessible to the Commissioner. A self-investigation based on such procedural approaches resulted in predictable conclusions.

In May 1976, the Review Panel on New Drug Regulation issued its Assessment of the Commissioner's Report of October 1975.

During proceedings prior to the issuance of that Report, the Executive Secretary, an HEW employee, immediately assumed an aggressive and vocal advocate role for FDA policies and the Commissioner's interpretations and conclusions. Despite this intervention the Panel Members, with the exception of the Chairman who was subsequently revealed to have HEW personal and financial ties, concluded that the Commissioner's Report was inadequate to resolve a significant number of the important "allegations." It was recommended that the Review Panel be authorized to select an independent investigator and staff to pursue such an investigation. The Secretary of HEW refused to make such an authorization, thus rejecting the recommendations of the Department's own Advisory Committee. Such interference by "interested" parties and rejection of recommendations unfavorable to Management's position by eminent Advisors are strikingly similar to accounts provided by witnesses during the August 1974 Hearing. The finality of the Secretary's decision must not remain unchallenged if the Public interest is to be served.

Almost two (2) years have passed since fourteen (14) concerned professionals publicly voiced their misgivings about FDA Management decision making processes and the lack of effective consumer protection. Despite fervent public assurances, neither the Food and Drug Administration nor the Department of Health, Education and Welfare have adequately

considered and investigated the significant issues which so directly affect the American people.

The shroud of secrecy must be removed from FDA decision-making processes. FDA Officials and staff must be held publicly accountable for their decisions. Evaluation of "raw" data should be mandatory. Clinical safety and efficacy data cannot be justifiably withheld under "trade secret" provisions while the same data appear under guise of scientific literature but with significant omissions, inaccuracies, distortions, and unwarranted interpretations. Industry contacts should be for substantive purposes and formally documented. Meetings between Industry and FDA Officials with exclusion of the professional staff reviewers should not exist. Restrictions should be placed on the shuffling between industry and FDA positions. The quality of scientific research needs upgrading. This can only be accomplished by careful clinical studies and monitoring. Industry, FDA and the scientific community share this responsibility. Procedures should be established to ensure that professional staff be protected from unwarranted harassment and punitive measures.

Serious questions raised during the testimony before these Subcommittees remain unresolved. Without such resolution and institution of effective changes, such testimony will have been futile. It will also be a distinct discouragement to other sincere and concerned public servants. It is my hope that these Subcommittees will not allow the evasion of such public responsibility to go unchallenged.

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DEPARTMENT OF PSYCHIATRY

August 23, 1976

Senator Edward Kennedy
Senate Health Subcommittee
Washington, D.C.
U.S.A.

Dear Senator Kennedy:

I hope that I am not too late with my further comments which I would like to have added to my testimony of July 20th.

I would like to raise a rather pessimistic question as to whether any reform of regulations and procedures can substitute for sensitive, humane treatment of staff and consultants. There were certainly some very poor practices which we encountered at the agency. I refer in particular to Dr. Crout's treatment of us: first telling us one thing, then doing another without informing us; Dr. Gardner's not permitting us a response to a supposedly unofficial rebuttal. These events were symptomatic of the kinds of problems we encountered. As consultants, maybe we were right and maybe we were partly wrong in our interpretations, but there seemed to be no process to deal with discrepancies between our opinions and the opinions of supervisory personnel. For example, instead of consulting with us about this, Dr. Scoville wrote a memo and labelled us as "anti-drug" when Dr. Denhoff is well-known as a person who believes in the use of drugs, as is Dr. Solomons, and I myself had previously been approached by the sponsor to serve as a drug researcher for their project.

I feel particularly badly about Dr. Gardner's refusal to honor my request to respond to the rebuttal from Dr. Conners, and his statement "you and the other consultants will be kept informed of future actions we take in regard to this application". This was simply not true and was not done. It is my understanding that the new reviewing panel, chaired by Dr. Freedman, was not provided with much of the material which we used. But they did receive the rebuttals to our presentation, and without any comments on those from us, it must have been very difficult for them to arrive at any other conclusion than that we were overly emotional at the September 29 meeting. I tried to communicate with the new reviewing panel, and wrote the letter to Dr. Crout which was included in my 1974 testimony. What may not be apparent is that Dr. Crout's response to my deadline in the letter to him was to have a secretary call me and tell me not to send any material to the new panel as a consultant. Naturally, it was not possible to discuss this with the secretary who was simply passing on a message. It is this kind of treatment which led to some of the morale problems which we and others suffered.

It might also be interesting to ask a question which has never, to my knowledge, been asked. Why were we as consultants willing to make the enemies we made? We had all had pleasant and friendly relationships with others in the field such as Drs. Conners, Eisenberg, Wender, etc. What possible benefit could it be to us to make such enemies? I suggest the only possible answer is that we sincerely believed that we were doing something important and that we had a major disagreement with these and other individuals who were acting as investigators or consultants for the sponsors. If there is any other explanation which makes sense, I would like to know what it is.

Many of the feelings which I had when I was a consultant to the agency were stimulated all over again when I heard the testimony on the 20th of July this year. I believe that if the FDA supervisory echelons wanted to, they could have prevented much of the trouble. If we were correct in suspecting that they were most interested in "testing the winds" to see which way it was blowing and then acting accordingly, then it would make sense that they could not have explained their actions to us. On the other hand, if we were not correct in this, then why did they leave themselves open to this kind of interpretation?

For example, if Dr. Crout, after praising us on the 29th of September, and even subsequently, had had second thoughts about what we did, how we did it, or our conclusions, he could easily have written or called me and the other consultants and said, in effect, "I know I said that the meeting went well and that I was impressed by the presentation and the weight of the evidence, but I have had some second thoughts about whether we could sustain this position at a hearing if requested by the sponsor. I think we ought to discuss this further. Could you read my comments and then return for the session with me?" I am confident that this type of communication from him would have led us to respond in the spirit of co-operation which was unfortunately so lacking throughout our FDA experience. By not doing so, they left themselves open to an interpretation that they were interested in their own goals, or discourteous, or worse.

I accuse Dr. Crout of improper behavior in respect of these events. The rebuttals received cast serious aspersions upon us as consultants: I cannot read them today without frustration and anger. Yet these were seen by the Freedman panel without any comments from us. It seems to me that Dr. Crout's decision to operate in this fashion leaves open the inference of "committee shopping" for a favourable opinion. This is a serious charge which I believe deserves further investigation. I share the concern of another testifier on the 20th of July of this year who referred to the promotion of senior officials who demonstrated the kind of action we had documented and the fears that this will vitiate to an unknown extent, any benefits from reformed legislation and regulations.

My last comment has to do with the matter of the publication of incorrect or misleading information. I do not know whether anything can be done about this. In October of 1974, after we and the Freedman committee had agreed that the multiclinic study was uninterpretable, the sponsors themselves published a paper praising their own study in the Journal of Learning Disabilities, never indicating this study's rejection. This journal goes to large numbers of parents, teachers, and other professionals. I was concerned about this and wrote to Dr. Freedman, hoping that we could together write to the journal and have them publish a statement clarifying the situation. I was afraid that if he did not participate that the sponsor would simply use the criticisms of us levelled by the Freedman committee to nullify anything that I personally said. Unfortunately Dr. Freedman was unwilling to have his name used even though he agreed with me. I think he said that it was because he would like to maintain his credibility with government and industry.

This is an example of a situation where sponsors and investigators could publish misleading information without any possibility of correction.

Finally, it should be pointed out that there were errors in the paper Dr. Conners published about his own research in Pediatrics. At the September 29 meeting, he stated that this was a "preliminary" paper and that it would be corrected in subsequent papers. In fact, it was not corrected in subsequent papers and some of the same incorrect information was published again in the prestigious journal "Psychopharmacologia". I respectfully request that it would be worthwhile to consider what constraints there may be upon FDA staff or consultants in attempting to correct misleading publications which appear about drugs prior to their approval.

I appreciate the opportunity to make these comments and I hope that the diligent pursuing of these issues and disciplinary action, if warranted, will be undertaken so that the aims that we all seek may be accomplished.

Very sincerely yours,

Roger D. Freeman, M.D.
Associate Professor of Psychiatry
Director of Services for
Handicapped Children

RDF

THE UNIVERSITY OF BRITISH COLUMBIA

VANCOUVER 8, CANADA

V6T 1W5 (604) 228-2032

DEPARTMENT OF PSYCHIATRY

August 30, 1976

Mr. Walter Sheridan
4901 Edgemore Lane
Bethesda, Maryland 20014
U.S.A.

Dear Mr. Sheridan:

Further to my letter of August 23, addressed to Senator Edward Kennedy, enclosed please find a copy of a letter which I sent to Dr. Daniel X. Freedman on December 31, 1974, which I feel might add to my submission to the Subcommittee on Health.

Very sincerely yours,

R. D. Freeman.
per P.M.

Roger D. Freeman, M.D.
Associate Professor of Psychiatry
Director, Services for
Handicapped Children

RDF
Enc.

THE UNIVERSITY OF BRITISH COLUMBIA
2075 WESBROOK PLACE
VANCOUVER, B.C., CANADA
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DEPARTMENT OF PSYCHIATRY

31 December 1974

Dr. Daniel X. Freedman
Professor and Chairman
Department of Psychiatry
Division of Biological Sciences
University of Chicago
Chicago, Illinois 60637

Dear Dr. Freedman: Re: Article by Page et al., J.L.D., Vol. 7 (8)

I am sure you are weary, as I am, of the Cylert controversy, but I must ask your consideration of the following situation of which you may be unaware. Abbott has itself submitted and published a favorable report on the Multiclinic Study. I have enclosed a copy in case you have not seen it. As you know, this journal goes to very large numbers of non-physicians. Few, if any, of the readers will be aware that there was doubt about the value of this study on the part of both our Task Force and your group. I remind you that your Ad Hoc Panel Report stated "This type of investigation is useful in providing information about the general utility of a drug, but the execution of this particular multiclinic study renders it uninterpretable as a controlled study." Dr. C. J. Klett submitted a separate report which said, in part, "These studies have so many problems, it is difficult to know where to begin. Any study that ends up with only 238 patients considered acceptable for efficacy analysis out of a total of 413 just has to be badly executed or monitored..."

No inkling of these criticisms is to be found in the paper. I feel some qualifying remarks should be submitted to the journal for publication as a letter to the Editor. If I do this alone, it is not unlikely that Abbott will reply by using your comments about our Task Force Report to detract from my point.

I would like to ask whether you would be willing to co-sign with me a letter to the Editor of the Journal of Learning Disabilities which would be careful and conservative, indicating that the study reported upon was the subject of controversy and that the evidence it provides is not unambiguous. I would be happy if you would prepare it, or else I could send you a draft.

Your attention to this matter is appreciated.

Yours sincerely,

Roger D. Freeman, M.D.
Associate Professor
Director, Services for Handicapped Children

Senator KENNEDY. An excellent statement and comment.

I very much agree with it.

How do you respond to the point that, if we follow your recommendations, trade secrets will be compromised?

Dr. CAROL KENNEDY. That they will be compromised?

Senator KENNEDY. And unfair competitive advantages be given if you go through some of your sunshine provisions and follow your recommendations, that there will be compromises——

Dr. CAROL KENNEDY. I do not see how there can be.

With chemical data, OK, that is fine. It should not be made public in these provisions.

I am not qualified to speak on animal testing but in terms of making clinical safety and efficacy data public, I do not see how it would be compromised, because it is made available anyway, except as I said, quite often in distorted form.

I do not believe this is fair to the American public, to permit publication of distorted, biased, false data or data that are inadequately interpreted.

I just do not see how this is a compromise.

Senator KENNEDY. You are pointing to a situation now where companies themselves may select material available——

Dr. CAROL KENNEDY. That is correct.

Senator KENNEDY. And it is in the public interest that the balance of the information and material be made available, is that correct?

Dr. CAROL KENNEDY. That is correct.

Senator KENNEDY. And that can be made through the FDA, as I understand it?

Dr. CAROL KENNEDY. Yes.

Senator KENNEDY. And that really serves the public interest?

Dr. CAROL KENNEDY. In my opinion it does.

Senator KENNEDY. In my opinion it does, too.

Dr. JERRY KENNEDY. I do not think I can improve on that statement.

Senator KENNEDY. Strong husband and wife team, there.

Dr. JERRY KENNEDY. I am willing to concede.

Senator KENNEDY. Dr. Nestor, we welcome you back.

Dr. NESTOR. Very brief comment.

No. 1, I would like to restate again that I stand behind my former testimony.

No. 2, I say that things have not improved.

I testified before you in August 1974 that for 2½ years I had not done 2½ or 3 months of formally assigned work.

I can now state that in over 4 years I have not done more than 4 months of formally assigned work.

Senator KENNEDY. Is this of your own desire?

Dr. NESTOR. No.

I read novels, make phone calls, listen to the radio.

Senator KENNEDY. But you want to work, as I know from your background and experience. You had a distinguished record of public service, a distinguished record in the agency itself, and yet we heard that the Cardio-Renal Division has been pretty well decimated.

That has been an area of expertise which you have.

Dr. NESTOR. Yes.

Senator KENNEDY. You have served with great distinction. For whatever other reasons we have not been able to detect—perhaps you

know the reasons—you have been denied that opportunity, as I understand it.

Dr. NESTOR. Yes.

You realize what that does to an individual professionally, who is highly trained and highly motivated to sit and do nothing for over 4 years.

I would like to raise that question.

While I have the opportunity, I would like to make three or four general points.

Senator KENNEDY. Fine.

Dr. NESTOR. One, the key to the whole problem at the Food and Drug Administration that will solve most of the problems and reverse that agency in 48 times is the motivation, competence, integrity, and bias and prejudice of leadership.

If you come up with a method of properly screening the Commissioner, the Deputy Commissioner, the General Counsel, and the Director of the Bureau of Medicines, so that before they are appointed you know what their attitudes are in advance, you can eliminate a great deal because practically all of the problems come from poor leadership.

The second major point is that I would urge you to do something to pass the Employment Rights and Accountability Act that Mr. Nader presented to you on September 27, 1974, when he testified that he had gotten this together for Senator Proxmire in 1971, and in his hearings before you, this is introduced in your hearing record, and that is desperately needed to make these civil servants accountable and responsible.

Now, three or four specifics and then I will shut up.

I would like to reiterate the point that Dr. Carol Kennedy made that all contacts with industry must be formal and must be on the record.

All meetings should be arranged in advance at a mutually convenient time with a statement of who is going to be present and what the subject is, and there must be a verbatim record of these meetings.

We so many times have had meetings where, at the end of the meeting, we thought one thing and the industry thought another, and 6 months later they said to us, no, we thought you agreed with this.

Meetings with industry must be on the record.

All telephone calls must have memorandum, and as much as possible things should be done by correspondence.

Now, the reason I say this is we have talked about the revolving door between industry and Food and Drug.

You will never eliminate that in the very nature of this scientific enterprise. But this means that everything must be kept on a formal basis so there is a record of every contact.

Senator KENNEDY. The logging provisions, are they not being initiated?

Dr. NESTOR. One of the faults here, people come here and tell you the ideal, or we have regulations that say things, but they are never enforced.

It is one thing to say the right thing, and it is another thing to do the right thing.

Senator KENNEDY. We were under the impression, at least from other testimony, that logging provisions were being initiated and contacts with industry were being recorded.

I might mention that I introduced logging legislation, we passed it out of the Judiciary Committee, and I think on the vote we had in the Senate probably 6 or 8 weeks ago, we got probably 33 votes for it.

We were defeated because of this feeling, among some of my colleagues, that we do not want to create more paperwork among the various agencies.

All of you made a strong case as well as in our Judiciary Committee—classic example obviously the ITT case—where those provisions ought to be followed.

Some agencies are doing it at the present time.

Consumer Products Safety is doing it and supports it strongly.

A number of the other agencies are attempting to do it.

I could not agree with you more.

We will look into that in greater detail.

We were under the impression and finding out what is being done——

Dr. NESTOR. There would be far fewer contacts if they knew they were being recorded.

This would cut down on the volume of work.

No. 2, all actions on new drugs at every level should be done by endorsement in writing.

In other words, if the division medical officer writes a summary and recommendations, the division chief ought to be forced in writing on the record to approve or disapprove.

This should go all the way up and down the line.

There is simple management procedure which has never really been enforced at Food and Drug and it is why I say that a lot of these things could be reversed overnight with proper leadership, who wants to put in well-recognized management procedures.

Three, I would agree that trade secrets—I think 301(J) of the act was much too broadly interpreted.

Commissioner Schmidt has admitted that publicly.

Section 301(J) of the act only said any method or process which is considered trade secret—how in God's name can animal and human pharmacology data be considered any method or process?

Until those things are opened for peer review by the scientific community, this sort of thing is going on.

Now, efficacy, there was no doubt at all, if you will review the history of the Kefauver-Harris Acts, which I have, that the intent was that efficacy would be therapeutic benefit and therapeutic usefulness. Definition of Food and Drug has permitted in industry use—well, they claim they sent in the drug and we claim it only lowers cholesterol, and it does lower cholesterol, and they call it efficacious, when it may not have therapeutic benefit, but in most cases they prove to be harmful.

Efficacy must be redefined or restated as meaning therapeutic benefit and therapeutic usefulness.

The final thing is a plea for more adequate animal testing before drugs are put into humans.

Now, what is commonly overlooked, Food and Drug can come up with a beautiful program of animal testing, and beautiful program of human testing and what everybody overlooks is the relationship between the two for practical purposes.

The animal and human tests are going on simultaneously side by side, so that by the time the animal tests show carcinogenicity or cataracts, several hundred humans will have gotten the drug.

I took this to the Commissioner in June 1970 and it still has not been straightened out.

Animal tests are supposed to screen to determine toxicity, determine dosage and so on. They are not being used. They are being done as a matter of form simply because they have to be done.

I think that finishes what I have to say.

[Information supplied for the record follows:]

John O. Nestor, M.D.
2108 Key Blvd., Apt. 962
Arlington, Virginia 22201

July 26, 1976

Chairman Edward M. Kennedy
Subcommittee on Administrative
Practice and Procedure
United States Senate
Washington, D. C. 20510

Dear Chairman Kennedy:

At your FDA oversight hearing on July 20, 1976, you invited me to elaborate on my testimony in writing if I so desired. I accept that invitation since, in the brief time allotted for verbal response at that hearing, it was impossible to go into any detail.

Because of the many years of discord and dissension at the FDA and because of the charges of misconduct, it is essential that an Employee Rights and Accountability Act, similar to the draft furnished to you by Mr. Ralph Nader at the time of his testimony before you on September 27, 1974, be made law. This would protect all government employees who try to do an honest job and enable the government to get rid of those who do not.

The key to most of the problems at the FDA resides in the motivation, integrity, competence, bias, and prejudice of the top leadership which dominates, controls, and manipulates the Agency to conform to its will and desires. Unless this leadership is committed to enforcing the spirit and letter of the Federal Food, Drug, and Cosmetic Act the way Congress intended, there will continue to be discord and dissension at the FDA because there will always be a number of civil servants who will insist on compliance with the law the way it is written and not the way the leadership of the moment thinks it should have been written.

The obvious solution to the problem is better screening of prospective appointees to the positions of Commissioner, Deputy Commissioner, General Counsel, and Bureau Directors of FDA. This could be accomplished by requiring approval of all such appointees by the Senate after appropriate investigations and hearings just as in the case of cabinet officers. For example, I do not think that Dr. Charles Edwards would have become Commissioner in 1969 if this procedure had been followed. After his appointment

had been announced but before he arrived at the FDA, he was widely quoted in the news media as having stated that he saw his job as facilitating the flow of new drugs to the market. This was just what the pharmaceutical companies but not consumer representatives wanted to hear. Shortly after Dr. Edwards arrived on the scene, Chairman L. H. Fountain had him up before his House Intergovernmental Relations Subcommittee to explain that remark and to remind Dr. Edwards that it was the job of the FDA Commissioner under the law to see that a new drug was not approved for marketing unless it was supported by substantial evidence of safety and efficacy derived from well controlled studies. Obviously, Dr. Edwards had assumed his new position as Commissioner with a distorted idea of his duties.

New, competent, and properly motivated top leadership could promptly correct the deplorable state of affairs at the FDA which has been exposed by your several hearings conducted over the past two years. The present down-hill course of the agency could quickly be reversed by the implementation of a few obviously needed changes such as the following:

1. Require that all written recommendations by an employee be acted on promptly by written endorsement for the record.

2. Since the so-called revolving door whereby people leave the regulated industries for employment at the FDA and vice versa cannot be entirely eliminated because of the nature of the expertise needed by each organization, the FDA should require that all contacts between it and these regulated industries be formal and on the record. As much as possible, communications should be by correspondence. Telephone contacts should be kept to a minimum and fully documented by detailed memoranda. Except for emergency situations, all meetings should be arranged in advance at a mutually convenient time at the FDA with the identity of the participants and the subject for discussion established in advance. It is imperative that a verbatim record of every such meeting be made and retained. This procedure will eliminate much confusion, misunderstanding and criticism.

3. Section 301(j) of the Federal Food, Drug, and Cosmetic Act refers to "any method or process which as a trade secret is entitled to protection". It is obviously ridiculous to treat animal and human pharmacology data pertaining to the safety and efficacy of drugs as a "method or process" entitled to protection as a trade secret. The FDA should immediately issue a Regulation stating that animal and human pharmacology data pertaining to drugs are not considered to be trade secrets under the law.

4. The efficacy or effectiveness of a drug, as used in the Federal Food, Drug, and Cosmetic Act, must be interpreted by the FDA as meaning a drug which produces therapeutic benefit or usefulness and not just one that results in a change in a laboratory measurement without any proven benefit. To anyone who has studied the Congressional record and history of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act which introduced the requirement of efficacy in evaluating new drugs, it is obvious that efficacy was discussed as and understood to mean a drug which produced therapeutic benefit or usefulness. For example, co-sponsor Chairman Harris of the House Committee on Interstate and Foreign Commerce in his report to accompany H.R. 11581 dated September 22, 1962, before the Amendments were passed wrote under the heading, PREMARKETING PROOF OF EFFECTIVENESS OF NEW DRUGS, the following:

> "The scientists of the Food and Drug Administration may and sometimes do have serious reservations about the ability of the drug to accomplish the therapeutic benefits claimed for it."
>
> and
>
> "The Administration claims that many new drugs that have cleared the safety requirements of the law are marketed with unproved claims of therapeutic effectiveness."

Despite this, the Food and Drug Administration is accepting and acting under a very superficial definition which considers a drug to be efficacious if it merely changes a laboratory measurement when that change is listed as an indication for use. This is best illustrated by the cholesterol lowering or antilipidemic agents. Typically, the drug sponsor claims that the drug lowers serum lipid levels but not that this produces a therapeutic benefit. In fact, the FDA requires that these drugs include in their labeling the following statement:

> "It has not been established whether the drug induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question."

Actually, this quote is not correct. All of these lipid lowering drugs currently on the market do cause significant adverse reactions - some of them serious and severe - which obviously effect morbidity. For example, well controlled post-marketing studies have demonstrated that one of these drugs (Choloxin) has produced a significant increase in both morbidity and mortality in human subjects who had previously recovered from one or more myocardial infarcts. Obviously, the drug is not safe or effective for treating atherosclerosis even though it is effective in lowering the level of blood lipids. Incidentally, even though this drug has been proved to be unsafe and ineffective for this indication for use by these post-marketing studies, it is still on the market for this purpose and available to any physician who decides to write a prescription for it.

5. Change the regulations controlling the use of investigational new drugs so that the studies in animals serve the purpose of obtaining the information necessary to protect the intended human subjects. Currently, the animal and human pharmacology studies are essentially being performed simultaneously and concurrently with only a short lead-time for the animal studies. The result has been several instances where, by the time the animal studies had revealed serious and severe adverse reactions such as cancer or cataracts, many human subjects had been exposed unnecessarily.

6. Add to the regulations governing the use of investigational new drugs in humans the requirement that it is the joint responsibility of the drug sponsor, the clinical investiggator and the FDA to see to it that any human subject who has been exposed to the possibility of a serious and severe adverse reaction as the result of the investigation will be followed as long as necessary with appropriate periodic examinations. The drug sponsor, the clinical investigator, and the human subject should be required to agree to this in advance as a condition to participation in the investigation.

7. Pass a law to require that after a new drug is approved for marketing by the FDA under the present procedure and for the first three years it is on the market, any physician and patient who jointly choose to use it must agree as a condition for use to submit a detailed case history to the FDA for inclusion in the existing new drug application. If they do not wish to do this they can rely on the already established and accepted treatment for the condition if there is one.

This procedure will enable the FDA to more promptly and accurately ascertain not only the number, type, and severity of adverse reactions associated with the use of the drug, but also its effectiveness and the need for it in treating the conditions or illnesses for which its use is proposed. It will also make it much easier for the FDA and the drug companies to follow-up patients who have been inadvertently exposed to serious adverse effects (such as cancer or cataracts) that were unknown at the time the drug was originally marketed.

I hope these suggestions will be helpful to you and your Subcommittee.

Sincerely,

John O. Nestor

John O. Nestor, M.D.

Enclosures
3 Items Pertaining
to Choloxin

WHEN DIET ALONE FAILS TO LOWER CHOLESTEROL

CONSIDER
Choloxin®
(Sodium Dextrothyroxine)

A Proven Cholesterol-Lowering Adjunct to Diet.

An effective agent for low density lipoproteins in Euthyroid, Non-Cardiac Patients.

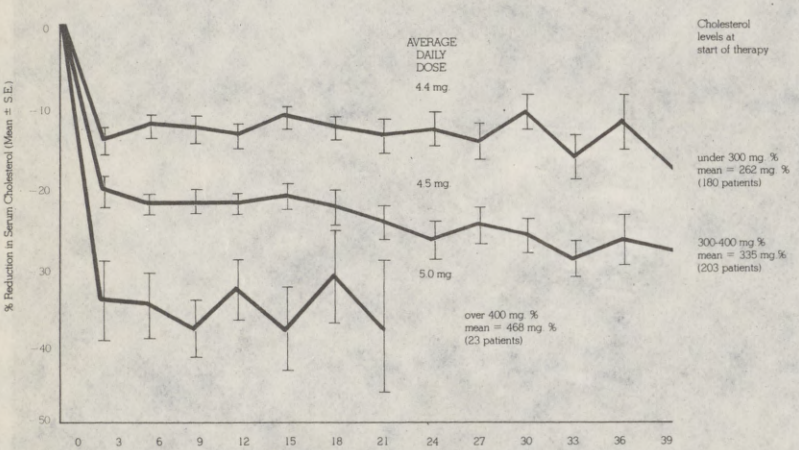
CHOLOXIN® (Sodium Dextrothyroxine) is the convenient and practical way to manage the hard-to-manage patient who doesn't always follow the diet regimen that you've outlined.

Convenient once-a-day dosage encourages patient cooperation, and it's economical for long-term therapy.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN (Sodium Dextrothyroxine) is a thyroid analogue which effectively lowers elevated serum cholesterol 15 to 35% (see chart below) in low density lipoproteins.

CHOLOXIN (Sodium Dextrothyroxine) has undergone ten years of clinical trials and seven years of practice. The clinical trials consisted of 337 clinical studies involving over 3,000 hypercholesterolemic non-cardiac patients. It is among the most thoroughly evaluated drugs ever presented to physicians.



NOT ALL PATIENTS ARE REPRESENTED AT EACH TIME INTERVAL.

FLINT LABORATORIES
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Deerfield, Illinois 60015

NOTE:
See following page for full prescribing information.

Choloxin®
(Sodium Dextrothyroxine)

Effectively Lowers Elevated Cholesterol With
Convenient Once-A-Day Dosage

Four strengths ... 1, 2, 4, and 6 mg ... are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg	1.0-2.0 mg	4.0-8.0 mg	4.0-8.0 mg
Pediatric Hypercholesterolemic	0.05 mg /kg body weight	0.05 mg /kg	0.1 mg /kg body weight	4.0 mg
Hypothyroid Cardiac	0.5-1.0 mg	1.0 mg	4.0 mg	4.0 mg

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as O-3,5,3',5'-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hypercholesterolemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication. **Before prescribing, note the following. Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN (sodium dextrothyroxine) is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN (sodium dextrothyroxine) dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.**

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris, history of myocardial infarction, cardiac arrhythmia or tachycardia either active or in patients with demonstrated propensity for arrhythmias, rheumatic heart disease, history of congestive heart failure, and decompensated or borderline compensated cardiac status
2. Hypertensive states (other than mild, labile systolic hypertension)
3. Advanced liver or kidney disease
4. Pregnancy
5. Nursing mothers
6. History of iodism

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN (sodium dextrothyroxine) therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN (sodium dextrothyroxine) therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN (sodium dextrothyroxine) is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN (sodium dextrothyroxine) is required. This drug may increase the oxygen requirements of the myocardium especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN (sodium dextrothyroxine). As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN (sodium dextrothyroxine) than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN (sodium dextrothyroxine) in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may not be advisable or possible to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN (sodium dextrothyroxine) therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug, if can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein bound-iodine levels. These increased serum PBI values in the presence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism, similarly they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN (sodium dextrothyroxine) therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN (sodium dextrothyroxine) for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are for the most part due to increased metabolism and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient although its relationship to CHOLOXIN (sodium dextrothyroxine) therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN (sodium dextrothyroxine), a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN (sodium dextrothyroxine) potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is approximately 0.1 mg (100 mcg) per kilogram. The initial daily dosage should be approximately 0.05 mg (50 mcg) per kilogram to be increased in up to 0.05 mg (50 mcg) per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4 and 6 mg tablets.

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Deerfield, Illinois 60015

Drug Therapy of Hyperlipoproteinemia

Robert I. Levy, MD

MANAGEMENT of hyperlipoproteinemia has been advanced considerably in recent years through new insights into lipid and lipoprotein metabolism, as well as into the mode of action of hypolipidemic drugs.[1] A variety of highly effective lipid level-lowering drugs is now available.[2] Because of the heterogeneity of the hyperlipoproteinemias, no single drug is useful in all the disorders. We now know that elevated lipid levels are the result of increased production or decreased removal of specific lipoproteins. Thus, the efficacy of a specific drug is determined by its effect on production or removal of the lipoproteins present in excess in each type of hyperlipoproteinemia.[3]

Hypolipidemic drugs can control hyperlipoproteinemia by one of two

See also p 2299.

mechanisms: (1) by increasing lipoprotein clearance or (2) by decreasing lipoprotein production. Treatment should always begin with an appropriate dietary prescription, which should be continued even after drug treatment is introduced, because the combined therapeutic effect is additive.[4] Before administering a drug, the patient should be maintained on a diet for two to six weeks, at which time lipid values should be monitored regularly. If there is no alteration in baseline levels, therapy may be supplemented with a drug. Prolonged maintenance with a particular drug should be contingent on a substantial reduction in lipid levels (approximately 15% within four to six weeks), as well as on the absence of any serious side effects. Individual adjustments in dosage may be necessary to reduce any abnormalities.

From the National Heart and Lung Institute, Bethesda, Md.

Reprint requests to National Heart and Lung Institute, Bethesda, MD 20014 (Dr Levy).

LIPOPROTEIN CLEARANCE INCREASE

Cholestyramine Resin

Cholestyramine resin is an anion exchange resin that binds bile acids and increases the catabolism of low-density lipoproteins (LDLs). It is hydrophilic but insoluble in water. It remains unchanged in the gastrointestinal tract and is unabsorbed.

Indications.—Cholestyramine is the drug of choice for patients with pure hypercholesterolemia (familial type II hyperlipoproteinemia).[5] Because of its variable effect on very low-density lipoproteins (VLDLs) and intermediate-density lipoproteins (IDLs) (it may increase their production), it is contraindicated in the endogenous or mixed hypertriglyceridemias (types III, IV, and V hyperlipoproteinemia), where it may increase triglyceride levels.

Dose.—Cholestyramine resin is available in powder form prepared in 9-gm packets containing 4 gm of active drug and 5 gm of filler and flavoring. It is taken orally and mixed with a liquid, such as lemonade or fruit juice, or with pulpy fruits, such as applesauce. The initial dose is 16 gm/day given in two to four divided doses. Recent evidence suggests that two daily doses may be as effective as four. The dose can be increased by 4 to 8 gm every two to three weeks until a maximum of 32 gm/day is reached.

Side Effects.—Constipation is the most common side effect, particularly among older patients, but is often easily treated with stool softeners. Other complications may include nausea, vomiting, cramps, and abdominal distention. These usually respond to a reduction in dosage. More serious side effects such as steatorrhea, intestinal obstruction, and hyperchloremic acidosis (in young children) are rare.

Drug Interactions.—Cholestyramine can affect the absorption of acidic compounds and fat-soluble vitamins. Drugs such as digitalis, warfarin sodium, iron, thyroid preparations, tetracycline, thiazides, and phenylbutazone should be taken at least one hour before cholestyramine is. Their blood concentrations or clinical effects should be monitored carefully in order to adjust dosage appropriately.

Dextrothyroxine

Dextrothyroxine is the dextrarotatory isomer of thyroxine, which lowers plasma cholesterol without causing hypermetabolism. It increases both the production and clearance of hepatic cholesterol and increases LDL removal rates.

Indications.—Dextrothyroxine is es-

pecially useful in disorders characterized by LDL excess (type II hyperlipoproteinemia). Its effects on VLDL and IDL have not been fully evaluated.

Dose.—Dextrothyroxine is manufactured in 2- and 4-mg tablets. The initial dose is 2 mg/day orally, increased monthly by 1 to 2 mg, until a maintenance dose of 4 to 8 mg/day is attained.

Side Effects.—The principal complications of dextrothyroxine that limit its usefulness as a hypolipidemic agent are cardiac in origin (eg, increased angina and arrhythmias). **The drug was withdrawn from the Coronary Drug Project because it was associated with excessive cardiovascular morbidity and mortality in subjects with preexisting coronary heart disease (CHD).**

Other possible side effects include glucose intolerance, abnormal liver-function tests, glycosuria, and neutropenia.

Drug Interactions.—Dextrothyroxine interferes with warfarin anticoagulation, which can require as much as a 30% reduction in warfarin dosage.

Colestipol Hydrochloride

Colestipol hydrochloride is an investigational bile acid sequestrant that has not yet been cleared for use in man by the Food and Drug Administration. It is insoluble, and its effect on plasma cholesterol is similar to that of cholestyramine. Its effect on lipoprotein metabolism has not yet been elucidated.

Indications.—The indications for its use are the same as for cholestyramine and it, too, has not been associated with any substantial drop in plasma triglyceride levels.

Dose.—Colestipol is available in water-insoluble beads. The usual dose is 4 to 5 gm three times per day, although doses of up to 10 gm three times per day have been used.

Side Effects.—Side effects and drug interactions appear to be essentially identical to those noted for cholestyramine.

LIPOPROTEIN PRODUCTION DECREASE

Niacin

Niacin is an effective hypolipidemic agent when administered in doses exceeding its daily requirement as a vitamin. Within four to six hours, it depresses plasma triglyceride concentrations by reducing VLDL synthesis. The drug also has an indirect lowering effect on IDL and LDL levels, which occurs only after several days.

Indications.—Niacin is primarily indicated in types III, IV, and V hyperlipoproteinemia. It can also be useful in primary type II hyperlipoproteinemia, especially in combination with cholestyramine.

Dose.—The initial dose of niacin is 100 mg orally three times a day (preferably with meals). This can be increased 300 mg/day every four to seven days for a maintenance dose of 3 to 9 gm/day. (The usual adult dosage is 1 gm three times a day.) The drug is available in tablets of 100 and 500 mg, but experience has shown better absorption of the 100-mg tablets. Niacin is available in several preparations, but the cheapest and perhaps the safest is plain nicotinic acid.

Side Effects.—The most annoying side effects are intense cutaneous flushing and pruritus, which usually develop within one to two hours of a dose. The symptoms generally regress as tolerance to the superficial vasodilation effects of the drug is developed.

Gastrointestinal complications can also occur, but these are transient and usually can be alleviated if the drug is taken with meals.

Other side effects include abnormal liver function tests, abnormal glucose tolerance, hyperuricemia, glycosuria, and increased skin pigmentation (acanthosis nigricans). Great caution is therefore advised in considering use of the drug in patients with liver disease, diabetes mellitus, or gout.

The findings of the Coronary Drug Project (a secondary coronary prevention trial done in patients who had one or more previous heart attacks) show that, in spite of a statistically significant decrease in recurrent nonfatal myocardial infarctions, the drug did not affect overall mortality from CHD.[6] Moreover, it was associated with an excessive incidence of arrhythmias, as well as skin and gastrointestinal problems.

Drug Interactions.—Niacin can increase the vasodilation of ganglioplegic antihypertensive agents.

Clofibrate

Clofibrate is a branched-chain fatty acid ester whose principal hypolipidemic action is a depression of VLDL levels. The apparent mechanism seems to be both a decrease of VLDL production and acceleration of its catabolism to LDL, although recent evidence suggests the predominance of the latter activity. The effect of clofibrate on LDL levels is unpredictable.

Indications.—Clofibrate is the drug of choice for treatment of type III hyperlipoproteinemia because its side effects are less troublesome than those of nicotinic acid. It may also be useful in controlling excessive triglyceride levels, which characterize type IV. Its value in treating type II is limited because of its variable effect on LDL metabolism.

Dose.—Clofibrate is prepared in 500-mg capsules. The maximum dose is 1.5 to 2 gm/day, administered orally in two divided doses.

Side Effects.—A particularly attractive feature of clofibrate was its purported high degree of safety and relative absence of side effects. Nausea, diarrhea, and weight gain can occur, but they are generally infrequent. Other symptoms such as myositis, skin rash, and abnormal liver function tests are rare. The Coronary Drug Project has shed new light on the potentially serious side effects of clofibrate. These include a reported twofold increase in cholelithiasis in the clofibrate-treatment group, as well as a statistically significant increase in cardiovascular signs and symptoms (increased heart size, arrhythmias, angina) in these patients with a history of myocardial infarction.[6] The drug did not affect overall cardiovascular mortality. This study suggests that this drug should be used cautiously, if at all, in patients with preexisting cardiovascular disease.

Drug Interactions.—Clofibrate enhances the hypoprothrombinemic effects of warfarin sodium and may have similar effects on other protein-bound drugs (such as phenytoin).

OTHER HYPOLIPIDEMIC DRUGS

PAS-C

Aminosalicylic acid recrystallized in ascorbic acid (PAS-C) is a new investigational preparation that has re-

cently been reported to be successful in lowering serum cholesterol and triglyceride levels.[7] Its mode of action is still unclear.

The drug is indicated for the treatment of primary types IIa and IIb because of its depressant effect on LDL levels.

Initial doses have been reported to range from 4.5 to 7.5 gm/day, taken orally at mealtimes in three divided doses of three to five tablets. The maintenance dose is 8 to 9 gm/day for adults, 5 to 6 gm/day for children.

Some gastrointestinal disturbances have been noted, but serious side effects were absent. Moreover, the drug remained effective for a prolonged period of administration.

Excessive alcohol intake was found to offset the hypolipidemic action of the combination of aminosalicylic and ascorbic acids.

Sitosterol S

Sitosterol S is a plant sterol similar in structure to cholesterol. It has been found to inhibit cholesterol absorption, presumably by increasing LDL clearance, although its effect on lipoprotein metabolism has not been fully explored.

Sitosterol S is indicated for states characterized by LDL excess. It is available as a liquid, of which 30 ml equals 6 gm of sitosterol. The recommended dose is 30 ml one-half hour before meals and at bedtime.

The drug may have a mild laxative effect, and diarrhea and nausea are not uncommon. No serious complications have been noted.

Neomycin Sulfate

Neomycin sulfate is an antibiotic produced from *Streptomyces gradiar*, which has a hypolipidemic effect only when administered orally. Its mechanisms of action are not dependent on changes in intestinal flora and appear to resemble those of cholestyramine by increasing bile acid and LDL catabolism.

Neomycin is available in tablets containing 0.35 gm of drug and is administered in divided doses totalling 0.5 to 2.0 gm/day.

Side effects include mild diarrhea. Experience with the drug is limited because of its potential for ototoxicity or nephrotoxicity, particularly in patients with reduced renal function.[8]

Combination Chemotherapy

The control of hyperlipoproteinemia by a combination of drugs that act by alternate mechanisms has been clinically useful, especially in the more intractable familial disorders. Cholestyramine and niacin can function synergistically to reduce extremely high levels of LDL in type II homozygotes and in some heterozygotes. Other possible combinations include cholestyramine with clofibrate, sitosterol S, and neomycin, but these are still considered investigational.

CONCLUSION

A clearer understanding of lipoprotein metabolism and the mechanism of action of hypolipidemic drugs has provided a more rational basis for the selection of appropriate therapy. However, the ultimate benefit of a lifelong commitment to such therapy is still unproved. Hypolipidemic drugs should be used cautiously until we have more cogent proof that the elimination of hyperlipidemia will prevent or delay atherosclerosis.

Nonproprietary Names and Trademarks of Drugs

Colestipol hydrochloride—*Colestid*.
Dextrothyroxine sodium—*Choloxin*.

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The Coronary Drug Project

Findings Leading to Further Modifications of Its Protocol With Respect to Dextrothyroxine

The Coronary Drug Project Research Group

As noted in the first definitive report from the Coronary Drug Project,[1] physicians face a difficult dilemma concerning pharmacologic therapy of hyperlipidemia in an attempt to prevent first or recurrent episodes of clinical coronary heart disease (CHD). They know that susceptibility to premature CHD is directly related to serum levels of cholesterol, and of low-density and very-low-density lipoproteins. They are also aware that elevated serum lipids-lipoproteins frequently can be reduced over long periods of time by available drugs. However, they lack answers to key questions about these pharmaceutical agents: Do they prevent CHD and prolong life? Are they reasonably safe in long-term usage? The scarcity of scientific data on these critical questions is especially troublesome in view of the fact that prevention or treatment of coronary disease by control of hyperlipidemia makes sense only as long-term therapy, and questions about drug toxicity are especially gnawing under this circumstance.

The Coronary Drug Project (CDP)—a nationwide collaborative study sponsored by the National Heart and Lung Institute—is the most extensive effort ever undertaken to answer these questions with regard to men who have already experienced one or more episodes of myocardial infarction (MI).[1-4]

The present report deals with recent findings of the CDP concerning apparent adverse effects noted to date with dextrothyroxine sodium that have led to discontinuation of this drug regimen in the CDP.

For a complete list of the key bodies of the Coronary Drug Project and senior staff members see page 1008.

Reprint requests to 303 E Chicago Ave, Chicago 60611 (Jeremiah Stamler, MD).

Methods

The background, design, and organization of the CDP were described in detail in the earlier report.[1] The primary objective of the CDP has been to test the efficacy and safety of several lipid-influencing drugs in the long-term therapy of CHD in men aged 30 to 64 years, with proved previous MI. For this purpose, 8,341 patients were recruited by the 53 CDP clinical centers and were randomly assigned to six groups: conjugated estrogens, 2.5 mg/day; conjugated estrogens, 5.0 mg/day; clofibrate, 1.8 gm/day; dextrothyroxine sodium (DT4), 6.0 mg/day; nicotinic acid, 3.0 gm/day; and placebo. (As previously reported, the 5.0 mg/day estrogen regimen was discontinued in 1970 chiefly because of an excess number of nonfatal cardiovascular events in this group compared to placebo.[1] At the same time, dextrothyroxine was discontinued in the subgroup of patients with frequent ectopic ventricular beats [FEVBs] on the base-line resting electrocardiogram. This precautionary step was taken because this subgroup experienced a somewhat higher early mortality than the corresponding placebo subgroup. A total of 27 patients in the DT4 group and 74 in the placebo group had such FEVBs at entry. [The numbers of patients—27 and 74 in the DT4 and placebo groups, respectively—with FEVBs on the base-line ECG are slightly different from those originally reported.[1] This is due to subsequent reclassification of a few patients with respect to FEVB status.] Similar adverse effects were not then apparent among the approximately 1,000 other patients taking this medication. Consequently, prescription of dextrothyroxine was continued for these men.)

Patients randomized into the CDP were men aged 30 to 64 years, with documented evidence of one or more MIs, categorized as class 1 or 2 of the functional classification of the New York Heart Association (NYHA),[5] and free from a specified list of excluding diseases and conditions. All patients were confirmed to be at least three months beyond their most recent MI, and free of evidence of recent worsening of their coronary disease or of other major illnesses. They were also classified as to risk. Risk 1 included men with a single MI, free of defined serious complications during the acute episode. Risk 2 included men with two or more MIs, and men with a single MI who, during the acute episode, did have one or more defined complication (eg, pericarditis, congestive failure, shock, arrhythmia, extension of infarction).

A separate, random allocation schedule was utilized by the Coordinating Center for each of the two risk groups within each participating clinic. Each schedule was designed to assure approximately equal numbers of patients in the five drug groups, and approximately five patients in the placebo group for every two patients in any of the other groups.

The study is conducted as double-blind in the sense that neither the patient nor the clinic staff is informed of the patient's drug allocation, except as may be required in a verified medical emergency. Initial prescription of assigned medication was three capsules per day, supplying one third of ultimate full dosage (see above), with an increase at monthly intervals to six and then to the maximum of nine capsules per day, unless the managing physician altered the regimen for specified reasons.

Each patient is to be observed for a period of at least five years. He reports to the clinic every four months

Table 1.—Nonfatal Events and Deaths by Cause*

Event	DT4 No. of Men	DT4 No. of Events	DT4 %	Placebo No. of Men	Placebo No. of Events	Placebo %	DT4 − Placebo SED†	% Difference: DT4 − Placebo / Placebo
Death—all causes	1,083	160	14.8	2,715	339	12.5	1.88	+18.4
Death—all cardiovascular	1,083	146	13.5	2,715	317	11.7	1.54	+15.4
Death—non-cardiovascular	1,083	9	0.8	2,715	19	0.7	0.43	...§
Death—cause unknown	1,083	5	0.5	2,715	3	0.1	2.13	...§
Death—all CHD	1,083	119	11.0	2,715	274	10.1	0.82	+ 8.9
Death—sudden‡	1,083	63	5.8	2,715	162	6.0	0.18	− 3.3
Definite nonfatal MI	1,053	89	8.5	2,618	202	7.7	0.75	+10.4
Major coronary events (Definite nonfatal MI and CHD death)	1,083	197	18.2	2,715	449	16.5	1.22	+10.3
All suspect or definite CV events (nonfatal or fatal)	1,083	736	68.0	2,715	1,758	64.8	1.88	+ 4.9

*Excludes 27 dextrothyroxine (DT4) and 74 placebo patients with frequent ectopic ventricular beats at entry.[1]
†SED indicates standard error of difference.
‡Excludes sudden deaths attributed to noncardiovascular causes.
§Percent changes not calculated when percent deaths is less than 1.0.

for a follow-up visit. A complete standardized examination, including a resting ECG, is made annually. Complaints and findings suggestive of illness or toxic reaction are thoroughly evaluated by the research clinic. In all circumstances, the CDP Protocol and Manual of Operations allow full leeway for optimal medical care for patients with MI.

Data in a standard format are sent to the Coordinating Center and are continuously monitored for "events," including death, recurrent MI, congestive heart failure (CHF), intermediate coronary episodes called acute coronary insufficiency (ACI), angina pectoris (AP), electrocardiographic changes, stroke, and venous thromboembolism, and other findings such as flushing, nausea, jaundice, insomnia, tremor, or deviations of serum enzyme levels from base-line values.

At a scheduled meeting of the Data and Safety Monitoring Committee in the fall of 1971, extensive interim reviews were accomplished of data relating to all end points under surveillance. Data representing an average

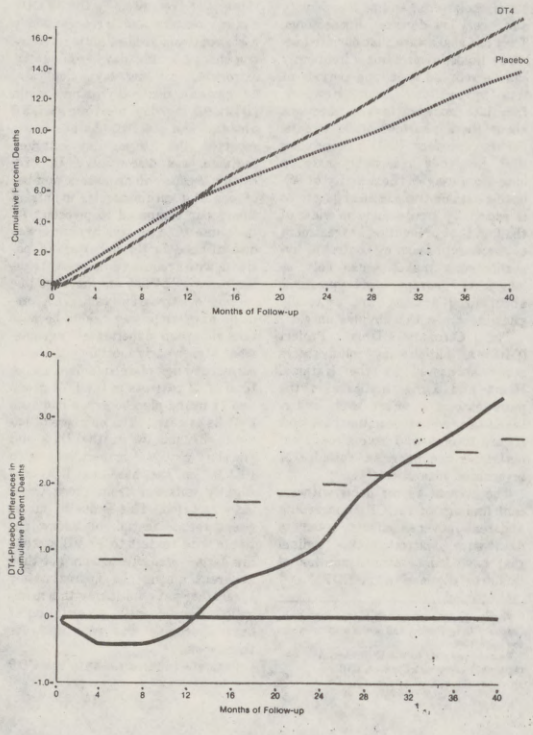


Fig 1.—Life-table cumulative rates for deaths from all causes for DT4 and placebo groups (top), *and differences between DT4 and placebo groups in these cumulative rates* (bottom). *Broken lines in lower graph denote two-standard-error values at various time points. Excludes 27 DT4 and 74 placebo patients with FEVBs at entry.*

Table 2.—Percentage of Men with Various Findings at Entry*

Entry Characteristic†	Percentage Distribution	
	DT4 (1,083 Men)	Placebo (2,715 Men)
Age at entry <55	58.6	57.4
Age at entry ≥55	41.4	42.6
White	93.8	93.2
Nonwhite	6.2	6.8
Risk group 1	66.4	65.9
Risk group 2	33.6	34.1
One MI, uncomplicated	66.4	65.9
One MI, complicated	14.3	14.5
Two or more MIs	19.3	19.6
NYHA class 1	45.8	46.7
NYHA class 2	53.2	53.3
History of CHF—no	85.0	84.1
History of CHF—yes	15.0	15.9
History of AP—no	40.6	42.1
History of AP—yes	59.4	57.9
History of ACI—no	82.0	83.4
History of ACI—yes	18.0	16.6
History of IC—no	92.5	91.5
History of IC—yes	7.5	8.5
Heart rate <70/min	53.8	55.4
Heart rate 70-79/min	29.3	27.6
Heart rate ≥80/min	16.9	17.0
Qualifying ECG—ST-T criteria only	18.8	16.9
Qualifying ECG—class 2 waves	34.5	34.1
Qualifying ECG—class 1 waves	46.6	49.0
Base-line ECG—no Q-QS abnormality	40.7	38.1
Base-line ECG—minor Q-QS abnormality	17.2	17.6
Base-line ECG—moderate Q-QS abnormality	20.1	20.5
Base-line ECG—major Q-QS abnormality	22.1	23.7
Base-line ST depression—none	74.2	75.4
Base-line ST depression—minor	17.6	15.3
Base-line ST depression—moderate or major	8.2	9.3
Noncigarette smokers	66.1	62.1
Cigarette smokers	33.9	37.9
Systolic BP<140 mm Hg	69.0	69.2
Systolic BP≥140 mm Hg	31.0	30.8
Diastolic BP<80 mm Hg	35.6	34.3
Diastolic BP 80-89 mm Hg	36.0	37.4
Diastolic BP≥90 mm Hg	28.3	28.3
Serum cholesterol<250 mg/dl	52.2	53.3
Serum cholesterol≥250 mg/dl	47.8	46.7
Serum triglycerides<5.0 mEq/liter	53.1	49.6
Serum triglycerides≥5.0 mEq/liter	46.9	50.4
Serum uric acid<8.0 mg/dl	83.4	80.2
Serum uric acid≥8.0 mg/dl	16.6	19.8
Fasting plasma glucose<100 mg/dl	58.5	57.7
Fasting plasma glucose≥100 mg/dl	41.5	42.3
1-hr plasma glucose<205 mg/dl	78.2	77.1
1-hr plasma glucose≥205 mg/dl	21.8	22.9
Relative body weight<1.25	80.0	77.6
Relative body weight≥1.25	20.0	22.4
Multivariate prediction score‡		
<5.0	14.6	14.8
5.0- 9.9	44.8	41.3
10.0-14.9	18.3	20.0
15.0-24.9	14.4	13.7
≥25.0	7.9	10.2

*Excludes 27 dextrothyroxine (DT4) and 74 placebo patients with FEVBs at entry.[1]
†MI signifies myocardial infarction; NYHA, New York Heart Association; CHF, congestive heart failure; AP, angina pectoris; ACI, acute coronary insufficiency; IC, intermittent claudication; BP, blood pressure.
‡This is an expected percentage of deaths over 36 months, obtained from a multiple logistic regression analysis in placebo group patients with the use of the following variables: time since date of entry; ST depression; cardiomegaly; diuretics; ventricular conduction defects; intermittent claudication; and physical activity. Except for the time-since-entry variable, these are all base-line variables.

follow-up of 36 months were available as of Aug 1, 1971. Ninety-two percent of the patients had been observed for two years or more, 60% for at least three years, and 17% for at least four years. As a result of this review, the Data and Safety Monitoring Committee recommended that a decision be made to discontinue dextrothyroxine medication. This recommendation was then ratified by the Policy Board, approved by the Steering Committee and Technical Group, and implemented.

Results

Morbidity and Mortality.—OVERALL FINDINGS.—As of Aug 1, 1971, with an average follow-up of 36 months of patients receiving medication, the proportion of deaths in the DT4 group was 14.8%; in the placebo group, 12.5%, a difference which approaches two standard errors. The overall mortality was 18.4% higher for the DT4 group (Table 1). Further analysis by the life-table method revealed that the absolute difference in mortality between these two groups tended to increase progressively with duration of medication (Fig 1). At the 28th month of follow-up and thereafter, these differences exceeded two standard errors of the difference. The observed DT4-placebo difference in overall mortality is not statistically significant as judged by the statistical methods utilized in this study. (These methods take into account the multiplicity of groups, the frequency of data review in the CDP, and the consequent enhanced probability of achieving differences normally considered significant, eg, two standard errors. They yield more conservative estimates of statistical significance than "classical" procedures—compare reference 1.)

As is evident from Table 1, for both DT4 and placebo groups, about 90% of the deaths were ascribed to cardiovascular causes; about 80% were attributed to CHD; and about half the deaths were sudden (ie, occurring within one hour of onset of symptoms). For the specific cardiovascular causes, the DT4 group generally manifested higher rates than the placebo group. This was also true for incidence of nonfatal MI, of major coronary events (definite nonfatal MI and CHD death), and incidence of all cardiovascular events.

These differences between the DT4 and placebo group cannot be ascribed to a greater initial risk of recurrent cardiovascular events in the patients allocated to DT4, since detailed univariate and multivariate analyses demonstrated the two treatment groups to be highly comparable at entry (an expected consequence of the

Table 3.—Percent Deaths by Selected Base-Line Characteristics*

Base-line Characteristics†	DT4			Placebo			DT4 — Placebo	% Difference: DT4 — Placebo
	No. of Men	No. of Deaths	% Deaths	No. of Men	No. of Deaths	% Deaths	SED‡	Placebo
All	1,083	160	14.8	2,715	339	12.5	1.88	+18.4
Age<45	169	18	10.7	410	36	8.8	0.70	+21.6
Age 45-54	466	63	13.5	1,149	127	11.1	1.39	+21.6
Age≥55	448	79	17.6	1,156	176	15.2	1.18	+15.8
Risk group 1	719	78	10.8	1,790	197	11.0	−0.11	−18.2
Risk group 2	364	82	22.5	925	142	15.4	3.06	+46.1
One MI, uncomplicated	719	78	10.8	1,790	197	11.0	−0.11	−1.8
One MI, complicated	155	24	15.5	393	41	10.4	1.65	+49.0
Two or more MIs	209	58	27.8	532	101	19.0	2.62	+46.3
NYHA class 1	507	61	12.0	1,269	115	9.1	1.90	+31.9
NYHA class 2	576	99	17.2	1,446	224	15.5	0.94	+11.0
History of CHF—no	921	118	12.8	2,284	253	11.1	1.39	+15.3
History of CHF—suspect or definite	162	42	25.9	431	86	20.0	1.58	+29.5
History of AP—no	440	34	7.7	1,142	113	9.9	−1.33	−22.2
History of AP—suspect or definite	643	126	19.6	1,573	226	14.4	3.06	+36.1
Heart rate<70/min§	576	55	9.5	1,482	158	10.7	−0.74	−11.2
Heart rate 70-79/min	313	60	19.2	738	88	11.9	3.09	+61.3
Heart rate≥80/min	181	45	24.9	456	87	19.1	1.62	+30.4
Q-QS findings§								
None or minor abnormality	619	79	12.8	1,492	147	9.9	1.97	+29.3
Moderate or major abnormality	451	81	18.0	1,184	186	15.7	1.10	+14.6
ST depression§—none or minor	982	129	13.1	2,428	261	10.7	1.98	+22.4
ST depression§—moderate or major	88	31	35.2	248	72	29.0	1.08	+21.4
Q-QS and ST Depression§								
None or minor Q-QS *and* ST depression	577	63	10.9	1,368	114	8.3	1.81	+31.3
Moderate or major Q-QS *or* ST depression	493	97	19.7	1,308	219	16.7	1.46	+18.0
Ventricular or atrioventricular conduction defects§								
Neither	930	125	13.4	2,344	286	12.2	0.97	+9.8
One or both	140	35	25.0	332	47	14.2	2.84	+76.1
Systolic BP<140 mm Hg	747	94	12.6	1,879	221	11.8	0.58	+6.8
Systolic BP≥140 mm Hg	336	66	19.6	836	118	14.1	2.35	+39.0
Diastolic BP<80 mm Hg	386	44	11.4	931	118	12.7	−0.64	−10.2
Diastolic BP 80-89 mm Hg	390	61	15.6	1,015	116	11.4	2.13	+36.8
Diastolic BP≥90 mm Hg	307	55	17.9	769	105	13.7	1.77	+30.7
Serum cholesterol<250 mg/dl	565	78	13.8	1,448	166	11.5	1.45	+20.0
Serum cholesterol≥250 mg/dl	518	82	15.8	1,267	173	13.7	1.19	+15.3
Serum triglycerides<5.0 mEq/liter	575	74	12.9	1,347	166	12.3	0.33	+4.9
Serum triglycerides≥5.0 mEq/liter	508	86	16.9	1,368	173	12.6	2.39	+34.1
Cardiomegaly on x-ray film								
No	918	116	12.6	2,228	222	10.0	2.20	+26.0
Yes	165	44	26.7	487	117	24.0	0.68	+11.2
Digitalis use at entry								
No	930	111	11.9	2,316	242	10.4	1.23	+14.4
Yes	153	49	32.0	399	97	24.3	1.84	+31.7
Diuretics use at entry								
No	942	122	13.0	2,335	243	10.4	2.10	+25.0
Yes	141	38	27.0	380	96	25.3	0.39	+6.7

*Excludes 27 dextrothyroxine (DT4) and 74 placebo patients with frequent ectopic ventricular beats at entry.[1]
†MI signifies myocardial infarction; NYHA, New York Heart Association; CHF, congestive heart failure; AP, angina pectoris; BP, blood pressure.
‡SED indicates standard error of difference.
§ECG readings not available for 13 DT4 and 39 placebo patients.

stratified randomization procedure and the large numbers) (Table 2). Adjustment of total mortality for minor differences in risk of the two groups, as accomplished by a multiple regression analysis utilizing 33 base-line factors, yielded an adjusted percent mortality for the DT4 group of 15.2%; for the placebo group, 12.3%; ie, persistence of a sizeably higher rate for the DT4 group.

SUBGROUP FINDINGS.—It is conceivable that the effectiveness of a drug may vary from one subgroup of patients to another, ranging from favorable to unfavorable depending on the severity of the preexisting disease. Therefore, a key aspect of data and safety monitoring in the CDP has been a detailed periodic analysis of mortality in subgroups of patients, identified by demographic, clinical, electrocardiographic, roentgenographic, and biochemical measurements made at base line. Several of these analyses yielded data essentially similar to the overall findings, ie, mortality from all causes was consistently higher by modest amounts for the DT4 subgroups compared with the corresponding placebo subgroups. This was true for the DT4 subgroups identified on the basis of status at entry with regard to age, NYHA functional class, history of CHF, electrocardiographic Q-QS and ST segment findings, cardiomegaly on x-ray film, lipid levels, and use of digitalis or diuretics (Table 3). However, evaluation

Table 4.—Percent Deaths by Combinations of Base-Line Characteristics*

Combinations of Base-Line Characteristics‡	DT4			Placebo			DT4 — Placebo	% Difference: DT4 — Placebo
	No. of Men	No. of Deaths	% Deaths	No. of Men	No. of Deaths	% Deaths	SED†	Placebo
No AP, risk 1	317	21	6.6	821	75	9.1	−1.37	−27.5
No AP, risk 2	123	13	10.6	321	38	11.8	−0.38	−10.2
AP, risk 1	402	57	14.2	969	122	12.6	0.80	+12.7
AP, risk 2	241	69	28.6	604	104	17.2	3.71	+66.3
No AP, HR<70/min	243	11	4.5	640	54	8.4	−1.99	−46.4
No AP, HR≥70/min	194	23	11.9	484	56	11.6	0.10	+2.6
AP, HR<70/min	333	44	13.2	842	104	12.4	0.40	+6.5
AP, HR≥70/min	300	82	27.3	710	119	16.8	3.85	+62.5
AP, risk 2, HR≥70/min:								
None of three	179	7	3.9	461	36	7.8	−1.77	−50.0
Any one only	409	37	9.0	1,066	117	11.0	−1.08	−18.2
Any two only	370	72	19.5	856	120	14.0	2.41	+39.3
All three	112	44	39.3	293	60	20.5	3.88	+91.7
AP, HR≥70/min, DBP≥90/min:								
None of three	185	4	2.2	487	36	7.4	−2.56	−70.3
Any one only	442	51	11.5	1,101	131	11.9	−0.20	−3.4
Any two only	341	80	23.5	862	126	14.6	3.67	+61.0
All three	102	25	24.5	226	40	17.7	1.43	+38.4
All risk 1 + risk 2 with AP	842	91	10.8	2,111	235	11.1	−0.25	−2.7
Risk 2 with AP	241	69	28.6	604	104	17.2	3.71	+66.3
Risk 1 with HR<70/min + risk 2 without AP and with HR<70/min	460	30	6.5	1,210	120	9.9	−2.17	−34.3
Risk 1 with HR≥70/min + risk 2 with AP and/or HR≥70/min	623	130	20.9	1,505	219	14.6	3.58	+43.2

*Excludes 27 dextrothyroxine (DT4) and 74 placebo patients with frequent ectopic ventricular beats at entry.[1]
†SED indicates standard error of difference.
‡AP, angina pectoris; HR, heart rate; DBP, diastolic blood pressure.

Table 5.—Student's t Statistics (Disregarding Signs) for the First, Second, and Third Most Important of 48 Base-Line Variables in Maximizing DT4-Placebo Difference*

Replication†	Student's *t* Statistic		
	First Variable	Second Variable	Third Variable
A. Observed vital status	3.17	3.19	2.56
B. Random vital status			
1	3.03‡	2.06	2.51‡
2	3.02	2.16	2.21
3	2.98	2.27	2.08
4	2.81	2.18	2.12
5	2.78	2.49	2.47
6	2.76	2.70‡	2.45
7	2.62	2.38	2.12
8	2.61	1.99	2.00
9	2.54	2.23	2.21
10	2.54	1.85	1.83
11	2.40	1.94	1.81
12	2.39	2.35	1.76
13	2.31	2.15	1.96
14	2.27	1.86	1.70
15	2.26	1.59	1.40
16	2.15	2.07	2.02
17	2.11	1.94	1.87
18	2.10	1.76	1.52
19	2.00	2.04	1.80
20	1.86	1.84	1.57

*Based on (A) observed vital status of CDP patients, and (B) twenty computer replications with the use of a random assignment of vital status.
†The 20 replications under part B are ranked according to the size of the *t* value for the first variable.
‡Maximum for part B of the 20 *t* values in each column.

of the mortality experience in this way also yielded evidence of *marked* excess in mortality for several DT4 subgroups, compared with corresponding placebo subgroups. These subgroups included men with one or more of the following characteristics: a history of one complicated MI or multiple MIs (ie, risk 2 patients); a history of AP; higher heart rates; higher blood pressures at entry; and electrocardiographic signs of atrioventricular (AV) conduction defects.

Cross classification further showed that the greater death rate in DT4 than placebo patients was concentrated in subgroups with two or more of these findings (Table 4). Thus, for men classified as risk 2 and with a history of AP at entry, mortality was 66.3% higher for the DT4 than for the placebo subgroup (28.6% for DT4, 17.2% for placebo). For patients with AP and resting heart rate of 70 beats per minute and greater, mortality was 62.5% higher for the DT4 than for the placebo subgroup (27.3% and 16.8% for DT4 and placebo, respectively). For men with all three characteristics (risk 2, AP, heart rate greater than or equal to 70 beats per minute), mortality was 91.7% higher for the DT4 than for the placebo sub-

Table 6.—Percent Deaths at Specified Analysis Dates*

Analysis Date	DT4 No. of Men	DT4 No. of Deaths	DT4 % Deaths	Placebo No. of Men	Placebo No. of Deaths	Placebo % Deaths	DT4 — Placebo SED†	% Difference: DT4 — Placebo Placebo
Subgroup A								
10/1/70	623	102	16.4	1,505	168	11.2	3.29	+46.4
8/1/71	623	130	20.9	1,505	219	14.6	3.58	+43.2
Interval: 10/1/70-8/1/71	521	28	5.4	1,337	51	3.8	1.50	+42.1
Subgroup B								
10/1/70	460	19	4.1	1,210	93	7.7	−2.60	−46.8
8/1/71	460	30	6.5	1,210	120	9.9	−2.17	−34.3
Interval: 10/1/70-8/1/71	441	11	2.5	1,117	27	2.4	0.09	+4.2

*Percentages calculated for the following subgroups: Subgroup A.—Risk 1 patients with heart rate ≥ 70/min + risk 2 patients with AP or heart rate ≥ 70/min or both; and Subgroup B.—Risk 1 patients with heart rate < 70/min + risk 2 patients without AP and with heart rate < 70 beats per minute.
This excludes 27 dextrothyroxine (DT4) and 74 placebo patients with frequent ectopic ventricular beats at entry.[1]
†SED indicates standard error of difference.

Table 7.—Percent Deaths at Specified Analysis Dates for Two Subgroups*

Analysis	DT4 No. of Men	DT4 No. of Deaths	DT4 % Deaths	Placebo No. of Men	Placebo No. of Deaths	Placebo % Deaths	DT4 — Placebo SED†	% Difference: DT4 — Placebo Placebo
Subgroup A								
10/1/70	241	55	22.8	604	78	12.9	3.57	+76.7
8/1/71	241	69	28.6	604	104	17.2	3.71	+66.3
Interval: 10/1/70-8/1/71	186	14	7.5	526	26	4.9	1.32	+53.1
Subgroup B								
10/1/70	842	66	7.8	2,111	183	8.7	−0.73	−10.3
8/1/71	842	91	10.8	2,111	235	11.1	−0.25	−2.7
Interval: 10/1/70-8/1/71	776	25	3.2	1,928	52	2.7	0.74	+18.5

*Excludes 27 dextrothyroxine (DT4) and 74 placebo patients with frequent ectopic ventricular beats at entry.[1] Subgroup A comprises risk 2 patients with AP; subgroup B, risk 1 and 2 patients without AP.
†SED indicates standard error of difference.

group (39.3% for DT4, 20.5% for placebo).

It is also evident from Table 4 that when none of these findings were present at entry, mortality was lower for DT4 than for placebo patients. Thus, for patients with no AP and heart rate less than 70 beats per minute, the DT4 mortality was 46.4% lower than the mortality in the placebo subgroup (4.5% and 8.4% for DT4 and placebo, respectively). Likewise, for patients with no AP, heart rate less than 70 beats per minute, and diastolic blood pressure less than 90 mm Hg, DT4 mortality was 2.2%, or 70.3% lower than the placebo mortality of 7.4%.

The last two sections of Table 4 present data developed by computer analyses which deliberately sought to dichotomize the DT4 patients into two subgroups, with excess risk maximally segregated in one of these. In these analyses, the focus was on three variables—risk, AP, and heart rate. In each case, mortality was higher for DT4 than for placebo patients in one of the subgroups, and lower for DT4 than for placebo patients in the other subgroup. Data on differences between DT4 and placebo mortality

Table 8.—Percentage of Patients with Record of Various Treatment Statuses*

Treatment Status	DT4 No. of Men	DT4 %	Placebo No. of Men	Placebo %	DT4 — Placebo SED†
Prescription of zero capsules‡	872	7.2	2,213	3.7	4.16
Prescription of reduced dosage‡	872	16.3	2,213	9.5	5.35
Reduced adherence to prescription‡	872	4.0	2,213	4.4	0.46
Dropout from study§	939	4.5	2,420	5.9	1.64
Zero or reduced prescription, reduced adherence, dropout§	939	22.5	2,420	17.7	3.17

*As of most recent follow-up visit; dextrothyroxine (DT4) and placebo groups.
†SED, standard error of difference.
‡Includes all patients who completed at least one follow-up visit, except for patients who died, dropped out, or where medication was withdrawn because of recent MI or ACI.
§Includes all patients except those who died.

over time for the two subgroups described in the last section of Table 4 are presented in Fig 2. For the one subgroup, mortality for DT4 patients trended progressively higher over time than mortality for the placebo subgroup, and exceeded the two-standard-error level from 20 months on. In contrast, for the other subgroup, mortality for the DT4 subgroup was consistently less over time than mortality for the placebo subgroup and was at the two-standard-error level from the 4th through the 36th month of follow-up.

This type of apparently disparate subgroup finding, expressed most markedly in the foregoing examples, posed the major problems weighed by the study leadership in arriving at the decision concerning discontinuation of medication for patients receiving dextrothyroxine. The first and key question, because of the Project's concern for minimizing risks of drug toxicity, was the following: Is the apparent marked excess in mortality for certain DT4 subgroups a valid phenomenon, warranting a decision to stop medication for these subgroups? In view of the method for identifying these subgroups, this question was not easy to answer. That is, at the outset of the study, no

Table 9.—Percentage of Patients Ever Taking Reduced Dosage of CDP Medication, by Reason

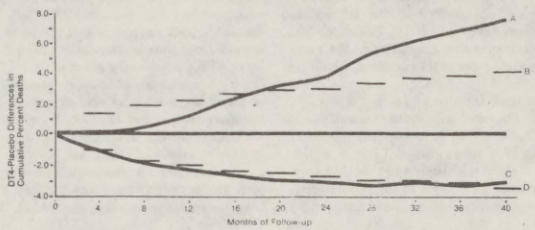
Reason	Percentage of Patients		DT4 — Placebo
	DT4 (1,074 men)*	Placebo (2,687 Men)*	SED†
Hepatic findings	3.4	1.6	3.54
Peptic ulcer	0.7	0.9	−0.45
Gastrointestinal irritation	3.8	3.2	0.95
Diabetes mellitus	0.7	0.2	2.64
AP‡	9.1	3.9	6.46
CHF‡	3.5	2.0	2.74
Arrhythmia	2.8	1.7	2.13
MI‡	8.5	8.1	0.36
Clinical hypermetabolism	1.1	0.2	3.85
Decreased libido	1.9	1.2	1.59
Feminization	0.8	0.5	1.29
Flushing	0.5	0.4	0.24
Itching	0.9	0.6	1.12
Rash	1.4	1.6	−0.46
Other complaints of patients	3.4	1.7	3.27
Other reasons	26.1	21.5	3.01
One or more reasons	42.1	35.4	3.83

*Excludes patients who have not completed any follow-up visits; DT4 indicates dextrothyroxine.
†SED, standard error of difference.
‡AP, angina pectoris; CHF, congestive heart failure; MI, myocardial infarction.

Table 10.—Percentage of Patients Who Ever Complained of Side Effects, by Type

Type of Side Effect	Percentage of Patients		DT4 — Placebo
	DT4 (1,074 Men)*	Placebo (2,687 men)*	SED†
Decrease in appetite	2.0	1.5	1.02
Increase in appetite	3.0	3.1	−0.18
Weight loss	2.2	0.9	3.31
Decrease in muscle strength	3.1	1.7	2.63
Rapid heart beat	4.1	2.5	2.62
Quivering of fingers	2.2	1.0	2.95
Excessive sweating	3.4	1.7	3.27
Sleeplessness	4.1	3.0	1.67
Shortness of breath at night	2.8	1.1	3.71
Other shortness of breath	4.6	2.2	3.93
AP‡	9.8	4.1	6.78
Gastrointestinal problems	14.7	12.9	−1.46
Blurring of vision	1.6	2.9	−2.33
Decreased libido	8.7	9.0	−0.34
Breast tenderness	4.5	3.0	2.21
Flushing	4.3	3.9	0.53
Itching of skin	5.2	5.5	−0.36
Urticaria	1.2	1.3	−0.23
Other types of rash	5.7	5.2	0.58
Frequent urination	2.5	2.0	0.96
Pain when urinating	0.4	1.1	−2.18
Delayed flow of urine	0.6	1.3	−1.98
Ankle swelling	0.9	0.9	0.11
Other problems	26.8	22.9	2.55
One or more problems	56.7	52.8	2.16

*Excludes patients who have not completed any follow-up visits; DT4 indicates dextrothyroxine.
†SED, standard error of difference.
‡AP, angina pectoris.



hypothesis had been formulated concerning possible toxicity of DT4 in certain subgroups identified by base-line characteristics. The subgroups with excess mortality were selected during the course of the Project, in part based on medical judgment from the limited experience of earlier studies, and in part based on computer searches. Under these circumstances, classical tests of statistical significance and usual criteria of significance cannot be properly utilized to assess the possibility that observed differences can arise by chance. This is because the usual tests of significance do not allow for the extra opportunities to achieve normally significant values—eg, two standard errors for testing a difference—afforded by an approach with computer searches (compare the data of Table 4) seeking maximum values of the ratio

$$\frac{\text{DT4 - Placebo}}{\text{Standard Error of Difference.}}$$

In these circumstances, the two-standard-error boundary can be viewed only as an initial guideline for evaluating apparent excess mortality in selected DT4 subgroups.

To cope with this problem, two other approaches were utilized. First, a Monte Carlo simulation technique was used to test the possibility that the excess mortality for selected DT4 subgroups could be a chance phenomenon. The major steps of this analytical method were as follows:

1. A stepwise multiple linear regression technique was used to determine those base-line variables among a total of 48 which maximized the

Fig 2.—DT4-placebo differences in cumulative percent mortality for two subgroups. A. DT4-placebo differences for risk 1 men with heart rate greater than or equal to 70 beats per minute plus risk 2 men with AP or heart rate greater than or equal to 70 beats per minute, or both. B. Two-standard-error values appropriate to line A. C. DT4-placebo differences for risk 1 men with heart rate less than 70 beats per minute plus risk 2 men without AP and with heart rate less than 70 beats per minute. D. Two-standard-error values appropriate to line C. Excludes 27 DT4 and 74 placebo patients with FEVBs at entry.

Table 11.—Percent Change from Base Line in Mean Levels of Specified Variables for Cohorts of Men in Study for at Least One or Two Years*

Variable	DT4		Placebo		DT4 — Placebo
	No. of Men	% Change from Base Line	No. of Men	% Change from Base Line	
Total serum bilirubin					
One year	901	+15.3	2,206	+6.4	+8.9
Two years	639	+17.4	1,519	+9.2	+8.2
Direct serum bilirubin					
One year	897	+12.8	2,198	−2.8	+15.6
Two years	634	+11.0	1,515	−4.7	+15.7
Serum SGOT					
One year	909	+16.4	2,243	+7.7	+8.7
Two years	644	+18.1	1,580	+10.4	+7.7
Serum alkaline phosphatase					
One year	955	+23.1	2,424	+0.7	+22.4
Two years	703	+24.3	1,792	+2.6	+21.7
Plasma fasting glucose					
One year	959	1.1	2,433	1.1	0.0
Two years	707	1.3	1,804	1.5	−0.2
Plasma glucose 1 hr post oral 75 gm load					
One year	957	+5.4	2,420	−2.4	+7.8
Two years	706	+6.1	1,792	−2.2	+8.3
Plasma urea nitrogen					
One year	959	−1.7	2,433	−0.5	−1.2
Two years	707	−1.0	1,802	0.0	−1.0
Serum uric acid					
One year	959	−2.1	2,437	−3.3	1.2
Two years	709	−5.0	1,808	−4.5	−0.5
Hematocrit					
One year	978	0.0	2,482	0.1	−0.1
Two years	790	0.3	2,019	0.1	0.2
Absolute neutrophil count					
One year	972	−6.7	2,472	−3.0	−3.7
Two years	786	−6.4	2,004	−1.9	−4.5
WBC					
One year	977	−4.7	2,481	−2.6	−2.1
Two years	791	−4.5	2,020	−3.3	−1.2
Systolic BP†					
One year	958	0.3	2,431	0.7	−0.4
Two years	760	1.1	1,958	1.6	−0.5
Diastolic BP†					
One year	958	−2.5	2,431	−1.0	−1.5
Two years	759	−2.0	1,957	−0.9	−1.1

*For dextrothyroxine (DT4) and placebo groups.
†BP, blood pressure.

DT4-placebo difference in total mortality. The three variables found to contribute most to this DT4-placebo difference were heart rate, history of AP, and AV conduction defects.

2. Step 1 was repeated substituting a *random* assignment of vital status for the *observed* life-death status for each patient. For each of the two groups, this random assignment of vital status was constrained so that the probability of designating a patient as a "death" was equal to the observed proportion of deaths for his treatment group. The three variables identified in this way as maximizing the DT4-placebo difference were, as expected, different from those identified in step 1, using the *observed* vital status.

3. Step 2 was repeated 20 times, each time with a different set of random numbers for the replication. Again, the three variables which maximize the DT4-placebo difference were identified by means of a stepwise regression process.

Student's t statistics were computed for each of the three variables at the time of entering the equation. The t value relating to the first, second, and third most important variables obtained from the 20 replications are given in Table 5. The corresponding t values for the three most important variables found in step 1, using the observed vital status, are also given in Table 5.

The conclusion from this analysis is that the size of the excess mortality in DT4 subgroups of Table 4 is definitely larger than what would be expected as a result of the computer selection process—as demonstrated by the distribution of t values in Table 5, based on actual vs random assignment of mortality status for DT4 and placebo patients. Therefore, the observed excess mortality for selected DT4 subgroups is very likely a real, not a chance phenomenon.

The second method of approach to this matter was based on the fact that DT4 subgroups with possible excess mortality had been identified by the fall of 1970, as a result of the intensified monitoring effort stimulated by the first apparently adverse finding with this drug in the small group of 27 patients with FEVBs at entry (compare reference 1). The trends were not clear-cut in the fall of 1970, and the problems of statistical assessment were then unresolved. Therefore, the decision was made at that time to continue medication for all

Table 12.—Percentage of Patients With Measurements Ever Outside Specified Limits

Measurement	Dextrothyroxine (DT4) No. of Men	Dextrothyroxine (DT4) %	Placebo No. of Men	Placebo %	DT4 — Placebo SED*
Total serum bilirubin					
≥0.8 mg/dl	1,074	37.2	2,683	30.8	3.81
≥1.7 mg/dl	1,074	2.6	2,683	1.5	2.32
Direct serum bilirubin					
≥0.4 mg/dl	1,074	30.8	2,683	20.5	6.75
≥0.7 mg/dl	1,074	4.3	2,683	2.3	3.27
Serum SGOT					
≥40 Henry units	1,074	40.2	2,683	32.0	4.79
≥70 Henry units	1,074	5.8	2,683	6.2	−0.48
Serum alkaline phosphatase					
≥10 K-A units†	985	46.9	2,510	21.7	14.79
≥16 K-A units	985	4.5	2,510	1.5	5.19
Plasma fasting glucose					
≥110 mg/dl	985	26.8	2,510	26.8	0.01
≥120 mg/dl	985	13.0	2,510	14.3	−1.00
Plasma glucose 1 hr post oral 75 gm load					
≥220 mg/dl	985	27.3	2,510	20.6	4.28
≥240 mg/dl	985	16.5	2,510	21.1	−3.05
Urine glucose positive	1,074	14.3	2,687	8.5	5.37
Plasma urea nitrogen					
≥20 mg/dl	985	24.9	2,510	26.5	−0.98
≥30 mg/dl	985	0.7	2,510	1.3	−1.51
Urine protein					
≥1+	1,074	13.3	2,687	12.2	0.93
≥2+	1,074	4.6	2,687	5.2	−0.82
Serum uric acid					
≥8 mg/dl	985	20.5	2,510	24.0	−2.20
≥10 mg/dl	985	4.2	2,510	4.3	−0.18
Hematocrit					
≤38%	989	2.3	2,521	2.3	0.04
≤36%	989	1.0	2,521	1.0	0.05
Absolute neutrophil count (ANC)					
≤3,500/cu mm	989	51.8	2,521	43.0	4.69
≤1,800/cu mm	989	3.0	2,521	2.3	1.25
WBC					
≤5,000/cu mm	989	22.3	2,521	18.4	2.65
≤3,000/cu mm	989	1.8	2,521	1.6	0.49
ANC/WBC					
≤0.5	989	33.3	2,521	24.5	5.26
≤0.4	989	6.6	2,521	4.0	3.22
Systolic BP‡					
≥160 mm Hg	1,074	26.7	2,687	29.2	−1.53
≥180 mm Hg	1,074	7.8	2,687	8.9	−1.06
Diastolic BP‡					
≥ 90 mm Hg	1,074	56.0	2,687	62.4	−3.66
≥100 mm Hg	1,074	8.2	2,687	7.9	0.31

*SED, standard error of difference.
†King-Armstrong.
‡BP, blood pressure.

DT4 subgroups. Once these subgroups had been selected, it became possible, prospectively, to test the hypothesis that any apparent suggestive excess mortality as of the fall of 1970 was a chance phenomenon, and, therefore, would not persist. The subgroup A portion of Table 6 presents data bearing on this hypothesis for one of the subgroups of DT4 patients in the last section of Table 4 and in Fig 2. These data show that the trend to excess mortality for the DT4 subgroup was a persistent one; ie, it gave no evidence of diminishing—let alone reversing itself—during the interval following initial computer identification of this subgroup (from Oct 1, 1970, to Aug 1, 1971). Detailed multivariate analyses further revealed that this interval trend was not due to any tendency for the surviving DT4 men of this subgroup to be generally at higher risk than their placebo counterparts because of differences in base-line characteristics. In fact, there was a slight tendency in the opposite direction, so that adjustment by multiple linear regression with the use of 33 base-line variables yielded interval mortality figures of 5.6% (instead of 5.4%) and 3.7% (instead of 3.8%) for the DT4 and placebo subgroups, respectively, ie, an adjusted relative difference of 51.4% (instead of 42.1%). Other subgroups identified in the fall of 1970 as showing excess mortality with DT4 have manifested similar interval trends (compare Table 7, subgroup A, for example). These findings were consistent with the conclusions of the simulation analyses as of Aug 1, 1971 (Table 5), ie, excess mortality in selected DT4 subgroups was probably not a chance phenomenon, but rather was probably due to the drug. The evidence was, therefore, clear-cut on the need to discontinue DT4 in patients of this type.

The second problem remained: What about the complements of the subgroups selected because of higher mortality for DT4 than for placebo patients? For the subgroup of 460 dextrothyroxine patients characterized at base line as risk 1 with heart rate less than 70 beats per minute, or as risk 2 without AP and with heart rate less than 70 beats per minute, mortality experience appeared to be trending favorably compared to the corresponding placebo subgroup (compare Fig 2 and the last section of Table 4). However, once again absence of hypotheses formulated at the onset of the study as to subgroup effects, and other considerations as well (compare reference 1), rendered conventional statistical evaluation impossible. Again, therefore, evaluation was made of the mortality trend after selection of this subgroup, ie, from Oct 1, 1970, to Aug 1, 1971 (Table 6, subgroup B). As indicated in the last line of subgroup B, Table 6, no favorable trend for the DT4 as compared with the placebo subgroup was apparent for this time period. In fact, with adjustment by multiple linear regression (33 variables) to account for minor disparities in comparability of these two subgroups, the adjusted percent of deaths became 2.7% and 2.4% for the DT4 and placebo subgroups, respectively, for this time interval, ie, the proportion of decedents was estimated to be 12.5% higher for the DT4 than for the placebo subgroup. Other subgroups identified in the fall of 1970 as showing a seemingly favorable mortality experience for DT4 yielded adverse rather than

Table 13.—Mean Serum Fasting Cholesterol and Triglyceride Levels at Base Line (BL) and Yearly Intervals for Cohorts of Men in the Study*

Cohort	Years of Follow-up	DT4 No. of Men	DT4 Mean Level, mg/dl	DT4 % Change From BL	Placebo No. of Men	Placebo Mean Level, mg/dl	Placebo % Change From BL
Serum Cholesterol							
At least one year of follow-up	BL	927	249.8		2,363	249.2	
	1		225.5	−9.7		254.0	+1.9
At least two years of follow-up	BL	662	248.6		1,699	250.1	
	1		224.0	−9.9		254.7	+1.8
	2		223.9	−9.9		255.7	+2.2
At least three years of follow-up	BL	309	252.5		795	250.2	
	1		225.1	−10.9		254.5	+1.7
	2		226.0	−10.4		255.5	+2.1
	3		227.3	−10.0		255.0	+1.9
Serum Triglyceride							
At least one year of follow-up	BL	969	5.74		2,453	6.16	
	1		5.05	−12.1		6.30	+2.1
At least two years of follow-up	BL	716	5.65		1,819	6.13	
	1		4.96	−12.2		6.25	+1.9
	2		4.79	−15.2		6.34	+3.5
At least three years of follow-up	BL	346	5.87		878	6.10	
	1		5.11	−12.9		6.42	+5.2
	2		4.84	−17.5		6.41	+5.1
	3		4.93	−16.0		6.26	+2.7

*For at least one, two and three years, dextrothyroxine (DT4) and placebo groups.

favorable trends for the interval from Oct 1, 1970, to Aug 1, 1971 (compare Tabie 7, subgroup B, for example).

On the basis of all these data, it was decided to discontinue medication for all DT4 patients, for the following reasons:

1. Overall mortality in the entire DT4 group appeared worse than mortality in the placebo group.

2. It was not possible to identify unequivocally a subgroup of patients not subject to excess mortality risk with DT4 treatment, ie, there was no definitive evidence that all patients subject to excess mortality risk with DT4 have been removed from subgroups with apparently favorable mortality trends.

3. The trend for DT4 patients for the interval Oct 1, 1970, to Aug 1, 1971, was unfavorable for all patients, including DT4 subgroups in which the initial mortality trend appeared to be favorable. While the possibility of making a statistically valid assessment of DT4 efficacy for such a subgroup remained subsequent to its identification as of Oct 1, 1970, the discouraging interval trend militates against this possibility. Also, the anticipated numbers of new events in such a DT4 subgroup and its placebo counterpart for the remainder of the study were considered to be too small to give a reasonable prospect of detecting a positive effect. Moreover, should this aspect of the Project continue, it was recognized that it would be necessary for reasons of safety to discontinue DT4 for individual patients who developed AP, MI, CHF, ACI, or tachycardia, ie, those who evolved into the higher-risk category. This resultant progressive dilution of the already small number of men in such a DT4 subgroup would compound the problems of assessing therapeutic efficacy.

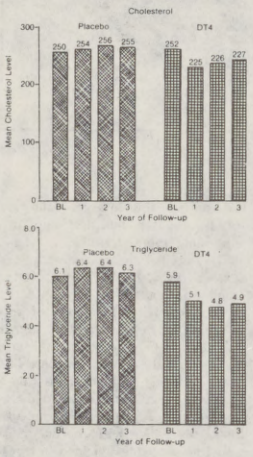


Fig 3.—Mean levels of serum cholesterol (in milligrams per deciliter) and serum triglycerides (in milliequivalents per liter) at base line (BL) and annual intervals for cohort of men observed for at least three years with no missing determinations. (For cholesterol, DT4—309 men, placebo—795 men; for triglycerides, DT4—364 men, placebo—878 men.)

In view of these difficulties, the decision was made to discontinue medication for all patients receiving dextrothyroxine. In so doing, the study leadership recognized that the findings of the CDP left open the possibility that dextrothyroxine may be efficacious for a limited group of carefully selected MI patients and for persons free of clinical CHD. Other trials would be necessary to assess these possibilities.

Side Effects and Toxic Effects.—In terms of patient complaints of side

effects and physician detection of possible toxic manifestations, DT4 was generally well tolerated in the dosage utilized by the CDP. This was reflected by the low rate of dropout and reduced drug adherence in the DT4 group (Table 8). However, the percent of patients for whom CDP physicians prescribed reduced dosage or discontinuation of medication was higher for the DT4 than for the placebo group (Table 8). The reasons for changes in prescription were multiple. For a number of specific causes, the percentages of patients taking a reduced dosage were significantly higher for the DT4 than for the placebo group—notably for AP, also for CHF, arrhythmia, clinical evidence of hypermetabolism, hepatic signs, and diabetes mellitus (Table 9). Correspondingly, percentages of patients who ever complained of various side effects were significantly higher for several items in the DT4 group than in the placebo group (Table 10).

In addition to clinical evidence of side effects and toxic effects, laboratory data revealed that DT4 produced marked changes in several biochemical and hematologic variables, including sustained increases in total and direct serum bilirubin level, serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase level, plasma glucose level one hour after oral administration of a 75-gm load, and glycosuria; and decreases in absolute neutrophil and total white blood cell count (WBC) (Table 11). In some patients, changes in these variables were to levels generally regarded as outside normal limits (Table 12). However, in most cases no associated clinical abnormalities were noted. Hence, the significance of these shifts in biochemical-hematologic values in dextrothyroxine-treated patients remains unknown.

Effects on Serum Lipids.—Dextrothyroxine in the dosage employed induced a sustained significant fall in serum lipid levels (Table 13 and Fig 3). The net effect for all active patients, irrespective of prescription and adherence, was a fall of about 12% in serum cholesterol level, and 15% to 20% in fasting serum triglyceride level (the observed fall corrected for the concomitant rise for the placebo group). A similar net reduction of serum cholesterol occurred for patients with hypercholesterolemia with or without concomitant hypertriglyceridemia. No tendency was noted to so-called escape or attenuation of the lipid-lowering effect over time.

Comment

The Coronary Drug Project previously reported that as of Feb 1, 1970, with an average of 18 months of follow-up, it had recorded evidence suggesting an excess risk of mortality with its dextrothyroxine regimen (6.0 mg/day) for a small subgroup of 27 post-MI patients with FEVBs in the resting ECG at entry.[1] For this reason, DT4 medication was discontinued in 1970 as a precautionary measure for the survivors of this subgroup.

Thereafter, the CDP took particular care to accomplish especially detailed monitoring of the clinical course of the approximately 1,000 men who were still taking this medication, in accordance with its continuing determination and concern to minimize any possibility of subjecting study patients to potential harm.

As of Aug 1, 1971, with an average of 36 months of follow-up, the Coronary Drug Project registered an 18.4% higher proportion of deaths for the group of patients still taking DT4 compared with the placebo group (the absolute percentages were 14.8% and 12.5% for the DT4 and placebo groups, respectively). As expected in men who have recovered from one or more previous MIs, more than 90% of deaths in both groups were due to cardiovascular causes; the great majority were recurrent episodes of CHD, often sudden death. The percentages of patients dying from coronary disease and from all cardiovascular causes, and the percentage experiencing nonfatal recurrent MI were all higher for the DT4 than for the placebo group. Evaluation by the life-table method further showed that, over time, the rate of mortality from all causes for the DT4 group became progressively greater than the rate for the placebo group. Detailed analyses indicated that the higher percentages of nonfatal and fatal events in the DT4 group could not be ascribed to greater proneness at entry of this group to recurrent cardiovascular disease, compared to the placebo group, since the randomization procedure had, as expected, rendered the two groups highly comparable. While the differences in morbidity and mortality were not statistically significant, they were, nonetheless, cause for serious concern.

This concern was enhanced by additional data showing that the percent mortality was markedly higher for certain subgroups taking the DT4 medication compared to corresponding placebo subgroups—eg, those at entry with a history of a single, complicated MI or two or more MIs; with a history of AP; with a resting heart rate of 70 or more beats per minute; with elevated blood pressure; with electrocardiographic conduction defects; and particularly those with combinations of these findings. These recorded overall excesses in percent of deaths in DT4 subgroups were, on further analysis, shown to persist over time. They could not, in all likelihood, be attributed to chance variation or to the methods used to select these subgroups after the study was under way. Moreover, they were in accord with suggestive findings from earlier small studies on the types of patients apparently prone to experience complications, especially with higher doses of dextrothyroxine sodium (8.0 or more milligrams per day).[2]

Detailed analyses of the mortality trends also revealed early trends toward a favorable outcome for DT4 patients in the complements of the subgroups described in the previous paragraphs. However, these analyses also demonstrated that these apparently favorable trends did not persist over time. These findings support—although they cannot unequivocally prove—the hypothesis that the early trends were probably artifactual, ie, a resultant of the process of selecting these subgroups after the study was in progress.

In view of these findings, it was concluded that the wisest and safest course was to discontinue DT4 not only for the subgroups identified as experiencing a marked excess in mortality, but for the entire group taking this medication.

With the 6.0-mg dosage of dextrothyroxine sodium, there was a low, but statistically significant, incidence of complaints by patients and find-

ings indicative of side effects and toxic effects of the drug. Consistent with earlier small studies,[6] these included AP, CHF, arrhythmia, as well as clinical hypermetabolism, diabetes mellitus, and possible abnormalities of hepatic function. In addition, extensive biochemical monitoring by the CDP yielded unique data demonstrating that dextrothyroxine tended to decrease glucose tolerance, induce glycosuria, increase serum bilirubin level, SGOT, and alkaline phosphatase level, and reduce WBC and absolute neutrophil counts. In a significant proportion of patients, these shifts were to levels generally regarded as outside normal limits. The long-term significance of these findings is unclear, particularly since they were rarely associated with patient complaints, clinical signs, or frank illness.

As anticipated in the original design of the study, DT4 successfully reduced serum lipid content. Nevertheless, no clear-cut evidence was recorded of any sustained positive effect on CHD. Several explanations for this phenomenon may be hypothesized. First, it is possible that serum cholesterol is no longer related to risk of CHD after one or more MIs, in contrast to its significant association with first events of atherosclerotic coronary disease. Data have been published from Toronto and New York in support of this hypothesis.[7,8] If this is valid, then reduction of serum cholesterol in patients after recovery from MI would presumably come too late to be of any benefit. While this explanation may be valid, it must be noted that one other study yielded data supporting a contrary conclusion.[9] Moreover, the massive data of the CDP for its 2,789 patients in the placebo group also point to a different conclusion from the negative findings of the Toronto and New York studies[7,8] (a further report by the CDP with additional data supporting our previous conclusions is now in preparation). With simultaneous control of as many as 39 other variables possibly related to post-MI prognosis, repeated analyses of the CDP placebo group experience show that serum cholesterol level at entry is related to risk of sudden death, all CHD death, and death from all causes. Therefore, it remains reasonable to hypothesize that sustained reduction of serum cholesterol level by safe means may have a beneficial effect on long-term prognosis for post-MI patients.

An alternative explanation of the CDP findings for morbidity and mortality with DT4 relates to the matter of adverse effects. As is well known, thyroid hormones and their dextrorotatory analogues have multiple effects in addition to their influence on serum lipids. These include calorigenic effects, due in part possibly to inability to render DT4 totally free of the naturally active levothyroxine sodium. Assays of several samples of the DT4 dispensed by the CDP indicate that they contain less than 0.5% levothyroxine, ie, the daily 6.0-mg dextrothyroxine dosage is contaminated by less than 30μg of levo hormone. Whatever the contribution of the levo and dextro components, the CDP data indicate that the dispensed DT4 may exert calorigenic and other systemic effects, and these may be significant in regard to aggravation of AP in post-MI patients with this complaint, and in regard to precipitation of de novo AP, CHF, arrhythmia, MI, and death in post-MI patients.

Experimental data accumulated over decades on animals given thyroid hormones—with and without concomitant feeding of cholesterol and fat—are consistent with the foregoing concepts that the net effect of DT4 may be the resultant of a complex interplay of multiple metabolic influences, positive and negative. These include the potential for protection against atherogenesis through lipid-lowering effects, and the potential for injury from tendencies to produce sclerotic changes in arteries, and myocardial lesions.[10-12] The data of the CDP indicate that the risk of complications may be especially serious for post-MI patients manifesting more marked impairment of myocardial function, ie, those with a history of a complicated heart attack, two or more MIs, AP, tachycardia at rest, and conduction defects.

Viewed from this perspective, the equivocal CDP results with dextrothyroxine in patients with less marked impairment of myocardial function indicate the need for further trials of this drug. The CDP findings do not foreclose the possibility that a net beneficial therapeutic outcome may be realized with this drug in properly selected patients, most particularly hyperlipidemic persons without clinical CHD, and possibly those CHD patients without evidence of impaired myocardial function.

Summary

The Coronary Drug Project (CDP) is a national collaborative study to evaluate long-term effects of several drug regimens influencing lipid metabolism, compared with placebo, in men aged 30 to 64 years who had recovered from one or more myocardial infarctions (MIs). From 1966 to 1969 the 53 CDP clinical centers recruited 8,341 patients who were randomly assigned to the Project's six groups.

As previously reported, the 5.0-mg/day estrogen regimen was discontinued in 1970 chiefly because of an excess number of nonfatal cardiovascular events in this group compared to placebo.[1] A small subgroup of 27 patients receiving dextrothyroxine—those with frequent ectopic beats of ventricular origin on the resting electrocardiogram taken at base line—was noted at that time to have experienced a somewhat higher mortality than 78 similar men receiving placebo. Therefore, dextrothyroxine medication was stopped as a precautionary measure for the survivors of this subgroup.

By the fall of 1971, with an average follow-up of 36 months, the accumulated data systematically reviewed quarterly by the CDP Data and Safety Monitoring Committee—showed that the proportion of deceased in the remaining 1,083 patients receiving dextrothyroxine was 14.8%, compared with 12.5% for the corresponding 2,715 patients receiving placebo, ie, an 18.4% higher proportion of deaths for the dextrothyroxine than for the placebo group. The absolute difference in mortality rate between these two groups increased progressively with duration of medication. The dextrothyroxine group, in addition to having a higher proportion deceased from coronary and all cardiovascular causes than the placebo group, also had a higher proportion of patients experiencing recurrent nonfatal MI.

Excess mortality was concentrated in dextrothyroxine subgroups with a

history at entry of one complicated MI, two or more MIs, angina pectoris; with more rapid heart rates; with higher diastolic blood pressures; with ECG conduction defects; and particularly in dextrothyroxine subgroups with combinations of these traits.

No significant sustained reduction in mortality was recorded for dextrothyroxine subgroups without these traits, compared to corresponding placebo subgroups.

Based on these findings, the decision was made to discontinue dextrothyroxine medication for all patients.

This decision is in conformity with the determination and concern of the Coronary Drug Project to minimize possibilities of subjecting study patients to potential harm.

All data from the study for the remaining treatment groups—estrogen (2.5 mg/day), clofibrate (1.8 gm/day), and nicotinic acid (3.0 gm/day)—are continuing to be reviewed systematically at regular intervals for both possible adverse trends as well as beneficial effects.

Nonproprietary and Trade Names of Drug

Dextrothyroxine sodium—*Choloxin*

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Senator KENNEDY. Dr. Gillespie.

Dr. GILLESPIE. I basically stand behind what I said at the hearings the last time.

Dr. Van Houweling has supplied a memo for the record which indicates that Dr. Kowalk was not present at the meeting which I attended. But he also stated that the reason that we were told not to discuss our residue requirements was, it was a meeting with university people rather than with the drug sponsor.

At the time of the meeting we were not aware that those were university people rather than drug sponsors.

In fact, in our opinion, the drug was being sponsored by Cornell University. It was sometime later that we learned a specific drug manufacturer was involved in sponsoring the compound we called Cornell mastitis formula.

Senator KENNEDY. Dr. Kowalk.

Dr. KOWALK. I stand by the testimony I made at the last hearing.

Dr. Van Houweling has replied that in my referring to committees, that he has never appointed any committees. He said that the Commissioner appointed them. And I submit that the Commissioner does not exist in a vacuum. That if he appointed a committee, somebody had to ask that these appointments be made or they were appointed because there was a difference in viewpoint that had to be ironed out. Since the difference in point of view was always originating from the Bureau of Veterinary Medicine and Dr. Van Houweling's group, I would assume the responsibility for the birth of the committee lays with the Bureau of Veterinary Medicine.

I feel at this time, because of the Secretary's statement, that he is going to ask the investigating committee to come down to the working level to inquire upon the points of testimony that have been raised that are of primary importance. I think in our particular area, I have not been very thorough or detailed, and the investigators may ignore certain vital areas. We have only touched the surface. Thus I would like to add a little to the testimony that I made at that time.

As you know, as soon as you appear on a committee or appear at a hearing, you are labeled a bell ringer, "whistle blower," or I do not know what else. As far as any future in the agency, I think that most of us here are really laying our professional lives on the line because it seems as though supervisors are afraid to have someone working for them who might go running off to Congress at the slightest hint of difficulty.

It is unfortunate that we have had to be put into this position.

We have not wanted to be put into the position of criticizing anyone.

We have always had good working relations with the people in our Bureau. We think very highly of all of them.

But in order to see justice done and because of difficulties we have had with the Bureau of Veterinary Medicine, and Dr. Van Houweling, somebody has to speak up.

Senator KENNEDY. The record is very clear, Dr. Kowalk, that you were subpenaed to speak up.

Everyone in here was.

Dr. KOWALK. Right.

However, we do not want to really be sources of information that will embarrass our agency and make anyone look bad and our futures are at stake when we do so.

Senator KENNEDY. Of course, quite clearly that should not be the case.

I think realistically it is.

We cannot be naive about it. That obviously should not be the relationship between the Congress and the agency.

I think it has been in the past. I am obviously strongly opposed to that. As far as I am concerned, with any person that comes through with the advice and consent of the Senate in the future, we are going to try to insure and insist that that person allow professionals to speak up.

We feel strongly about it.

I believe that it's the feeling and sense of Republican and Democratic members of this committee, alike.

I think no professional employee, people who have competency and dedication, the 34 people that we have here this morning, ought to have that sense or feeling about any agency.

You are working really for the interests of the American public. That is what we are working for, as well. The kind of atmosphere which you and others describe, quite frankly is intolerable in our system, and it is intolerable with any agency of the Government.

Having said that, I want to be realistic and to understand that that openness does exist. We are committed to attempting to remedy that situation. We can do it best with your help.

Dr. KOWALK. I thank you, Senator Kennedy.

I think I will say that my supervisors have been very patient, and I would like to say at this time that three of us have received promotions and they have not seen fit to hold it against us.

However, I think that even unconsciously such men cannot avoid feeling that way.

With this as a preface I would like to say the following: Ever since the beginning of Dr. Van Houweling's administration in the Bureau of Veterinary Medicine, we in the Bureau of Foods have been subjected to harassment and pressure to change our reviews.

This pressure was brought to bear in many ways by the Bureau of Veterinary Medicine: By personally isolating some of us and by sheer numbers and mental intimidation, cause us to change our reviews. By encouraging and rewarding those in this organization apparently who would take part in its harassment, and doing, I presume, the reverse with subordinates who would not cooperate in that area. At least I make this assumption from the way the procedures seem to be going in the Bureau of Veterinary Medicine.

Also, by going over our heads, first to our immediate supervisor, then to the Division Director, the Associate Bureau Director, and then, finally, to the Bureau Director, and also by use of committees, as I have stated, they have continually tried to force us and intimidate us into changing our reviews.

This always was done under the guise of fulfilling their administrative mandate although Dr. Van Houweling states in his response that

the Bureau of Foods always prevails in its opinion. This may be so but it is not because they defer to us.

This has usually been to get us to relent, to be more liberal in our reviews, and thus allow drugs and/or feed substances on the market without proper residue or toxicology data.

If we had not had the steadfast support of some of our leaders in the Bureau of Foods, many of these substances would not be on the market and current attempts to take certain of them off the market would not now be in progress.

Finally, because he could not control our reviews, he attempted to have our function transferred to his Bureau. We had to defend ourselves from being summarily transferred to the Bureau of Veterinary Medicine on more than one occasion.

Again, this was resisted by our supervisors. They told us they had to come up with a good reason why they should not go along with a transfer. We gave them the reasons and again we prevailed. But not because of any deference on BVM's part.

Also, I might say there was a letter from Senator Magnuson to inquire about this effort to get our review function transferred to the Bureau of Veterinary Medicine. The Commissioner in his official reply to the Senator said that this was not being considered. I think he changed his mind.

It is something we will be eternally grateful for, and I think the consumers of the United States should be grateful to the Senator for his letter.

Senator KENNEDY. Let me ask you this: Is this the current situation or is this the situation that was?

Dr. KOWALK. This has been a chronic situation.

It occurred continually. There was always discontent, and there was always arguing between the Bureaus, and I still say that Dr. Van Houweling's disagreements came from those below him, because he encourages and rewards those who perform this service for him.

Senator KENNEDY. Is it continuing now? Let the record show that Dr. Gillespie nodded affirmatively.

Dr. KOWALK. There has been, and is now, set up another part of our agency specifically to handle veterinary drugs.

The Bureau of Foods has handled in the past pesticides, food additives, colors, and cosmetics, and has never had any problems.

But in this particular area, we have had to have special treatment, a special organization to deal with the problem of veterinary medicine, to handle and satisfy their administrative responsibility.

The Bureau of Foods at the time we came here had some of the most renowned toxicologists in the country aiding us in making our decisions.

These were not enough to satisfy Dr. Van Houweling.

[Information supplied for the record follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

November 10, 1976

Honorable Edward M. Kennedy
Chairman, Subcommittee of Health
and Administrative Practices
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

As per your request on July 20, 1976 the following are suggestions I have as to how FDA might function more efficiently and speaks to the problem areas we are familiar with.

The science of toxicology as it relates to predicting human safety through the use of animal bio-assays and experimentation is relatively new. This science has developed largely within FDA while carrying out its mandate under the law. Although scientists have for many years used animals in simple acute experiments, the modern concept of long-term testing and safety factors to establish human safety is more recent.

Each time this function has been split, regulatory science has suffered, for instance: initially much of the scientific research capabilities within FDA existed entirely within the Bureau of Science in which the expertise of both Bureau of Drugs, the Bureau of Foods, as well as the Bureau of Veterinary Medicine was concentrated in one area with great effectiveness. Then there was a split of function, each scientific discipline going to different Bureaus. We used to have pesticide research and petition review within the same Agency, now it is split and gone over to EPA, the resource of expertise, experience and knowledge is split also. Thus, each branch takes its portion of the total function and they never do again function as a whole, i.e., with the previous interaction and cross fertilization of ideas necessary to essential development and integrity. Each supervisor has his own priorities and ideas and all go in different directions. The units function as though each of the others did not exist.

There is still a large reservoir of this resource remaining within the Bureau of Foods. It is my opinion that this should be kept intact and developed. There should be an attempt to bring the pieces together to allow a gathering of resources and the consequent strength and cohesion that would follow.

In addition a great deal of the problems inherent in the present configuration of the Agency itself is the simple isolation of various units within the Agency relegated to different parts of the D.C. area and its environs. We even have a great part of our research plant located in Jefferson, Arkansas. The regulatory scientist, or the petition review function of the Bureau of Foods is, at the moment, being forced to consider a move to another building in Washington because of the lack of space.

This will further isolate these people and prevent their interaction with research personnel and the combined effort I have been speaking of as necessary to good science in decision making.

The splitting has reduced the effectiveness of all branches of the science as well as petition review.

There is also another area of conflict within the Agency that has to do with too much cohesiveness between the higher administration functions at the head of the Agency (Commissioner's office, etc.) and the scientific regulatory portion. Here the Agency would benefit from a clear seperation of responsibility. After bringing together and strengthening the scientific regulatory function, I would separate the influence of the policy function from the scientific and place each in separate spheres as much as possible to avoid the tendency that now exists within each Bureau to come out with scientific decisions that seek to avoid embarrasment to the Commissioner or to support policy and/or political decisions instead of the best scientific judgment possible. The need to negotiate our position and come up with compromise cannot be good science. The individual petition reviewer and his immediate superiors within the scientific community should be insulated from such influence. Their only constraints should be limited to that defined by the law and the realities and limitations inherent in the state of the art in the branch of science to which they are dedicated.

The regulatory scientist should give the best he can in the way of judgment to the administrator and the latter should then use their recommendations and make his judgment independently without influencing the science as emanating from the scientific branch. Each should be responsible within his own sphere to his own calling. To ask the scientist to adapt to administrative realities can only produce less than reliable science. To ask the administrator at the Commissioner's level or even the Bureau heads to carry both hats is stretching the credibility of the whole.

My recommendation is that if there is to be a split, there should be a clear separation of policy making management and science. Those at the Commissioner's and management level have the right to accept or reject what they wish in the way of scientific recommendation, but not to try to create a climate within which scientific judgment is required to adjust to the whims of management.

To implement such a desirable state of affairs I see the creation of a scientific community on par in the area of authority with that of the Commissioner who would then have the responsibility to implement, as he sees fit the best recommendations his scientists could give him. His responsibility and his options would then be clear and not muddled by the opinions of individuals within his own Agency telling him what they think he wants to hear. The scientists, on the other hand, would be free of the need to react to the pressures of loyalty or the need to preserve their professional status by succuming to such pressures.

As things were, although conditions have improved considerably, one never knew what the Commissioner knew or didn't know. Review scientists may be asked their views off the record, or they may be asked to negotiate their position so as not to embarrass the Agency, the Commissioner or someone else down the line of command.

This, in my opinion, is wrong. Yet it may occur and undoubtedly does occur in spite of the best attempts of our superiors to give us this freedom when we are dealing in areas that are sensitive and controversial. The Commissioner should be told the facts, all of them. This should be a part of the record. When he makes a decision he is then accountable as are each of the units down to the individual scientist. But each would be free to make the best decision he knows how. This type of unfettered science would be a boon to the toxicologists, their superiors and other scientific disciplines within the Agency.

The next step, of course, would be to people this scientifically independent Agency with men and women who are true scientists, whose mandate is to search for the truth, not prove any particular group (consumer or industry) right or wrong. The most important men here are the Agency heads. If they are true scientists they will encourage and develop the same type of attitude in their subordinates all the way down the line. These men should be chosen carefully.

This separation of responsibilities would act as a check and balance system to counter the tendency that now exists to foster the team approach across responsibilities from administrative down through the review scientific area and resultant attempts to make the facts fit the policy. To attain the independence necessary might require a complete separation. This separation would however, in my judgment, be the most logical and fruitful of all the approaches rendered thus far.

Another source of conflict has been the division of responsibility between the Bureau of Veterinary Medicine and the Bureau of Foods

The Bureau of Veterinary Medicine is a new Bureau and trying to develop expertise of its own in the area of animal safety. It would seen inefficient and wasteful and even confusing to have the function of human safety started anew within the Bureau of Veteriancy Medicine. All the lessons are lost; effort is wasted in false starts while the new agency attempts to arrive at truths in a science that have already been realized in the Bureau of Foods. The conflict caused by fighting over opposing views while the new starters learn the ropes can be especially wasteful and destructive.

The latter has been the cause of much of the frinction in the interaction between the two Bureaus (BVM-BF).

The emphasis it seems to me is in the wrong area. The Bureau of Veterinary Medicine has primary responsibility for animal health, the Bureau of Foods has primary responsibility in the area of human safety.

When a drug, feed additive or other chemical is used in food producing animals it contaminates the meat and by-products and becomes a part of the food.

Because of the present administrative set-up, a Bureau whose primary responsibility lies in the area of animal safety, administers and attempts to make decisions relative to human safety. This is resulting in disagreement and delay. The farmer and consumer suffer accordingly.

It would seem more logical to separate the administrative function in the area of human safety in foods from BVM and place it within the Bureau of Foods. This would then allow BVM to continue to operate within its area of animal safety and therapeutics. This separation would eliminate the conflict and allow the Bureau of Foods to function in the area in which it is most competent scientifically.

Sincerely yours,

A. J. Kowalk, D.V.M.
Division of Toxicology
Bureau of Foods

AJKowalk:dps 11/10/76

Senator KENNEDY. We are going to have to move along.

Dr. Scarr.

Dr. SCARR. Senator, I stand behind my original testimony.

I would change nothing.

I have no prepared statement.

I will be brief.

There are two areas that we could improve the administrative processes in BVM. One is almost a routine procedure. When high-level meetings are held, especially with industry, the veterinary reviewer who handled the material is not present, and often, because of lack of information or some other reason, conclusions are reached many times that are not supported by the facts.

One other item. It took quite a while to establish the policy that approval of a supplemental application reaffirms the entire NADA. It was only recently that we were getting some enforcement in this area.

Within the last couple of months General Counsel has decided to permit an exception in those cases where a supplement provides for an alternate manufacturer or an alternate site of manufacture.

This concerns me.

We have already had two supplemental NADA's approved for alternate sites of manufacture while outstanding problems exist. This procedure was alluded to earlier in the testimony of others, that is, when deficiencies become known to us due to new carcinogenicity or other data, we have an opportunity to review and correct the problem when the supplement is submitted and the entire application is reaffirmed.

I can see an erosion of the progress we have made up to now.

That concludes my remarks.

Senator KENNEDY. Dr. Cortell and then I will go back to Dr. Meyers.

Dr. CORTELL. I'm at a little bit of a loss, Senator Kennedy, for exactly where I fit into this sequence that you have gone through today.

I assume that I was asked to come to talk about the specific drugs that I testified about at the last hearing.

Senator KENNEDY. Slow-K.

Dr. CORTELL. Slow-K.

Senator KENNEDY. Has the box warning been added to the labeling yet?

Dr. CORTELL. No.

I gathered that was the point.

I really am at a loss to know why. I think that one of the reasons has to do with administrative procedures.

I support in great measure Dr. Dunham's comments about disintegration of the Division of Cardio-Renal Drugs.

I functioned as a consultant to this Division, I guess, for the past almost 5 years now and have seen it deteriorate greatly, to the point where I as an irregular consultant have assigned to me more drugs than the full-time reviewing officers have in the agency, as a medical officer.

With specific reference to Slow-K, and the box warning, the Director of the Bureau of Drugs recommended, as you know, a box warning in limitation of the indications of this drug to the Cardio-Renal Advisory Committee back in March, I believe.

To my knowledge Cardio-Renal Advisory Committee recommended that and nothing has come about as far as I can see from the agency since.

Senator KENNEDY. This is involving a drug that there were serious reservations about within your Department?

Dr. CORTELL. Right.

Senator KENNEDY. The drug was eventually approved and side-effects have shown up. Just about everyone has recommended the box warning, and still the box warning has not come out?

Dr. CORTELL. Exactly.

Senator KENNEDY. Dr. Meyers, you are a new witness here.

I think you gather the sense of our Panel's comments.

We are interested in what suggestions you might have in terms of the future improvement of the agency.

Dr. MEYERS. I was not prepared for recommendations.

Senator KENNEDY. Do you have any comment you would like to make?

Do you have any comments or suggestions?

Dr. MEYERS. On procedure?

Senator KENNEDY. Yes.

Dr. MEYERS. I think they have all been made.

I would concur with just about every one that has been made to eliminate as much as possible industry pressure, extraordinary industry pressure.

I appreciate the fact that industry has a big financial stake, and I would like to see products approved to increase sales, increase profits, which I think is all justifiable, but I believe that there is, in many cases, undue pressure.

Senator KENNEDY. All right.

We will welcome the written comments that any of you would like to make and urge you to make them.

Mrs. Dacosta?

Mrs. DACOSTA. I would like to say that I am no longer with the agency, as you probably know. I can also say that the reasons or the fact that I have not submitted data to either Dr. Schmidt at his request or yourself is not because I have been unwilling to submit this data.

As you probably know, I have a rough draft of a partial reply to Dr. Schmidt, which I was simply unable to complete because I had no cooperation from the typing staff there.

This document consisted of a rough draft of about 10 pages or so, with about 9 items for reference and documentation of the material I had written.

It took me exactly 2 months with continual requests from the Secretary to even get a rough draft back, which is inaccurate.

I started replying to each one of Dr. Schmidt's requests in order and trying to document them.

I made attempts to retrieve the documents from the files with no assistance, and quite frankly I just gave it up as a futile attempt for anything. It just seemed impossible.

I felt that in view of the fact that I was not getting the cooperation, it seemed an impossible task. It should not have been an impossible task. I made a decision that the work on my desk was more important.

So, I pursued that since I was the only person at that time that was conducting a certain number of duties and was familiar with the job on my desk.

So had I given the time to override the harassment and pure stumbling blocks that were put in my way, my work on my desk would have just laid idle because there was no one else to do it. So I elected to proceed to keep up with the work on my desk.

There have been some, I might add, there have been some comments in regard to repeatedly that there has not been cooperation from the personnel in the FDA and the administrators did not carry out their indication that they would supply us with secretarial staff and so forth.

This has been repeated. I can confirm it. I will not take the committee's time now, but I do have certain points that I would like to, either in writing, that I can supply later—they are very definite points that the Commissioner is in error in interpreting the Congressional Record.

I pointed out these things in some of the things I have written.

Senator KENNEDY. We would welcome those written comments.[1]

Mrs. DACOSTA. I will get them to you.

I would like to point out that since my leaving the FDA, at the time I left, the morale was at the lowest that I ever encountered in Government experience, and I had been working in Government for at least 22 years. Several members of my own unit division, Division Unit, have left subsequent to my leaving and several medical officers have left subsequent to my leaving.

And at the time of my leaving the Department seemed to be completely deteriorating. There was no Division Director per se. There was a rotating system of Division Directors, some of whom were obviously not adequately prepared to make final decisions.

I understand you would like for us to give you some opinions as to what modifications can be made in regard to bettering the situation for the future better organization. If it exists in that form or in another form in regard to preclinical data and trade secrets, as a pharmacologist, I cannot see that preclinical data would in any wise invade trade secrets.

Preclinical data should be scientific animal data conducted in a scientific manner and therefore is liable to publications in scientific journals.

I can see that there is certain areas of the chemistry that a company should, of necessity, have allocated to secret files.

I believe in applications for investigational new drugs, which is very initial development of the drug, that protocols should be submitted for preclinical data to the FDA while this work is going on so that they can, in fact, advise industry that this will or will not answer the question being sought.

That it is an inappropriate protocol and therefore I think that this would make for a better mesh with industry and certain understanding and there would not be needless waste of money and animals to no avail.

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[1] No written comments received for inclusion in the hearing record at press time.

I feel, also, that FDA personnel who are in the review situation of preclinical data should be periodically allowed, when they so desire, not that it should be a nuisance thing, but they should be allowed by their agency to actually go to the company to see periodically as a monitor, how these studies are being performed, rather than merely get a written summary of what the company said they are doing, I think there is a great deal of merit in that.

The other thing is that all too often metabolism studies in animals are done later rather than early.

I feel that this is the reason that a number of preclinical studies have to be repeated because metabolism—the studies are now done, toxicity studies are done in animals that have an entirely different metabolism from the human and is therefore very difficult to extrapolate data from that particular species to other species, and studies have been done in the wrong species, but nevertheless the law says that the study was done in one rodent and one higher animal.

I have no further comments.

Senator KENNEDY. I want to thank you and look forward to your other comments and testimony.

I just want to reiterate what I mentioned at the opening of the hearing. We feel this has been a great help to this committee. It will be of great help to the Panel which is reviewing your earlier allegations and charges and is going to be making recommendations to the Commissioner. I think any study would obviously be very much interested in the current situation as well.

The particular mandate for this Panel is to look back over the past.

I feel that our obvious interest is to find ways of remedying the present problems which you have identified.

Dr. CAROL KENNEDY. Can I say one thing?

Senator KENNEDY. You will have to be brief.

We were only given permission to meet until 1 o'clock.

Dr. CAROL KENNEDY. One thing which has not been brought out, which I am concerned about, is that if you recall 8 of those 14 original witnesses who testified in the August hearings were from the Division of Neuropharmacology. Two of us who had left the agency did not submit our material directly to the Commissioner, but submitted them to the Panel.

One of those persons' testimony was not investigated at all and has not been apparently considered for investigation by the Panel.

Also, two sets of the allegations pertain to things that I submitted but there are other very important issues which directly pertain to the evaluation of drugs in children.

One specifically I will mention, Tofranil, which was, as you recall, turned down by medical reviewers. It was arbitrarily overruled by the Division Director and the head of the Bureau.

It was conditionally approved on the basis that long-term necessary safety studies would be conducted.

One and one-half years after that conditional approval was made no safety studies had even been initiated.

Now, there are other things, such as alterations of records and other very important allegations.

Are these going to be dropped?

Senator KENNEDY. No; they are certainly not.

They are going to be investigated.

I tried to make that as clear on the record yesterday as possible.

I think the Panel understands that. That is certainly what we want reviewed.

I believe that is the commitment that we received from the Secretary of HEW, that was given to Senator Javits and myself.

Dr. CAROL KENNEDY. I was not clear if it wasn't just those four sets of allegations which they requested be reinvestigated or if it would be these others, the unresolved issues.

Senator KENNEDY. It is the four sets of issues, but I would think that any information which is obviously related and important to the four would be reviewed as well.

Dr. Nestor, just a brief remark.

Dr. NESTOR. Yes.

I meant to say when I said the leadership was the key problem, the problem was not the institution.

It is individuals. There ought to be a screening method by the Senate as you have proposed in one of your laws to find out what these people are like, what their biases are, before they come aboard.

Senator KENNEDY. That is included in our legislation.

At this point I ordered printed in the hearing record any additional information submitted for inclusion.

[The information referred to follows:]

STATEMENT

BY

ALLEN T. EATON

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF

THE COMMITTEE OF LABOR AND PUBLIC WELFARE

AND

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICES AND PROCEDURE

OF

THE COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

Mr. Chairman and members of the Subcommitees, I am counsel to Drs. Burton L. Appleton, Marion Bryant, Alice Campbell, Carol Kennedy, Robert Knox, David Lidd, John O. Nestor, John Winkler and Mrs. Frances DaCosta, all who testified before the joint subcommitees almost two years ago. The two years have not been especially happy ones for the nine witnesses and the tension generated by the role in which the witnesses were cast has predictably taken its toll. If you will recall, Mr. Chairman, at the conclusion of the witnesses' testimony in 1974, the Commissioner of the Food and Drug Administration promised that the allegations made by the witnesses would be fully investigated. Instead, the investigation turned into an inquisition and the burden of proof was cast unfairly on the witnesses. The Commissioner's self investigation of the FDA was characterized by a number of deadlines which placed the witnesses at the option of abandoning their normal FDA work or doing the tedious work of documenting the allegations made before the subcommitees. This was a demanding task which often was accomplished without aid of adequate clerical assistance and was often done on nights and weekends.

In addition, they were referred to in the trade press as "dissidents" and other derisive terms. Since they testified before the subcommittees here in 1974, two of the witnesses have become hypertensive and a third one had a cardiovascular incident. Although there can be no absolute assurance that the tension related to this prolonged investigation caused their medical problems, it certainly must be considered.

In order to prevent the Bureau of Drugs witnesses from being subjected to this pressure for a longer period of time, we urge these subcommittees to insure that the Review Panel on New Drug Regulation is given investigative resources which will enable it to quickly investigate each allegation made by my clients. We also urge that the Review Panel be given resources to prevent the Bureau of Veterinary Medicine witnesses from being subjected to the same protracted limbo. We urge the subcommittees to exercise daily vigilance and to continue to assert its oversight function in an aggressive and effective manner.

5907 Chatsworth Lane
Bethesda, Md. 20014
July 9, 1976

Allen T. Eaton P.C.
Eaton, Stein & Efroymson
1712 N Street, N.W. Suite 300
Washington, D.C. 20036

Dear Mr. Eaton:

This letter is a follow-up to our conversation with respect to amendation of testimony at the Kennedy hearings of 1974. Specifically, the following is to be noted:

Referring to the publication titled Examination of the Pharmaceutical Industry, 1973-74, Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary United States Senate:

a. On page 2829, to Senator Kennedy's question: "Once you have approved a particular drug, what happens next?", please delete the last sentence of Dr. Lidd's response "And then, after that, to the Commissioner's office."

b. On page 2848, the drug which Dr. Lidd is discussing is "Serc." However, you will note that the question posed to Dr. Lidd by Senator Kennedy was in reference to the drug "Cylert." There apparently has been a misinterpretation in the recording of Senator Kennedy's testimony. I would appreciate it if the word "Serc" was substituted for the word "Cylert."

I appreciate your assistance in this matter.

Sincerely yours,

David Lidd

David Lidd, M.D.

Senator KENNEDY. The subcommittee will stand in recess.

[Whereupon, at 1:30 p.m., the subcommittee adjourned subject to the call of the Chair.]

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