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ANTIBIOTICS IN ANIMAL FEEDS

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HEARINGS

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE HOUSE OF REPRESENTATIVES

NINETY-FIFTH CONGRESS

FIRST SESSION

ON

USE OF ANTIBIOTICS IN ANIMAL FEEDS

SEPTEMBER 19 AND 23, 1977

Serial No. 95–68

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Committee on Interstate and Foreign Commerce

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ANTIBIOTICS IN ANIMAL FEEDS

MONDAY, SEPTEMBER 19, 1977

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 2123, Rayburn House Office Building Hon. John E. Moss., chairman, presiding.

Mr. Moss. The subcommittee will be in order.

During the 94th Congress the Subcommittee on Oversight and Investigations conducted a series of indepth regulatory reform-oversight hearings that included the programs of the Food and Drug Administration—FDA—whose primary mission is to protect the health and safety of American consumers.

At that time, one of the primary issues considered at the hearings was the failure of FDA to take prompt action to protect the public from nitrofurans, a class of highly suspect carcinogens. The subcommittee found that the nitrofuran case illustrated a breakdown in the operation and interaction of FDA's administrative, enforcement, and scientific responsibilities.

The subcommittee found extensive administrative delays. This failure to act promptly allowed dangerous drugs to remain in production and available to the public. Congress intended that the Food, Drug, and Cosmetic Act would insure that drugs were safe and effective. I have always maintained that FDA does not have the authority or the right to gamble with the health of our citizens.

The subcommittee recommended that FDA, apply the whole range of its powers already conferred by Congress, and request additional statutory powers if necessary, monitor industry activities more conscientiously to insure that proper standards are maintained with less reliance on mere assurances of the manufacturer, and that FDA require acceptable scientific protocols and monitor industry testing and recalls conscientiously.

I think that instance of evaluation by our subcommittee of nitrofurans demonstrates that the Food and Drug Administration continues to be lethargic and slow in implementing its proposed actions. The March 1976 testimony by FDA officials indicated that hearings on these drugs would be imminent. Those hearings have not yet been held. Action has been taken on two of these drugs solely because the sponsors declined to challenge the agency's ruling on their safety.

Today we begin our evaluation of feed additives, which, unlike the suspected carcinogen nitrofurans, present a more complex set of issues. Penicillin, tetracycline, and other antibiotics used in animal feed raise

basic questions about whether we are depleting our armamentarium for dealing with human disease, even to the extent of jeopardizing our health and safety by inviting needless epidemics.

Many scientists have warned that overuse of antibiotics in animal feed, particularly at subtherapeutic levels, might lead to the development of R-plasmid-bearing organisms in animals which could then spread to man. Thus, the use of antibiotics in animal feeds must be evaluated on three different levels: the human health hazards, the animal health hazards, and the effectiveness of antibiotics.

We intend in this set of hearings to examine these three issues in light of the basic legal authority for regulating antibiotics in animal feeds as contained in the Federal Food, Drug, and Cosmetic Act.[1] That act requires that a manufacturer obtain approval from FDA of a drug on the basis of safety and effectiveness before introducing it into interstate commerce.

During this set of hearings we will hear from the General Accounting Office, which has made a detailed survey of this situation along with representatives from Government and the scientific community.

At this time I would like to introduce our first witness, Mr. Gregory J. Ahart, Director, Human Resources Division of the General Accounting Office, who will discuss their report on the Food and Drug Administration's need to establish the safety and effectiveness of antibiotics used in animal feeds.

I would also like to note that the American Cyanamid Co. was invited to participate in these hearings, along with the Pfizer Corp. Unfortunately, both have declined. I have written to their respective presidents indicating my disappointment, and, without objection, I would like to insert those letters in the hearing record at this point. While I accept the decision of these two companies not to appear at this time, I must add that should we determine that their appearance would be necessary in the future in considering this question, I hope that such appearance will be voluntary and that we need not resort to compulsory process.

[The letters referred to follow:]

CONGRESS OF THE UNITED STATES,
HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
OF THE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C., September 16, 1977.

Dr. J. G. AFFLECK,
President, American Cyanamid Co.,
Wayne, N.J.

DEAR DR. AFFLECK: I am disappointed to learn that you have declined our invitation to appear before the Subcommittee on Oversight and Investigations at hearings concerning the possible adverse human health effects associated with the use of antibiotics in animal feeds. This invitation was extended in order to receive testimony from a broad spectrum of parties having an interest and knowledge in this area. We have called upon you because you have interests in this area, your company is a major producer, and you have conducted scientific testing of the safety and efficacy of antibiotic drugs. We believe your viewpoint and evidence at your disposal would be a valuable input as we consider this question.

Your staff has advised the staff of the Subcommittee that representatives of your company would be unable to testify due to time constraints and previous commitments. I think that it is indeed unfortunate that these hearings which

[1] 21 U.S.C. 301 et seq.

will include representatives from the government as well as the scientific community will be absent of representatives from the industry which will be affected by any regulatory action.

Sincerely,

JOHN E. MOSS,
Chairman, Subcommittee on Oversight and Investigations.

CONGRESS OF THE UNITED STATES,
HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
OF THE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C., September 16, 1977.

Dr. G. D. LAUBACH,
President, The Pfizer Corp.,
New York, N.Y.

DEAR DR. LAUBACH: I am disappointed to learn that you have declined our invitation to appear before the Subcommittee on Oversight and Investigations at hearings concerning the possible adverse human health effects associated with the use of antibiotics in animal feeds. This invitation was extended in order to receive testimony from a broad spectrum of parties having an interest and knowledge in this area. We have called upon you because you have interests in this area, your company is a major producer, and you have conducted scientific testing of the safety and efficacy of antibiotic drugs. We believe your viewpoint and evidence at your disposal would be a valuable input as we consider this question.

Your staff has advised the staff of the Subcommittee that representatives of your company would be unable to testify due to time constraints and previous commitments. I think that it is indeed unfortunate that these hearings which will include representatives from the government as well as the scientific community will be absent of representatives from the industry which will be affected by any regulatory action.

Sincerely,

JOHN E. MOSS,
Chairman, Subcommittee on Oversight and Investigations.

Mr. Moss. Mr. Ahart, we are pleased to have you and members of your staff present. I wonder if we could swear all of you who are going to testify at this time.

Do you solemnly swear that the testimony you are about to give this subcommittee shall be the truth, the whole truth, and nothing but the truth, so help you God?

Mr. AHART. I do.

Mr. JOJOKIAN. I do.

Mr. LINZ. I do.

Mr. WYRSCH. I do.

Mr. Moss. Identify yourself to the clerk for the hearing record.

TESTIMONY OF GREGORY J. AHART, DIRECTOR, HUMAN RESOURCES DIVISION, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY ALBERT JOJOKIAN, ASSISTANT DIRECTOR, HUMAN RESOURCES DIVISION; JIM LINZ, SUPERVISORY AUDITOR, HUMAN RESOURCES DIVISION; AND RAY WYRSCH, ATTORNEY ADVISER, OFFICE OF THE GENERAL COUNSEL

Mr. AHART. Thank you, Mr. Chairman.

I am Gregory J. Ahart, the Director of the Human Resources Division of the General Accounting Office.

To my right is Mr. Albert Jojokian, an Assistant Director of that Division. To his right is Mr. Jim Linz, Supervisory Auditor from the Human Resources Division. On my immediate left is Mr. Ray Wyrsch, from the Office of the General Counsel.

We are pleased to appear here today to discuss our report on the Food and Drug Administration's need to establish the safety and effectiveness of antibiotics used in animal feeds, which was issued to the subcommittee on June 27, 1977.

The Federal Food, Drug, and Cosmetic Act requires that an animal drug be approved as safe and effective by FDA before it is introduced into interstate commerce.

Antibiotics are used in veterinary medicine not only at therapeutic levels to treat animal diseases, but also at subtherapeutic levels to promote growth and prevent or control disease. Subtherapeutic levels of antibiotics are administered to food-producing animals including swine, poultry, and beef cattle through the use of medicated feeds.

Between 1960 and 1970 the use of antibiotics in animal feeds increased approximately sixfold. In 1970 antibiotics used in animal feeds represented about 43 percent of the approximately 17 million pounds used for all purposes. It was estimated that almost 100 percent of the chickens and turkeys, about 90 percent of the swine and veal calves, and about 60 percent of the cattle raised in the United States during 1970 received antibiotics in their feed.

ADVISORY PANEL REVIEWS OF ANTIBIOTIC SAFETY AND EFFECTIVENESS

Since about 1960 there has been increasing concern that use of low levels of antibiotics in animal feeds may lead to the development of antibiotic-resistant bacteria and that this resistance may be transferred between animals and man. Because many of the antibiotics used in animal feeds are also used to treat disease in man or animals, the development of antibiotic resistance may lessen the effectiveness of those drugs in treating disease.

Several advisory panels have recommended restrictions on the use of antibiotics in animal feeds because of the potential human health hazard resulting from such use.

NATIONAL ACADEMY OF SCIENCES

In June 1969 the National Academy of Sciences' Committee on Salmonella recommended that only minimal levels of antibiotics be used in animal feeds and water to promote growth and that antibiotics not be used routinely for disease prevention.

SWANN COMMISSION

In November 1969 England's Joint Commission on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, commonly referred to as the Swann Commission, recommended that permission to use antibiotics in animal feeds without prescription be restricted to those which, (1) are of economic value in livestock production, (2) have little or no use in treating disease in humans or animals, and (3) will not impair the effectiveness of other antibiotics in treating dis-

ease. The Commission specifically recommended that legislation permitting the supply and use of tetracyclines and penicillin without prescription be revoked.

On the basis of the Swann Commission's recommendations, England, in 1971, restricted to veterinarian's prescription the subtherapeutic use of certain antibiotics in animal feeds including penicillin and tetracyclines. Antibiotics which have little or no use in treating disease in man or animals and will not lead to the development of resistance to an antibiotic used to treat disease remained available without prescription.

FDA TASK FORCE

In January 1972 the FDA Task Force on the Use of Antibiotics in Animal Feeds noted that:

First, the feeding of certain antibiotics to animals has led to the development of antibiotic-resistant bacteria in food animals that may be transferred to humans;

Second, the continuous feeding of certain antibiotics to animals has been reported to compromise the treatment of certain animal diseases;

Third, limiting the types of antibiotics used in animal feeds is a step toward controlling the resistance problem.

Finally, the safety and efficacy of long-term subtherapeutic feeding of antibiotics for disease prevention and control have not been adequately demonstrated.

The task force established safety and effectiveness guidelines for antibiotics and recommended that antibiotics used in human medicine be prohibited from use in animals for growth promotion and disease prevention if they fail to meet the task force's guidelines. FDA established regulations implementing the task force recommendations in April 1973. The regulations provided that approval of subtherapeutic uses of antibiotics in animal feeds would be revoked as of April 20, 1975, unless manufacturers or other interested parties submitted data which resolved conclusively their safety and effectiveness under specific FDA criteria.

WORLD HEALTH ORGANIZATION

In October 1973 the World Health Organization's Working Group on the Public Health Aspects of Antibiotics in Feedstuffs recommended that only those antibiotics without therapeutic value be used for growth promotion. Specifically, the working group recommended that penicillins, tetracylines, sulfonamides, streptomycin, and neomycin not be used for growth promotion purposes.

NATIONAL ADVISORY COMMITTEE

In June 1975 FDA established an Antibiotics in Animal Feeds Subcommittee of its National Advisory Food and Drug Committee, a broad policy advisory committee, to review the evidence developed in response to the FDA's April 1973 regulations. The subcommittee reviewed data on three antibiotics used in animal feeds—penicillin, tetracyclines, and sulfaquinoxaline—and, in January 1977, recommended to the parent committee that:

First, all growth promotion and feed efficiency uses of penicillin be discontinued;

Second, growth promotion and feed efficiency uses of tetracyclines be discontinued where effective substitutes are available;

Third, disease prevention use of penicillin be discontinued when effective substitutes are available;

Finally, all disease prevention uses of sulfaquinoxaline and those disease prevention uses of tetracyclines for which effective substitutes are not available continue, but that their use be limited to those periods of time when there is the greatest threat of animal diseases.

There are currently no approved growth promotion and feed efficiency uses of sulfaquinoxaline.

On January 24, 1977, the National Advisory Food and Drug Committee voted to accept the subcommittee's recommendations with respect to penicillin and sulfaquinoxaline, but voted to recommend that tetracyclines remain available for growth promotion and disease prevention uses.

Contrary to the position taken by the committee, on April 15, 1977, FDA announced that it plans to restrict the use of penicillin, tetracyclines, and sulfaquinoxaline used in animal feeds. I will further discuss FDA's proposed restrictions later.

ANTIBIOTICS NOT MEETING SAFETY AND EFFECTIVENESS CRITERIA REMAIN ON THE MARKET

The safety of several antibiotics has not been decided. In addition, FDA has not established regulations specifying when and how most antibiotics used in animal feeds prevent animal diseases and stimulate growth.

The Federal Food, Drug, and Cosmetic Act requires that FDA withdraw approval to market an animal drug if experience or new scientific data shows that the drug is unsafe or if the drug has not proven to be effective under its approved conditions of use.

Based on guidelines established by FDA's task force, FDA established criteria for determining whether use of an antibiotic in animal feeds at subtherapeutic levels created a hazard to human or animal health, and whether such use was effective for its intended purposes. The criteria were developed in consultation with industry representatives, FDA task force members, and Canadian health officials. Antibiotics not meeting the criteria were to be withdrawn from the market.

CRITERIA

FDA's human and animal health safety criteria provide that a human or animal health hazard exists if an antibiotic enhances the capability of bacteria to cause disease. In addition, the criteria stated that the use of subtherapeutic levels of an antibiotic in animal feeds can be considered a hazard if such use creates:

First, a significant adverse effect on the relative quantity, prevalence, and shedding or excretion of salmonella organisms in animals;

Second, a significant increase of salmonella organisms in the animal resistant to antibiotics used therapeutically in man or animals;

Third, a significant increase of coliforms—intestinal bacteria—resistant to antibiotics used therapeutically in main or animals;

Fourth, a condition in which disease is more difficult to treat; or

Finally, a continuing increase in the amount of antibiotic necessary to achieve the desired response.

The effectiveness criteria require that labels of antibiotics for which disease prevention or control claims are made be qualified as to the situations in which the drug offers beneficial effects. The criteria also require that controlled studies be conducted to determine whether claimed disease prevention uses of antibiotics in animal feeds offer protection that is at least as effective as the recognized therapeutic use administered at the time clinical signs of disease become evident.

ANTIBIOTICS FAIL TO MEET CRITERIA

FDA scientists have determined that several antibiotics, including penicillin and tetracyclines, failed to meet one or more of the safety criteria and thus create a hazard to human and animal health when used at low levels in animal feed. In addition, many antibiotics have not been proven effective under the approved conditions of use. FDA, however, has permitted the continued use of subtherapeutic levels of these antibiotics in animal feeds.

The Bureau of Veterinary Medicine found that the use of penicillin in animal feeds causes, one, a significant increase in the percentage of salmonella organisms resistant to ampicillin, an antibiotic used in human and animal therapy, and, two, an increase in the percentage of intestinal bacteria resistant to more than one antibiotic and capable of transferring resistance to man.

No data has been submitted to FDA to support the effectiveness of subtherapeutic use of penicillin in animals for disease prevention and control.

With respect to tetracyclines, the Bureau of Veterinary Medicine found that, one, there was a significant increase in the percentage of salmonella resistant to tetracyclines, two, there was an increase in salmonella shedding in medicated versus nonmedicated animals when there were high numbers of drug-resistant bacteria, and, three, data were available indicating a trend toward compromise of subsequent therapy of salmonellosis, the infection caused by the salmonella organism.

A Bureau of Veterinary Medicine official recommended that Federal Register notices be published specifying acceptable claims and dosages for use of tetracyclines in animal feeds. Any claims not specifically covered by the Federal Register notices would be disallowed. The notices would not include most of the current claims for disease prevention and control. The notices, however, have not been issued.

At the conclusion of our review FDA had determined that only three antibiotics—bacitracin, flavomycin, and oleandomycin—had met all safety criteria for low-level use in one or more animal species. Also, FDA has not published Federal Register notices specifying the conditions under which most antibiotics used in animal feeds are effective. According to an FDA official, many of the antibiotics for which a safety determination has not been made are not used as human drugs and were not given the same priority for review as pencillin and tetracyclines.

GAO RECOMMENDATION AND AGENCY COMMENTS

We recommended that the Secretary of the Department of Health, Education, and Welfare direct the FDA Commissioner to promptly make a final determination as to the safety and effectiveness of antibiotics used in animal feeds based on available data and take appropriate steps to withdraw approval for subtherapeutic use in animal feeds of any antibiotic not shown to be safe and effective under the approved conditions of use.

HEW agreed with our recommendation and, on April 15, 1977, FDA announced its decision to restrict the use of three antiobiotics—penicillin, tetracyclines, and sulfaquinoxaline—used in animal feeds. HEW said that FDA will issue a notice of opportunity for hearing proposing to:

One, withdraw approval of penicillin for growth promotion purposes;

Two, discontinue use of pencillin for disease prevention when effective substitutes are available;

Three, restrict the use of tetracyclines for growth promotion to certain minor animal species;

Four, restrict the use of tetracyclines for disease prevention to uses for which effective substitutes are not available;

Finally, continue the present use of sulfaquinoxaline, but limit its use to those periods of time when there is a threat of disease.

HEW further said that FDA will propose that penicillin and tetracyclines be available for use only upon the written order of a licensed veterinarian.

On August 30, 1977, FDA published in the Federal Register a notice of opportunity for hearing proposing to withdraw approval for all animal feed uses of penicillin on the grounds that they have not been shown to be safe and lack substantial evidence of effectiveness for therapeutic use. Interested persons have been given 30 days to file objections to the proposal and request a public hearing.

At the same time, FDA announced that a Federal Register notice proposing to withdraw approval for certain subtherapeutic uses of tetracyclines will be issued shortly.

QUESTIONABLE USE OF THE NATIONAL ADVISORY COMMITTEE

The National Advisory Food and Drug Committee was established to review and evaluate agency programs and provide advice on policy matters of national significance. According to FDA regulations, such policy advisory committees deal with broad policy issues and should not get involved with specific regulatory matters.

However, FDA has sought and obtained advice from the National Advisory Food and Drug Committee on an issue concerning the use of antibiotics in animal feeds which, in our opinion, concerned regulation, not policy.

Such use of a policy advisory committee seems questionable in that the committee did not have sufficient expertise to adequately consider the highly complex regulatory issue.

FDA regulations differentiate between policy advisory committees which advise the Commissioner on broad, general matters, and technical advisory committees which advise on specific regulatory matters.

Members of technical advisory committees are required to possess specific expertise in the subject matter to be addressed by the committee; policy advisory committee members are not.

FDA's Special Assistant for Review of Antibiotics in Animal Feeds advised us that the National Advisory Food and Drug Committee had several physicians who had some limited training in antibiotic resistance, but only one member who might be considered an expert.

Also, one committee member, the president of an animal feedlot, voted on the continued use of antibiotics in animal feeds although he had a definite interest in such use. This raised a question of whether a conflict of interest existed.

Under FDA regulations, advisory committee members are special Government employees and are subject to the conflict of interest laws and regulations. HEW regulations instruct that a special Government employee should not participate in a matter which will have a direct and predictable effect on his financial interest.

The president of Farr Farms, a Colorado feedlot, took an active role in committee deliberations on penicillin, tetracyclines, and sulfa quinoxaline and seconded a motion which overturned a subcommittee's recommendation that the use of tetracyclines be restricted.

I should point out, Mr. Chairman, that the meeting in which this person participated was open to the public and the other members of the committee were aware of his position and interest.

The president of Farr Farms advised us that FDA had not discussed the restrictions of conflict-of-interest laws and regulations with him prior to his involvement in the committee's deliberations, and, that had FDA so advised him, he would not have participated. He also said that because all feedlots would be affected by restrictions on the use of antibiotics in animal feeds, he would not gain a competitive advantage over other feedlots.

AGENCY COMMENTS AND OUR EVALUATION

In a draft of our report submitted to HEW for comment, we proposed that the Secretary of HEW direct the FDA commissioner to promptly resolve the question of whether the president of Farr Farms was involved in a conflict of interest and determine whether participation of other members of the National Advisory Food and Drug Committee in the review of antibiotics used in animal feeds created conflicts.

HEW advised us that FDA has reviewed the participation of the president of Farr Farms in the January 24, 1977, National Advisory Food and Drug Committee decision of the use of antibiotics in animal feed and has determined that there was no conflict of interest created by his contributions. HEW said that FDA believes the participation of all committee members in the discussion to have been proper.

With respect to the use of the National Advisory Food and Drug Committee to review the use of antibiotics in animal feeds, HEW said that FDA is of the opinion that the committee was addressing a broad policy matter in accordance with FDA regulations.

HEW believed that we questioned the advisory committee's use because we assumed that the National Advisory Food and Drug Committee was addressing a particular matter in the context of the Federal

statutes relating to conflict of interest. HEW said that FDA does not believe the committee was addressing a particular matter because, (1) antibiotics encompass a number of individual products, (2) there are multiple manufacturers of these products, and (3) the use of antibiotics in animal feeds is widespread throughout the United States.

We believe that the appropriateness of subjects reviewed by FDA advisory committees is determined not by its conflict-of-interest regulations, but by its regulations concerning the use of advisory committees although review of purely regulatory matters would necessarily entail application of the conflict-of-interest regulations. HEW assumes that an issue is a broad policy issue appropriate for review by a policy advisory committee if it does not involve a particular matter. FDA regulations concerning the use of policy and technical advisory committees, however, are based not on whether the issue discussed is a particular matter in the context of its conflict-of-interest regulations, but on whether the issue is a policy or a regulatory issue.

HEW also noted that the Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee performed an indepth review of the use of antibiotics in animal feeds. According to FDA's chief counsel, this review gave a clearer regulatory focus to the committee's final recommendations than FDA had initially anticipated. As a result, we believe that the committee members should have met all qualifications for membership on a technical advisory committee, qualifications that differ greatly from those of policy advisory committee members.

RECOMMENDATION

We recommended that the Secretary of HEW direct the FDA Commissioner to take appropriate steps to insure that, (1) policy advisory committees are used to review only broad policy matters in accordance with FDA regulations, and (2) that their members are fully aware of their responsibilities with regard to and the restrictions of conflict-of-interest laws and regulations.

Mr. Chairman, that concludes my prepared statement. We will be happy to answer any questions that you or other members of the subcommittee may have.

Mr. Moss. Thank you very much.

Mr. Santini?

Mr. Santini. Thank you, Mr. Chairman.

I appreciate the authoritative commentary, Mr. Ahart, and your examining this vital issue.

Again the chairman of this distinguished committee is taking a leadership role in his legislative capacity in pursuing this vital issue.

I will address the issue from the concern that I think is shared by many Americans. Nobody would like to be consumed by a disease in a time of plague. Conversely, I think there are serious questions which deserve genuine answers when we explore this issue.

I am informed on the basis of my brief reading and examination of this topic that for 27 years approximately the three drugs that are the subject of your commentary and testimony have been used in poultry, swine, and cattle. All poultry, 90 percent of the swine, and 60 percent of the cattle are included.

It has been further estimated that it will cost $2.1 billion if these protective drugs are to be removed from consumption. That was in the H. C. William and J. R. Martin paper presented to the American Society of Animal Science in 1974.

We have a grave legislative responsibility and there is a serious regulatory enforcement issue to be examined here. To borrow on the fact that the drugs are used in all poultry, are we in fact caught up in another Chicken Little syndrome that the sky is going to fall on our heads at any moment and disaster is imminent and the only way to avert this disaster is regulatory enforcement? Or are we in an arena of genuine health liability that should compel immediate enforcement of those regulations?

In pursuit of that issue and because I believe that those advocating change carry the burden of proof, I would think that at least 51 percent of the evidence would have to be persuasive of the existence of deleterious consequence.

There are those who advocate that 1 percent is sufficient evidence and that any suggestion of imminent health hazard should be persuasive and conclusive in compelling regulatory constraint. I will not for one moment advocate that establishment of a genuine health hazard, whether 1 percent or 51 percent, should foreclose regulatory enforcement but I do think fair and reasoned examination of this issue does necessitate more evidence than at least has been presented to this member to date. That is why I am so proud to be a member of the perhaps one committee in the House of Representatives that assumes aggressive posture on this and almost every serious issue facing the regualtory agencies and the legislative body.

Is it true that no deleterious effects on American consumers have been reported or detected in 27 years of continuous usage of tetracyclines in animal feeds?

Mr. AHART. Let me ask Mr. Linz who is familiar with the details of this.

Before he answers, I would say this. Our role in this was to examine the FDA record and what was before the FDA. Our recommendation was not either to disapprove the drugs or——

Mr. Moss. The Chair would clarify for the gentleman from Nevada that the GAO, in keeping with its long tradition of being an effective service arm of the Congress, has examined the records only of the Food and Drug Administration as they relate to the antibiotics under discussion here today. It would be inappropriate for the chairman to request that they go beyond that. The Chair made no such request. They are not prepared to go beyond that in scope in responding to questions here this morning.

We had invited the witnesses from producing companies. They elected not to come. We will have the Food and Drug Administration people before us. We will call such other witnesses as will permit the full and balanced development of the hearing record.

This would not be the proper witness for such a question.

Mr. SANTINI. I thank the chairman for that clarification.

If I understand the purpose of the testimony and the clarification of the chairman correctly, you are not prepared to address the health hazard issue at all, but simply whether or not, as your report suggests,

the FDA has been dilatory in its regulatory responsibilities; is that correct?

Mr. AHART. That is correct, Mr. Santini. The statute gives a special competence to the Food and Drug Commissioner through the Secretary for making the judgments and taking the regulatory enforcement actions as provided by law. We do not make those judgments and we are not here to argue the case for or against the withdrawal of these drugs but only to lay out the facts as shown in the FDA record and the FDA actions that have and have not been taken.

Mr. SANTINI. I thank you, Mr. Chairman. I thank the gentleman for the response to the question.

Mr. Moss. The Chair recognizes the gentleman from California, Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. Ahart, in 1972 the FDA considered a report of the Task Force on the Use of Antibiotics in Animal Feed. The task force report warned about the dangers of antibiotics. Could the FDA have taken action to restrict the use of antibiotics on the basis of the information contained in the 1972 report?

Mr. AHART. Presumably the FDA could have acted on the basis of that information and the recommendations of the task force prior to the time it did. It was apparently its judgment that it wanted further study and evaluation by people outside of the FDA, the advisory committee, before it took specific regulatory action.

Yes; I think they probably could have acted sooner.

Mr. WAXMAN. The advisory committee was composed of how many members?

Mr. AHART. I think the formal advisory committee has 18 members. My recollection is that there were probably 14 that acted in this specific case last January.

Mr. WAXMAN. How many of those 14 were involved in a potential conflict of interest.

Mr. AHART. The only one that was apparent to us in our review was Mr. Farr, the president of Farr Farms.

The FDA has reviewed, as we understand it, the situation with respect to the other members that participated in the meeting and has found no apparent conflict of interest.

Mr. WAXMAN. Could you explain to the committee again the scope of Mr. Farr's potential conflict of interest. Specifically, how have Mr. Farr's personal or business interests posed a conflict with his responsibilities as a member of the advisory committee?

Mr. AHART. Mr. Farr is the president of Farr Farms, which is a large feedlot operation in Colorado and is a major user, as feedlots are in this country, of the kinds of antibiotics that we are talking about here this morning. So to the extent that his operation had become involved in utilization of antibiotics—and I think his statement was that he used them over a 25-year period—and if the withdrawal of these drugs from the market for those purposes was to take effect, then it would require a change in his operation of the feedlots. Presumably to the extent that any antibiotics involved promote growth and hold down disease there might be some detriment in the economic sense to his operation.

Mr. WAXMAN. Would Mr. Farr have incurred a direct financial loss if the use of antibiotics had been restricted or prohibited?

Mr. AHART. It would be a detriment in terms of slower growth on the part of cattle, hogs, or whatever he was raising and perhaps detriment on the basis, to the extent that there is a prophylactic purpose to be served by the subtherapeutic use of antibiotics, that more disease would exist among his herds of livestock.

Mr. WAXMAN. That advisory committee made the decision on whether the FDA should ban the use of antibiotics in animal feed. Is that correct?

Mr. AHART. The advisory committee is not a decisionmaking body. It is advisory only. The subcommittee had recommended that penicillin, the tetracyclines, and sulfaquinoxaline be restricted in use. The full advisory committee went along with the subcommittee's position with respect to everything but tetracyclines and did not recommend that they be restricted in their use.

Mr. WAXMAN. Do you know whether Mr. Farr was an active participant of the tetracycline discussion and an advocate of the position the advisory committee eventually adopted?

Mr. AHART. Mr. Farr was an active participant in the meeting. He did lay out his experience with the use of these antibiotics in his feedlot operation. Everybody knew he was a feedlot operator. He did second the motion to overturn the subcommittee's recommendation with respect to tetracyclines and, upon his second, the motion did carry.

Mr. WAXMAN. Do you know why FDA felt it necessary to create a separate subcommittee to review the data submitted by the manufacturers on safety and efficacy when the Bureau of Veterinary Medicine was simultaneously reviewing the data.

Mr. AHART. Let me ask Mr. Linz if he has any insight into why FDA felt it needed the additional consideration by the advisory committee.

Mr. LINZ. A considerable amount of data was gathered as a result of the April 1973 regulations which gave manufacturers 2 years to support the safety and effectiveness of the antibiotics. Initially in February of 1975, they planned to establish an expert panel of U.S. and Canadian scientists to review the data. They ultimately went to a subcommittee of the National Advisory Food and Drug Committee because it would be a quicker way to establish a committee.

Mr. WAXMAN. Did the subcommittee have any special expertise unavailable at the Bureau of Veterinary Medicine and elsewhere at the agency?

Mr. LINZ. No; they did not.

Mr. WAXMAN. Why would creation of a subcommittee have been a quicker way to resolve the issue?

Mr. LINZ. It was not a quicker way to resolve the issue. It was a quicker way to establish an advisory committee. The other option was to go through the formal advisory committee procedures of establishing a new advisory committee, which would take a considerable amount of time.

Mr. WAXMAN. Could the FDA have taken action in 1975 without forming a subcommittee?

Mr. LINZ. They probably could have taken action on the basis of BVM's review.

Mr. WAXMAN. As I understand it, the advisory committee reversed the decision of the subcommittee opposing continued use of tetracyclines. What justification did the advisory committee give for reversing the decision of the subcommittee?

Mr. LINZ. It was primarily because of the economic benefits from the use of tetracyclines. The feeling was that there were no effective substitutes for tetracyclines for certain disease prevention uses and the long history of tetracycline use.

Mr. WAXMAN. Was that justification made part of the advisory committee record in their statement reversing the subcommittee recommendation?

Mr. LINZ. I do not believe there was a specific statement as to why it was reversed.

Mr. WAXMAN. Is it your belief that the reason they reversed the subcommittee decision was because of the economic consequences of the industry removing tetracyclines?

Mr. LINZ. I believe the meeting indicated that there was concern (1) for the economic benefit from tetracyclines, (2) about the lack of specific data showing anything other than a theoretical hazard, and (3) that there were no specific disease outbreaks.

Mr. WAXMAN. Mr. Ahart, is FDA responsible for concerning itself with the economic consequences of removing potentially dangerous drugs from animal feed or are they charged with the protection of the public health and removal of dangers to that health?

Mr. AHART. Their role is principally one of protecting the health of the American public. In this particular case the statute requires that before a drug can be approved for marketing that it be shown to be both safe in the public health sense and that it be effective for the uses which are indicated for it. If it is not shown to be safe or if it is shown not to be effective for the uses indicated, under the statute FDA would have no option but to either not approve it if it was a new drug on the market or withdraw approval if a drug had already been marketed.

Mr. WAXMAN. As tetracycline was already in use, it would be covered by the statute governing marketed drugs. Is that correct?

Mr. AHART. It would be covered by the statute. Anytime new scientific evidence becomes available for a drug that has already been marketed and approved for certain purposes that shows that it is not effective or data cannot be brought forth which shows that it is effective or if data shows that it is unsafe or its safety has not been established, then through a regulatory action FDA can disapprove the use of that drug for that particular purpose.

Mr. WAXMAN. So the question before us is whether FDA's decision was pursuant to the statutory authority requiring that drugs be both safe and efficacious. I gather that their task force raised the question of the safety from continued use of that drug.

Mr. AHART. That is correct.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. MOSS. The Chair recognizes the gentleman from New Jersey, Mr. Maguire.

Mr. MAGUIRE. Thank you, Mr. Chairman.

Mr. Ahart, I wonder if you would give your attention to your statement that "Because all feedlots would be affected by restrictions on the use of antibiotics in animal feed, Mr. Farr would not gain a competitive advantage over other feedlots."

I guess this statement is representative of your view as to what point a distinction should be made between what does and what does not constitute a conflict of interest? In other words, as long as you could show that not only one individual would benefit but many others in a class would benefit, then, the conflict-of-interest issue would not arise?

Mr. AHART. No, that would not be the determining factor if I understand the conflict-of-interest laws and regulations.

As indicated in my statement, the question under HEW regulations is whether or not the matter will have a direct and predictable effect on the financial interest of the individual. Now in this case it would have a direct and predictable effect if in fact the action precluded Mr. Farr from utilizing tetracyclines in his feedlot operations.

I have with me here Mr. Wyrsch who is our attorney. He is very familiar with the law. He might wish to expand on the answer.

Mr. WYRSCH. I want to preface my remarks on the specific conflict of interest here by saying you will note that our report does not contain a definitive conclusion as to whether an actual conflict of interest existed.

Mr. MAGUIRE. Why not?

Mr. WYRSCH. Our office has consistently taken the position that it is not our role to render a formal legal opinion on whether an actual conflict of interest existed. Our approach has been to identify apparent conflicts of interest. I think we were of the opinion in the report, as clearly stated, that there was an apparent conflict of interest created by Mr. Farr's participation in the meeting. We referred this to the Food and Drug Administration for resolution of the conflict of interest and reported that in our report.

Mr. MAGUIRE. Is it your understanding that FDA at this point takes the position that there was no conflict?

Mr. WYRSCH. That is correct.

Mr. MAGUIRE. Is it your understanding that is based on this proposition that I enunciated at the outset of my question? In other words, are they agreeing with Mr. Farr that as long as they classify people——

Mr. WYRSCH. That is right, sir.

Mr. MAGUIRE. I know I am asking your understanding of this position, but I want to try to nail this down before they come before us.

Is it your understanding that they endorsed the proposition that you described Mr. Farr as having put forth; namely, as long as a class of people is involved rather than just an individual or individual company, that removes the question of conflict of interest?

Mr. WYRSCH. That is right, sir. There are a number of reasons I believe that they gave our office as to why no conflict of interest existed. It is on pages 42 and 43 of our report.

Mr. MAGUIRE. Do you have a judgment as to whether Mr. Farr's participation in this matter was personal or alternatively was it substantial?

Mr. WYRSCH. I think his participation was substantial in that he did make a statement before the hearing, and he did second the mo-

tion to overturn the subcommittee's recommendation. Whether it was personal, I would tend to say yes.

Mr. MAGUIRE. What about the question of whether or not it dealt with a particular matter? That language is used in 18 U.S.C. 208.

Mr. WYRSCH. I would say that within the meaning of 208(a), there was a particular matter before the committee. That is correct.

Mr. MAGUIRE. In your judgment was it connected with his financial interest or that of his company?

Mr. WYRSCH. Yes.

Mr. MAGUIRE. It would be difficult indeed, would it not, to come to any other conclusion, if one combines all the answers you have just given, that there was anything other than a conflict of interest here?

Mr. WYRSCH. I think if you match his participation with the definition of the conflict of interest within the meaning of 208(a), it would require an affirmative answer. However, there were several extenuating circumstances, I believe, in connection with his participation that our office took note of in our report. One is that the participation did occur in open session. Second, all the other individuals attending were clearly knowledgeable of his interest, being the president of Farr Farms. I believe you have to take note of those circumstances.

Mr. MAGUIRE. Am I correct in my understanding that Mr. Farr himself has indicated that had he been made aware of these laws and regulations which you and I have just discussed he would have refrained from participating?

Mr. WYRSCH. That is what he has told us.

Mr. Moss. Would the gentleman yield?

Mr. MAGUIRE. Yes.

Mr. Moss. What was the vote by which the subcommittee recommendation was overturned?

Mr. AHART. Do you know, Mr. Linz? Was it a unanimous vote?

Mr. LINZ. Yes; it was a unanimous vote.

Mr. AHART. I think it was a unanimous vote.

Mr. Moss. It was a unanimous vote by which the action was overturned?

Mr. AHART. As a matter of fact, I recall seeing the transcript of that meeting. There was, I believe, no response when the nays were called for.

Mr. Moss. Let's hold the record at this point and get the minutes which will reflect the vote.

Mr. AHART. I think we have that with us today.

Mr. Moss. Would you please refer to that for us?

Mr. AHART. I have a copy of the transcript of the January 24 meeting here. On page 134, I believe it is, of that transcript a gentleman—I believe the pronunciation is Mr. Choate—says that "the decision as I understand the amendment is that the regulation that is in force now stay in force." This is with respect to tetracyclines. The acting chairman of the meeting, Dr. Fernandez, said, "Yes, not changed. The motion has been seconded. Is there any discussion? All those in favor say aye."

The transcript notes that there was a chorus of ayes.

Dr. Fernandez asked, "Opposed?" The transcript notes "There was no response."

That would indicate to me a unanimous vote——

Mr. Moss. That was a voice vote, and there was no apparent opposition.

Mr. AHART. Yes.

Mr. Moss. I thank the gentleman for yielding.

Mr. MAGUIRE. I thank the distinguished chairman.

Mr. Ahart, it is my understanding that Mr. Farr was the only member of this committee when it voted who had what you would describe as technical expertise with respect to the issue before the committee. Am I correct in that understanding?

Mr. AHART. There were several physicians on the committee. I believe I indicated in my statement that one of these did have a special knowledge in the area of antibiotics. So there was that expertise as well as Mr. Farr's expertise, which would be as a layman basically, with respect to antibiotics but he certainly had a high knowledge of their use in feedlot operations.

Mr. MAGUIRE. He had more expertise with respect to antibiotics in animal feeds than any of the other panelists?

Mr. AHART. Certainly in animal feedlots respect to their operations; yes.

Mr. MAGUIRE. It is my further understanding that the record shows there were perhaps three very outspoken critics of the subcommittee's recommendations and that, in addition to Mr. Farr, one of the other three was also chairman of the board of directors of a drug company. Is that correct?

Mr. AHART. Let me ask Mr. Linz about his knowledge on that.

Mr. LINZ. Yes. The chairman of the Sterling Drug Co. was a member.

Mr. MAGUIRE. Is that Mr. Wescoe?

Mr. LINZ. Yes.

Mr. MAGUIRE. Mr. Ahart, in view of the record here that we have just developed, your associates after analyzing the facts and the law came to the conclusion that it would be very difficult indeed to avoid a finding of conflict. I assume you associate yourself with that position of your associates. Am I correct?

Mr. AHART. Yes. I think Mr. Wyrsch's analysis is correct.

Mr. MAGUIRE. What are we to make out of FDA's explanation of this matter?

Mr. AHART. Well, I think FDA is in the best position to explain why they feel there is no conflict of interest. As Mr. Wyrsch pointed out, as a matter of policy our office has not felt that we are in a position to make final judgment on that. He has also indicated that were we to do so in this case, our judgment would probably be yes, that there was a conflict of interest at least in the technical sense with some mitigating circumstances. I think FDA would have to explain their full rationale in reaching the conclusion that they did in this matter.

Mr. MAGUIRE. Would it be safe for me to conclude that based upon what you and your associates told us this morning, you have found FDA's arguments unpersuasive?

Mr. AHART. Unpersuasive in the sense of technical violation of the law, that is correct. I think we would agree with them that in making a judgment on whether he was or was not involved in a violation of

the law you have to consider the fact that he openly let everybody know that this was the business he was in, what interest he had in it, and everybody in the room was made aware of this. It was an open, public session, and this would be considered as well.

Mr. MAGUIRE. Wait a minute, Mr. Ahart. You have now reduced the concern, as I understand your comment, to a level of a technicality. Does the fact that everybody in a room knows what is going on while an action which has the character of a conflict of interest and which may have dramatic and far-reaching effects on people's lives and where members of the deliberating body may have a financial interest in the matter—does the fact that this occurs in the open in any way change either the wrongness of the procedure, if there is a conflict of interest, or the result on people's lives. I would submit that it does not. I would welcome your response.

Mr. AHART. I would agree with you that it does not impact directly on whether there was or was not a conflict of interest in violation of the law and regulations. As in any case where you have circumstances which mitigate the effect of that, those mitigating circumstances would be taken into consideration.

Mr. MAGUIRE. The law does not say, Mr. Ahart, that this is terrible until——

Mr. Moss. Would the gentleman yield?

Mr. MAGUIRE. Just a moment, Mr. Chairman.

Mr. Moss. The Chair is going to interject again to state the purpose of the GAO witness. The General Accounting Office is part of the legislative branch of Government. They are not a law enforcement agency. They have found a probable conflict, and they have set forth very explicitly their views on that conflict.

Then it is up to this committee, if it feels it should be pursued further, to pursue it with the appropriate authorities who are part of the executive branch. It is not the burden or the duty of the Comptroller General to pursue that matter further.

We have the facts. I think they have been set forth with clarity in a manner that will be helpful to any interested member, but we should not further belabor the point with the Comptroller General.

Mr. MAGUIRE. I thank the chairman for his very helpful clarification but I would hope that he would also recognize my concern at a point where——

Mr. Moss. I recognize the gentleman's concern. I only point out that he is an inappropriate witness for continuing pursuit of the question.

Mr. MAGUIRE. In view of the fact that I am having difficulty completing my sentences now, I will terminate my questioning, Mr. Chairman. Thank you.

Mr. Moss. The gentleman from Texas, Mr. Collins.

Mr. COLLINS. I have nothing to bring out at this time. Thank you, Mr. Chairman.

Mr. Moss. Mr. McLain?

Mr. MCLAIN. Thank you, Mr. Chairman.

I would like to just briefly follow up first on a point that was raised earlier. Under the Food, Drug, and Cosmetic Act who carries the burden, whether it be the sponsor or the agency, as to the question of safety and efficacy of a particular drug?

Mr. AHART. Basically the sponsor would carry that burden on both of those aspects.

Mr. MCLAIN. Following up on that, in April of 1973 when FDA issued their notice with the intention to withdraw the approval of certain antibiotics for subtherapeutic uses unless the sponsor submitted conclusive data as to safety and efficacy, who carried the burden in that case?

Mr. AHART. Clearly the sponsors would carry the burden to come in with conclusive data as to both aspects, efficacy and safety.

Mr. MCLAIN. Thank you, Mr. Ahart.

In your statement you make reference to a notice of opportunity for hearing issued by FDA on August 30, 1977. That notice was issued after you had completed your report at the request of this subcommittee.

I ask that that notice be inserted into the hearing record at this time.

Mr. MOSS. Without objection, the item will be included in the record at this point.

[Testimony resumes on p. 45.]

[The material referred to follows:]

federal register

TUESDAY, AUGUST 30, 1977

PART IV



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

PENICILLIN

Use in Animal Feed

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 505, 510, 558]

[Docket No. 77N-0231]

PENICILLIN IN ANIMAL FEEDS

Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposal would amend regulations to delete provisions that provide for use of penicillin in animal feeds.

DATE: Written comments by September 29, 1977.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Gerald B. Guest, Bureau of Veterinary Medicine (HFV-130), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857 (301-443-3410).

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the FEDERAL REGISTER, under Docket No. 77N-0230, the Director of the Bureau of Veterinary Medicine is issuing a notice of opportunity for hearing on a proposal to withdraw approval of the new animal drug applications (NADA's) for all penicillin-containing premixes on the grounds that new evidence not available until after such applications were approved, evaluated together with the evidence available when the applications were approved, shows that such drug is not shown to be safe for subtherapeutic use, that certain applicants have failed to establish and maintain required records and reports, and that new information demonstrates there is a lack of substantial evidence of effectiveness for these products.

Consistent with this action, the Director is hereby proposing to amend the regulations to delete the provisions that provide for the use of such drugs.

The Director has carefully considered the environmental effects of this action, and because it will not significantly affect the quality of the human environment, he has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration. Moreover, in a proposal published in the FEDERAL REGISTER of May 27, 1977 (42 FR 27264), the Commissioner of Food and Drugs requested data concerning the potential environmental impact of a series of regulatory actions designed to restrict the subtherapeutic use of antibacterials in animal feeds. If the public discussion and information gathered warrant, a comprehensive environmental impact statement will be prepared, evaluating the impact of all the actions as a single program.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 507, 512, 59 Stat. 463 as amended, 82 Stat. 343-351 (21 U.S.C. 357, 360b)) and under authority delegated to the Commissioner (21 CFR 5.1) and redelegated to the Director (21 CFR 5.84), it is proposed that Parts 505, 510, and 558 of Chapter I of Title 21 of the Code of Federal Regulations be amended, as follows:

PART 505—INTERPRETIVE STATEMENTS RE: WARNINGS ON ANIMAL DRUGS FOR OVER-THE-COUNTER SALE

1. By amending the introductory paragraph of § 505.10 to read as follows:

§ 505.10 Animal drug warning and caution statements required by regulations.

Animal feed containing streptomycin, dihydrostreptomycin, chlortetracycline, tetracycline, or bacitracin, with other drugs. (See § 510.515 of this chapter.)

* * * * *

PART 510—NEW ANIMAL DRUGS

§ 510.5 [Amended]

2. By amending § 510.5 *Certification of new animal drugs containing any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or derivative thereof*, as follows:

a. By deleting from paragraph (b) the word "Penicillin," appearing immediately following the italicized heading, and accordingly, capitalizing the word "Streptomycin".

b. By deleting from paragraph (c) the word "penicillin" appearing in the sentence following the italicized heading.

3. By amending § 510.515: (a) By deleting from the indtroductory paragraph the phrase "penicillin, streptomycin in combination with penicillin,"; (b) by deleting from paragraph (b) (7) (i) the concluding phrase 66, or not less than 90 grams nor more than 180 grams of penicillin and streptomycin in a combination containing 16.7 percent penicillin"; (c) by revoking paragraph (b) (7) (i) (c); (d) by revising paragraph (b) (10); (e) by revoking and reserving in the table in paragraph (c) items 1, 4, 5, 6, and 7; and (f) by deleting from the table in paragraph (c) the phrase "or procaine penicillin" from items 8, 9, and 10. Section 510.515 is set forth with the revised introductory paragraph, revised paragraphs (b) (7) (i) and (b) (10) and the amendments to the table in paragraph (c) to read as follows:

§ 510.515 Animal feeds bearing or containing new animal drugs subject to the provisions of section 512(n) of the act.

Animal feeds that bear or contain chlortetracycline, feed grade zinc bacitracin, and bactracin methylene disalicylate, with or without added suitable nutritive ingredients are exempt from the certification requirements of section 512 of the act provided they are the subject of and in compliance with regulations for their use in Part 558 of this chapter, or any one of the paragraphs of this section:

* * * * *

(b) * * *

(7) (i) It is intended for use solely as a treatment for complicated, chronic respiratory disease (air-sac infection), infectious sinusitis, blue comb (non specific infectious enteritis, mud fever), and hexamitiasis in poultry, and/or bacterial swine enteritis; its labeling contains adequate directions and warnings for such use; and it contains, per ton of feed, not less than 100 grams of chlortetracycline, or oxytetracycline, or a combination of such drugs.

* * * * *

(c) [Revoked].

* * * * *

(10) It is intended for use solely in the treatment of chronic respiratory disease (air-sac infection), infectious sinusitis, and blue comb (nonspecific infectious enteritis) in poultry and/or bacterial swine enteritis; its labeling bears adequate directions and warnings for such use; and it contains, per ton of feed, the equivalent of either not less than 100 grams and not more than 500 grams of bacitracin (as zinc bacitracin), or not less than 100 grams and not more than 200 grams of bacitracin (as bacitracin methylene disalicylate); except that, if it is intended for the treatment of bacterial swin enteritis, it contains, per ton of feed, 100 grams of bacitracin (as zinc bacitracin or bacitracin methylene disalicylate). When intended for the use specified in this paragraph (b) (10), it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section: *Provided, however*, That the level of antibiotic or antibiotic combination present is not greater than the minimum amount specified therefor in this paragraph (b) (10).

* * * * *

(c) * * *

Product	Species	Use levels	Indications for use
1. [Reserved]			
* * *	*	*	
4-7 [Reserved]			
8. Furazolidone and bacitracin methylene disalicylate or—Zinc bacitracin.			
9. Furazolidone and bacitracin methylene disalicylate or—Zinc bacitracin.			
10. Furazolidone and bacitracin methylene disalicylate or—Zinc bacitracin.			
* * *	*	*	

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

§ 558.15 [Amended]

4. By amending 558.15 *Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals*, as follows: a. By deleting from the table in paragraph (g) (1):

i. The entry of Merck Sharp & Dohme Research Labs. for the drug premix procaine penicillin.

ii. The entry of E. R. Squibb & Sons, Inc., for the drug premix procaine penicillin.

iii. The entry of Pfizer, Inc., for the drug premix penicillin.

iv. The entry of Pfizer, Inc., for the drug premix of penicillin and streptomycin.

v. The entry of Merck Sharp & Dohme Research Labs. for the drug premix procaine penicillin and streptomycin sulfate.

vi. The entry of American Cyanamid Co. and Rachelle Labs, Inc., for the drug premix chlortetracycline, sulfamethazine, and penicillin.

vii. The entry of Diamond Shamrock Corp. for the drug premix chlortetracycline, sulfathiazole and penicillin.

b. By deleting from the table in paragraph (g)(2): i. The eight entries of Merck Sharp & Dohme Research Labs. and Pfizer, Inc., for procaine penicillin, streptomycin combination.

ii. The entries of Merck Sharp & Dohme Research Labs. for procaine penicillin, streptomycin, arsanilic acid combination; nicarbazin, procaine penicillin; nicarbazin, procaine penicillin, 3-nitro-4-hydroxyphenylarsonic acid; amprolium, procaine penicillin; amprolium, procaine penicillin, 3-nitro-4-hydroxyphenylarsonic acid; and amprolium, ethopabate, procaine penicillin, erythromycin.

iii. The entry of Merck Sharp & Dohme Research Labs. for amprolium, ethopabate, procaine, penicillin, 3-nitro-4-hydroxyphenylarsonic acid.

iv. The two entries of Pfizer, Inc., for penicillin, streptomycin combinations.

v. The entries of Dow Chemical Co. for zoalene, penicillin; zoalene, 3-nitro-4-hydroxyphenylarsonic acid, penicillin; and zoalene, arsanilic acid, pencillin.

vi. The phrase "or procaine penicillin" from the entry of Norwich Pharmacal Co. for furazolidone and bacitracin methylene disalicylate or-zinc bacitracin or procaine penicillin.

§ 558.55 [Amended]

5. By amending § 558.55 *Amprolium* by deleting from the table in paragraph (e)(2) the two entries in items (i), (ii) and (iv), respectively, for the combinations with penicillin, and the combination with penicillin plus streptomycin.

§ 558.58 [Amended]

6. By amending § 558.58 *Amprolium and ethopabate* by deleting from the table in paragraph (e)(1) the entries in item (iv) for the combination with penicillin, and the combination with penicillin plus streptomycin.

§ 558.76 [Amended]

7. By amending § 558.76 *Bacitracin methylene disalicylate* by deleting from the table in paragraph (e)(1) the entry in items (v) and (vi) for the combination with penicillin.

§ 558.78 [Amended]

8. By amending § 558.78 *Bacitracin, zinc* by deleting from the table in paragraph (e)(1) the entry in items (v) and (vi) for the combination with penicillin.

§ 558.105 [Amended]

9. By amending § 558.105 *Buquinolate* by deleting and reserving paragraph (f)(1)(iv) and (vi).

§ 558.145 [Revoked]

10. By revoking § 558.145 *Chlortetracycline, procaine penicillin and sulfamethazine.*

§ 558.155 [Revoked]

11. By revoking § 558.155 *Chlortetracycline, procaine penicillin, and sulfathiazole.*

§ 558.274 [Amended]

12. By amending § 558.274 *Hygromycin B* by deleting from the table in paragraph (e)(1) the three entries in item (i) for the combinations in which penicillin is an ingredient.

§ 558.460 [Revoked]

14. By revoking § 558.460 *Penicillin.*

§ 558.530 [Amended]

15. By amending §558.530 *Roxarsone* by deleting and reserving paragraph (e)(4)(xvi).

§ 558.680 [Amended]

16. By amending § 558.680 *Zoalene* by deleting from the table in paragraph (e)(1) the entries in items (i) and (ii) for the combinations containing arsanilic acid plus penicillin, penicillin, and penicillin plus roxarsone.

Interested persons may, on or before September 29, 1977, submit to the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A–107. A copy of the inflation impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 24, 1977.

C. D. VAN HOUWELING,
Director, Bureau of Veterinary Medicine.

[FR Doc.77–24970 Filed 8–29–77;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 77N–0230]

DIAMOND SHAMROCK CHEMICAL CO., ET AL.

Penicillin-Containing Premixes; Opportunity for Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This is a notice of opportunity for a hearing on the proposal by the Director of the Bureau of Veterinary Medicine to withdraw approval of new animal drug applications (NADA's) for all penicillin-containing premixes intended for use in animal feed on the grounds that (1) new evidence shows that the penicillin-containing products have not been shown to safe for subtherapeutic use as required by section 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(e)(1)(B)) and § 558.15 (21 CFR 558.15); (2) the applicants have failed to establish and maintain records and make reports as required by section 512(e)(2)(A) of the act (21 U.S.C. 360b(e)(2)(A)) and § 558.15; and (3) new evidence shows that there is a lack of substantial evidence that penicillin-containing premixes are effective for therapeutic uses under section 512(e)(1)(C) of the act (21 U.S.C. 360b(e)(1)(C)).

DATES: Written appearances requesting a hearing must be submitted by September 29, 1977. Data and analysis upon which a request for a hearing relies must be submitted by October 31, 1977.

ADDRESS: Written appearances and data and analysis to the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Gerald B. Guest, Bureau of Veterinary Medicine (HFV–130), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857 (301–443–3410).

SUPPLEMENTARY INFORMATION

RELATED ACTIONS

In a notice published elsewhere in this issue of the FEDERAL REGISTER, the Director of the Bureau of Veterinary Medicine is proposing to delete the provisions that provide for the use of penicillin in animal feeds by amending § 505.10 *Animal drug warning and caution statements required by regulations* (21 CFR 505.10); § 510.5 *Certification of new animal drugs containing any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or derivative thereof* (21 CFR 510.5); § 510.515 *Animal feeds bearing or containing new animal drugs subject to the provisions of section 512(n) of the act* (21 CFR 510.515); § 558.15 *Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals* (21 CFR 558.15); § 558.55 *Amprolium* (21 CFR 558.55); § 558.58 *Amprolium and ethopabate* (21 CFR 558.58); § 558.76 *Bacitracin methylene disalicylate* (21 CFR 558.78); § 558.78 *Bacitracin, zinc* (21 CFR 558.78); § 558.105 *Buquinolate* (21 CFR 558.105); § 558.145 *Chlortetracycline, procaine penicillin and sulfamethazine* (21 CFR 558.145); § 558.155 *Chlortetracycline, procaine penicillin and sulfathiazole* (21 CFR 558.155); § 558.274 *Hygromycin B* (21 CFR 558.274); § 558.460 *Penicillin* (21 CFR 558.460) § 558.530 *Roxarsone* (21 CFR 558.530); and § 558.680 *Zoalene* (21 CFR 558.680).

DISCUSSION

Since the Director's discussion of the issues involved in this matter is necessarily detailed, he is setting forth, for the reader's convenience, an outline of the discussion as follows:

I. THE DRUG

II. INTRODUCTION

A. *Regulatory Background*

B. *Safety Concerns*

III. SUMMARY OF THE ARGUMENT

IV. STUDIES RELEVANT TO HUMAN AND ANIMAL HEALTH SAFETY CRITERIA

A. *Transfer of Drug Resistance (Criterion 1).*

The Pool of R-Plasmid-Bearing Organisms Is Increasing

1. Background.
2. Criterion.
3. Studies Relevant to Transfer of Drug Resistance:
(a) R-plasmid-bearing *E. coli* develop in domestic animals that are fed subtherapeutic levels of antibiotics, including penicillin.
(b) *E. coli* contribute their R-plasmids to man through several mechanisms.
(i) Direct contact with animals.
(ii) Contact with *E. coli*-contaminated food.
(iii) Widespread presence in the environment.
(c) R-plasmid-bearing human and animal strains of bacteria overlap.
(i) Epidemiological investigations—*E. coli* serotyping.
(ii) Direct ingestion evidence.
(iii) In vivo studies show that R-plasmids transfer from *E. coli* to pathogens.
(iv) R-plasmid compatibility studies.
(v) Hazards.
4. Director's Conclusions.

B. *Shedding and Resistance Characteristics of Salmonella (Criterion 2)*

1. Background.
2. Criterion:
(a) Shedding.
(b) Resistance characteristics.
3. AHI Studies on the Effects of Subtherapeutic Levels of Penicillin in Animal Feed in Chickens:
(a) Experimental design.
(b) AHI's summary of the results:
(i) Shedding.
(ii) Resistance characteristics.
(c) The Director's analysis:
(i) Shedding.
(ii) Resistance characteristics.
4. AHI Studies on the Effects of Subtherapeutic Levels of Penicillin in Animal Feed in Swine:
(a) Experimental design:
(i) Shedding.
(ii) Resistance characteristics.
(b) AHI's summary of the results:
(i) Shedding.
(ii) Resistance characteristics.
(c) Director's analysis:
(i) Shedding.
(ii) Resistance characteristics.
5. Questions Raised by Other Studies of Salmonella: (a) CDC reports; (b) FDA survey; (c) Neu, Cherubin, Longo, Flouton, and Winter studies; (d) Smith and Tucker studies; (e) Kabian, Gustafson study; (f) Other studies.
6. Director's conclusions.

C. *Compromise of Therapy (Criterion 2(c))*

1. Background and Criterion.
2. AHI's Compromise of Therapy Study in Chickens: (a) Experimental design; (b) AHI's summary of the results; (c) Director's analysis.
3. AHI Compromise of Therapy Study in Swine: (a) Experimental design; (b) AHI's summary of the results; (c) Director's analysis.
4. Questions Raised by FDA Funded Research: (a) Experimental design; (b) Director's analysis.
5. Director's Conclusions.
6. Optimal Level of Effectiveness (Criterion 4).

D. *Pathogenicity (Criterion 3)*

1. Background and Criterion.
2. Walton study.
3. Falkow study: (a) In vitro transfer; (b) In vivo transfer.
4. Questions Raised by Other Studies.
5. Director's Conclusions.

E. *Tissue Residues (Criterion 4)*

1. Background.
2. Criterion.
3. Data Submitted.
4. Director's Analysis and Conclusions.

V. EFFECTIVENESS

VI. CONCLUSION

I. THE DRUG

Name. Procaine penicillin G (benzylpenicillin) or feed grade penicillin, alone or in combination with other drugs.

Dosage form. Feed premix.

Approvals. The following companies hold or have effective approvals that are covered by this notice:

NADA 39–077; CSP 250 (chlortetracycline, sulfathiazole, and procaine penicillin); Diamond Shamrock Corp., 1100 Superior Ave., Cleveland, OH 44114.

NADA 35–688, Aureo SP–250 Feed Premix (Chlortetracycline, sulfamethazine, and procaine penicillin); American Cyanamid Co., P.O. Box 400, Princeton, NJ 08540.

NADA 46–667; Micro-Pen and Streptomycin Sulfate Premixes, (procaine penicillin G and streptomycin sulfate). Micro-Pen 6.25 and Streptomycin Sulfate 18.75, Micro-Pen and Streptomycin Sulfate 75, Micro-Pen and Streptomycin Sulfate 45, Micro-Pen and Streptomycin Sulfate 150; Elanco Products Co., Division of Eli Lilly Co., Indianapolis, IN 46206.

DESI 0072NV; Micro-Pen and MicroPen 100 (procaine penicillin G); Elanco Products Co.

NADA 35–207; Amprolium, Ethopabate and Penicillin; Merck, Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, NJ 07065.

NADA 46–598; Pro-Pen 50% Penicillin Mixture Medicated, Pro-Pen "20" Penicillin Mixture Medicated, Pro-Pen 90% Penicillin Mixture Medicated, and Pro-Pen "100" Penicillin Mixture Medicated; Merck, Sharp & Dohme Research Laboratories.

NADA 9-476; Nicarbazin, Penicillin with/or without Roxarsone; Merck, Sharp & Dohme Research Laboratories.

NADA 46-981 Pro-Strep (procaine penicillin, streptomycin sulfate); Merck, Sharp & Dohme Research Laboratories.

NADA 46-726; Streptomycin and Procaine Penicillin Premix 15+5, Streptomycin and Procaine Penicillin Premix 18.75+6.25, Streptomycin and Procaine Penicillin Premix 45+15, Streptomycin and Procaine Penicillin Premix 75+25; Pfizer, Inc., New York, NY 10017.

NADA 46-668; Penicillin Premix P-4, Penicillin Premix P-50, and Penicillin Premix P-100; Pfizer, Inc.

NADA 49-287; Chlorachel 250-Swine (chlortetracycline, sulfamethazine, and procaine penicillin G); Rachelle Laboratories, Inc., 700 Henry Ford Ave., P.O. Box 2029, Long Beach, CA 90801.

NADA 91-668; Super Chlorachel 250-Swine (chlortetracycline, sulfamethazine, and procaine penicillin G); Rachelle Laboratories, Inc.

NADA 46-666; Penicillin G Procaine for Animal Feeds 50 percent and Penicillin G Procaine for Animal Feeds 100 percent; E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540.

Under section 108(b)(2) of the Animal Drug Amendments of 1968 (Pub. L. 90-399), any approval of a new animal drug granted prior to the effective date of the amendments whether through approval of a new drug application, master file, antibiotic regulation, or food additive regulation, continues in effect until withdrawn in accordance with the provisions of section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b). Many such approvals were issued long ago, and some may never have been used by the holder of the approval. Consequently, the current files of the Food and Drug Administration (FDA) may be incomplete and may fail to reflect the existence of some approvals. Also, many approvals have been withdrawn by other agency actions, e.g., FDA's rulemaking procedure published in the FEDERAL REGISTER of February 25, 1976 (41 FR 8282). The burden of coming forward with documentation of unrecorded approvals in such circumstances is therefore properly placed on the person claiming to hold such approvals so as to permit definitive revocation or amendment of the regulations.

The Director of Bureau of Veterinary Medicine knows of no approvals affected by this notice other than those named herein. Any person who intends to assert or rely on such an approval that is not listed in this notice shall submit proof of its existence within the period allowed by this notice for opportunity to request a hearing. The failure of any person holding such an approval to submit proof of its existence within that period shall constitute a waiver of any right to assert or rely on it. In the event that proof of the existence of such an approval is presented, this notice shall also constitute a notice of opportunity for hearing with respect to that approval, based on the same grounds set forth in this notice.

Conditions of use. All uses of penicillin in penicillin and penicillin-containing combination drug products as cited in:

Sections 510.515, 558.15, 558.55, 558.58, 558.76, 558.78, 558.105, 558.145, 558.155, 558.274, 558.460, 558.530 and 558.680.

II. INTRODUCTION

A. Regulatory Background

Antibacterial drugs have been used at subtherapeutic levels (lower levels than therapeutic levels needed to cure disease) in animal feed for over 25 years. Growth benefits from this use were first observed when animals were fed the discard products from the fermentation process that was originally used in the manufacture of chlortetracycline. The precise mechanism of action, however, remains unclear.

Initially, certifiable antibiotics for use in animal feed such as penicillin were regulated under the provisions of section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357). Unlike the basic private licensing system applicable to new drugs, the provisions of section 507 created a public regulation or monograph system for regulating these products, in part because of the complexities in manufacturing the products and the lack of knowledge of their chemical structures. Antibiotic residues in food from food-producing animals were then regulated under the provisions of the act dealing with adulteration and misbranding. After enactment of the Food Additives Amendment of 1958 (Pub. L. 85-929), however, residues were principally regulated by section 409 of the act (21 U.S.C. 349), which also established a public monograph system of premarket approval. Under the antibiotic monograph procedure, the pioneer manufacturer generated and submitted the basic safety and effectiveness data in an FD Form 5 (now FD-1675). A regulation was subsequently published setting forth the standards of identity, strength, quality, and purity and the packaging and labeling requirements that the product must meet. FDA approval of the same product made by another manufacturer was then conditioned solely upon a demonstration that it met the requirements of the regulation, and this is normally accomplished by batch certification. Section 507(c) of the act (21 U.S.C. 357(c)), however, permits the agency to exempt by regulation any drug or class of drugs from the certification requirement when it concludes that certification is unnecessary for the manufacture of the drugs. Antibiotics for use in animal feeds as feed ingredients were exempted from the certification requirements in 1951 (see the FEDERAL REGISTER of April 28, 1951 (16 FR 3647)), and those for use as drugs were exempted in 1953 (see the FEDERAL REGISTER of April 22, 1953 (18 FR 2335)). These are now set out in §§ 510.510 and 510.515 (21 CFR 510.510 and 510.515).

Congress enacted the Animal Drug Amendments of 1968 (Pub. L. 90-399) and consolidated the provisions of the act dealing with the premarket approval of drugs intended for use in animals (sections 409, 505, 507) into one new section, section 512 (21 U.S.C. 360b), to regulate these articles more efficiently and effectively (Senate Committee on Labor and Public Welfare, Animal Drug Amendments of 1968, S. Rep. No. 1308, 90th Cong., 2d Sess. (1968)). This legislation also brought the manufacture of antibiotics under the private license system for new drugs (id.; Hearing on S. 1600 and H.R. 3639 Before the Subcommittee on Health of the Senate Committe on Labor and Public Welfare, 90th Cong., 2d Sess. (1968)). To efficiently accomplish this change, the amendments contained a transition clause (section 108(b)) which provided that all prior approvals continue in effect and be subject to change in accordance with the provisions of the basic act as amended. In summary, all persons legally marketing antibiotics under the provisions of sections 409, 505, and 507 of that act on August 1, 1969, the effective date of the Animal Drug Amendments of 1968, were considered as holding the equivalent of an approved new animal drug application; however, all holders of such approvals are also subject to all applicable requirements of the act and regulations.

B. Safety Concerns

In the mid-1960's, FDA became concerned about the safety to man and animals of subtherapeutic antibiotic use; it studied the effects of low-level subtherapeutic feeding of antibiotics for some years. The agency supported research, held symposia, and consulted with outside experts to review these nonmedical uses of antibiotics in animal feeds. Following a report issued by the British Government Joint Committee (the Swann Committee) "On the Use of Antibiotics in Animal Husbandry and Veterinary Medicine," the Commissioner of Food and Drugs in April 1970 established a Task Force of scientists, with consultants from government, universities, and industry, to review comprehensively the use of antibiotic drugs in animal feeds. Its conclusions were published in a notice of proposed rule making published in the FEDERAL REGISTER of February 1, 1972 (37 FR 2444), which initiated the mandatory testing procedure to resolve conclusively the issues of safety surrounding the subtherapeutic use of antibiotics in animal feeds.

The principal conclusions of the Task Force were the following: (1) The use of antibiotics and sulfonamide drugs, especially in growth promotant and subtherapeutic amounts, favors the selection and development of single and multiple antibiotic-resistant and R-plasmid-bearing bacteria;

(2) Animals that have received either subtherapeutic and/or therapeutic amounts of antibiotic and sulfonamide drugs in feeds may serve as a reservoir of antibiotic resistant pathogens and nonpathogens. These reservoirs of pathogens can produce human infections.

(3) The prevelance of multiresistant R-plasmid-bearing pathogenic and nonpathogenic bacteria in animals has increased and has been related to the use of antibiotics and sulfonamide drugs.

(4) Organisms resistant to antibacterial agents have been found on meat and meat products.

(5) There has been an increase in the prevalence of antibiotic- and sulfonamide-resistant bacteria in man.

In its report to the Commissioner, the Task Force also identified three areas of primary concern: Human health hazards, animal health hazards, and antibiotic effectiveness; and guidelines were established to show whether use of any antibiotic or antibacterial agent in animal feed presents a hazard to human and animal health.

The February 1972 proposal also announced that all currently approved subtherapeutic uses of antibiotics, nitrofurans, and sulfonamides in animal feeds would be revoked unless data were submitted to resolve conclusively the issues concerning safety to man and animals in accordance with the Task Force guidelines. That notice also proposed to establish a time table for filing commitments, conducting studies, and submitting relevant data and information. Based on the guidelines, the agency then began developing specific criteria by which safety and effectiveness of each antibiotic product might be established. The notice further suggested that protocols be submitted to the agency for comment. The criteria and studies to address them may be summarized as follows:

HUMAN AND ANIMAL HEALTH SAFETY CRITERIA

1. Transfer of drug resistance: (a) An antibacterial drug fed at subtherapeutic levels to animals must be shown not to promote increased resistance to antibacterials used in human medicine. Specifically, increased multiple resistance capable of being transferred to other bacteria in animals or man should not occur. (b) If increased transferable multiple resistance is found in coliforms, studies may be done to show whether this resistance is transferable to man.

2. The *Salmonella* reservoir: The use of antibacterial drugs at subtherapeutic levels in animal feed must be shown not to result in (a) an increase in quantity, prevalence or duration of shedding of Salmonella in medicated animals as compared to nonmedicated controls; (b) an increase in the number of antibiotic resistant Salmonella or in the spectrum of antibiotic resistance; (c) disease (caused by Salmonella or other organisms) that is more difficult to treat with either the same medication or other drugs.

3. The use of subtherapeutic levels of an antibacterial drug should not enhance the pathogenicity of bacteria, e.g., by increasing enterotoxin production. The association of toxin production characteristics with transfer factors must be investigated in well-designed studies. (Final resolution of this question was not expected within the 2-year period. Drug sponsors were expected to show evidence of work underway which would lead toward answers to this question.)

4. An antibacterial drug used at subtherapeutic levels in the feed of animals shall not result in residues in food ingested by man which may cause either increased numbers of pathogenic bacteria or an increase in the resistance of pathogens to antibacterial agents used in human medicine. Hypersensitivity to residues was to be addressed by a literature survey.

The Commissioner promulgated a final order that was published in the FEDERAL REGISTER of April 20, 1973 (38 FR 9811), and at that time the requirements imposed by the regulation became legally binding on all firms marketing antibacterial drugs used at subtherapeutic levels in feed. In the FEDERAL REGISTER of August 6, 1974 (39 FR 2839), the Commissioner proposed withdrawal of all approvals held by persons who had not complied with the initial requirements, and all these approvals were withdrawn by his order, published in the FEDERAL REGISTER of February 25, 1976 (41 FR 8282). Therefore, only those products listed in Part 558 (21 CFR Part 558) can be legally marketed at this time.

By April 20, 1974, the Bureau of Veterinary Medicine (Bureau) had begun a review of the data required by § 558.15 which was applicable to the principal antibiotics used subtherapeutically in animal feeds (penicillin and tetracycline), and by April 20, 1975, data concerning the safety and efficacy criteria for all antibiotic and sulfonamide drugs had been received. To assist the Bureau, the Commissioner asked the agency's National Advisory Food and Drug Committee (NAFDC) to review the data and issues involved and to make recommendations to him on the future uses of subtherapeutic antibiotics in animal feeds. A subcommittee of three members, the Antibiotics in Animal Feeds Subcommittee (AAFS), was appointed to work in conjunction with four expert consultants from disciplines related to the issue. The Bureau prepared 2 days' presentations concerning penicillin during which comments were heard from the drug industry, animal scientists, and other interested parties. The Bureau also prepared a comprehensive summary report with tentative recommendations for the subcommittee. (An identical procedure was carried out for the tetracyclines.) Two additional meetings were held during which subcommittee deliberations were conducted and other statements given.

In September 1976, the AAFS presented its preliminary recommendations to the parent NAFDC, and in January 1977, the subcommittee's final report was submitted to the NAFDC. The parent committee reviewed the recommendations on penicillin and accepted them. NAFDC recommended that FDA immediately withdraw approval for the subtherapeutic uses of penicillin, i.e., growth promotion/feed efficiency, and disease control.

In view of these recommendations and since the information submitted in response to § 558.15 following the guidelines and criteria had failed to resolve conclusively the issues of safety concerning subtherapeutic uses of penicillin in animal feeds, the Director of the Bureau of Veterinary Medicine is therefore proposing to withdraw approval of all subtherapeutic uses of penicillin alone and in combination with other drugs in animal feeds. Because the National Academy of Sciences/National Research Council Drug Efficacy Study Group concluded that the therapeutic use of penicillin in animal feed lacked substantial evidence of effectiveness, he is also proposing to withdraw approval of all penicillin use in animal feed.

III. SUMMARY OF THE ARGUMENT

Soon after his advisory of penicillin, Sir Arthur Fleming noted that some bacterial organisms could become resistant to the antibiotic. As the use of antibiotics has increased, the number and types of bacterial resistance have also multiplied. There is a serious concern that, in time, this will lead to declining usefulness of antibiotics in the treatment of both human and animal diseases.

The Bureau's primary concern is with that portion of increased antibiotic resistance in the ecological system which may result from the practice of using subtherapeutic levels of penicillin and other antibiotics in animal feed for prolonged periods. This practice, which sometimes produces increases in growth promotion/feed efficiency, provides an ideal environment for selective pressure to operate. When exposed to an antibiotic, the organisms that are drug resistant survive while the growth of other (drug-sensitive) bacteria is inhibited. Eventually, the antibiotic-resistant organisms predominate in the bacterial population, and continuous antibiotic pressure perpetuates this abnormal situation.

Bacterial antibiotic resistance is primarily determined by genetic elements termed "R-plasmids" (R-factors, R+). The Bureau's specific concern, therefore, is with the health hazard that may arise through an increase in the pool of R-plasmids in the animal population and the potential transfer of these R-plasmids and R-plasmid-bearing organisms to the human population and surrounding environment.

R-plasmids are small lengths of DNA that are separate from the bacterial chromosome. These R-plasmids carry transferable genes for drug resistance as well as the capacity to reproduce themselves. Plasmids may determine resistance to more than one antibiotic, and resistance to several antibiotics is common. Moreover, plasmids can transfer from one bacteria to another and from nonpathogenic to pathogenic strains. Transfer occurs, although with varying frequency among all members of the enteric bacteria and also to members of other families of bacteria. The pool of normal Gram-negative bacterial intestinal flora (largely *Escherichia coli*) serves as a reservoir of R-plasmids; the R-plasmid-bearing bacteria interchange among animals, man, and the environment. The potential for harm increases as the R-plasmid reservoir increases because the probability of R-plasmid transfer to pathogens increases. When the Commissioner required all holders of approved NADA's for the subtherapeutic use of penicillin in animal feed to submit data to resolve the safety questions raised, he was principally concerned with the effect of the antibiotics approved for subtherapeutic use in animal feed on the emergence of transferable drug resistance in the Salmonella reservoir and the *E. coli* of animals. In the Director's opinion, the results of the studies submitted and the data available are clear; the affected parties have failed to answer the safety questions raised.

Evidence demonstrates that the use of subtherapeutic levels of penicillin and other antibiotics in animal feed contributes to the increase in antibiotic resistant *E. coli* and in the subsequent transfer of this resistance to Salmonella. Further, many strains of *E. coli* and Salmonella infect both man and animals.

The holders of approved NADA's have submitted no evidence to demonstrate that the observed strains of *E. coli* and Salmonella in man and animals are mutually exclusive; in fact, the evidence is overwhelming to the contrary. Furthermore, in some cases the R-plasmids as well as the resistance genes from humans and animal sources are indistinguishable. Thus, the potential for harm exists, as illustrated by the studies submitted and verified by evidence from studies conducted by independent scientists. No evidence has been submitted by any NADA holder to resolve conclusively the safety questions raised by this potential in accordance with the requirements of § 558.15.

The holders of approved NADA's were also required to submit studies demonstrating that the subtherapeutic use of penicillin in animal feed would not compromise subsequent antibiotic therapy in man or animals, but animal studies submitted on their behalf by the Animal Health Institute to determine whether subtherapeutic penicillin use compromised subsequent therapy with related drugs were inconclusive because the studies were improperly designed. Thus, holders also failed to show conclusively that subtherapeutic penicillin use is safe in accord with that criterion.

Additionally, the NADA holders were required to prove that the subtherapeutic use of penicillin would not increase the pathogenicity of the infecting organism. They have submitted no adequate studies on the issue, and other recent evidence now suggests that the genetic determinants for toxic production may become linked with drug resistance genes. Thus, the sponsors failed to satisfy that criterion also.

No studies have ever been submitted on the issues of the safety of penicillin residues in food or the effect of long-term use on the penicillin levels needed to maintain their subtherapeutic effectiveness.

Finally, the National Academy of Sciences/National Research Council Drug Efficacy Study Group evaluated the effectiveness claims for the penicillin premixes and concluded that there was a lack of substantial evidence that the premixes were effective for their therapeutic claims. No adequate and well-controlled investigations showing that these products are effective have been submitted.

None of the specified human and animal health safety criteria have been satisfied, and the premixes lack substantial evidence of effectiveness for their therapeutic claims. For all the foregoing reasons, the Director is proposing to withdraw approval of all NADA's for the use of penicillin and combination products, e.g., chlortetracycline-sulfamethazine-penicillin, in animal feed.

IV. STUDIES RELEVANT TO HUMAN AND ANIMAL HEALTH SAFETY CRITERIA

A. *Transfer of Drug Resistance (Criterion 1). The Pool of R-Plasmid-Bearing Organisms is Increasing*

1. *Background.* One of the most important animal and human health safety criteria (number 1., set forth in II. B. above) concerns the role of subtherapeutic antibiotic use on the selection for and increase in the pool of microbial plasmids determining multiple drug resistance, and in the transfer of these plasmids among bacteria in animals and man. Resistance to antibiotics has been known as long as the antibiotics themselves have been known. Until 1959 it was believed that antibiotic resistance was a result of chance mutation and natural selection alone. However, in 1959, Japaneses investigators (Ref. 1) discovered that resistance to several common antimicrobial agents could be transferred simultaneously from one bacterium to another by cell-to-cell contact (conjugation). This was shown to be due to the transfer of extrachromosomal resistance determinants called R-plasmids, i.e., R-factors, or R+. Resistance produced by R-plasmids generally involves the production of enzymes that inactivate the antibiotic. For example, R-plasmid mediated penicillin resistance is due to the production of an enzyme, penicillinase, that inactivates the penicillin molecule. This same enzyme is also active against many semisynthetic penicillins, including ampicillin. R-plasmids may carry as many as nine drug resistance genes. The plasmids also carry other genes that determine the R-plasmid's replication, independent of the host chromosome, as well as information for transfer of the R-plasmids from one bacterium to another by conjugation. R-plasmids are transferred by conjugation to virtually all Enterobacteriaceae as well as to such unrelated Gram-negative bacteria as *Vibrio, Pseudomonas,* and *Pasteurella.* Thus, resistance may pass from strain to strain, species to species, and most importantly, from nonpathogen to pathogen. R-plasmids are now known to be the predominant cause of antibiotic resistance in Gram-negative organisms that cause human disease, e.g., *E. coli, Salmonella, Shigella,* etc.

While the development of antibiotics revolutionized the treatment of infectious disease in both man and animals, the magnitude of this achievement has been diminished by the widespread emergence of antibiotic resistant bacteria. R-plasmid mediated resistance is particularly ominous since selection of resistance to a single antibiotic may also lead to the simultaneous selection of resistance to a wide spectrum of other antibiotics. In recent years, antibiotic resistance has emerged in important pathogens; for example, in *Haemophilus, Neisseria gonorrhoeae,* and *Salmonella typhi.* R-plasmid mediated resistance has been identified in epidemics around the world, e.g., *Salmonella typhimurium.* Some of these organisms have acquired both ampicillin and chloramphenicol resistance, producing disease that will no longer respond to therapy. Hence, drug-resistant organisms have become an important concern in both human and veterinary medicine. (Ref. 2 and 3).

Because the use of antibiotics is extensive, an effort must be made to assure the future utility of these lifesaving products. In 1960, the annual production of antibiotics in the United States was 4.16 million pounds, of which 2.96 million pounds were used for therapeutic purposes in human and veterinary medicine and 1.20 million pounds in animal feed additives. By 1970, 9.6 million pounds were being used for human and veterinary medicine pharmaceuticals; for animal feed additives, 7.3 million pounds were being used. Moreover, according to "Synthetic Organic Chemicals, United States Production and Sales (1971–1975)" (U.S. International Trade Commission Publication 804), the 5-year average production for 1971 through 1975 was 11.16 million pounds for medicinal uses and 7.68 million pounds for nonmedicinal uses, including feed additive uses. Over those 5 years, the aggregate average of the total production for those nonmedicinal uses was 40.8 percent—but 43.6 percent in 1975. Thus the use of antibiotics in animal feeds is a considerable element in the overall use of antibiotics in this country and consequently must be considered a potentially significant contributor to the resistance problem.

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2. *Criterion.* The FDA Task Force concluded that a human health hazard exists if the subtherapeutic use of antibiotics in animal feeds leads to an increase in R-plasmid-bearing organisms, if these antibiotics used subtherapeutically are also used in human clinical medicine, and if R-plasmids subsequently appear in bacteria in man. It was the intent of the Task Force as well as the intent of § 558.15 to reduce the total load of resistant organisms in the environment and to ensure the effectiveness of antibiotics in the treatment of disease in man and animals. Accordingly, § 558.15 required the following:

An antibacterial drug fed to animals shall not promote an increase of coliforms that are resistant to antibacterial drugs used in human clinical medicine and capable of transferring this resistance to bacteria indigenous to the intestinal tract of man. Studies must be undertaken to assess the occurrence and significance of these events:

a. Controlled studies shall be undertaken to determine whether or not the administration of an antibacterial drug at low and/or intermediate levels to target animals results in an increase in the numbers of coliforms bearing R-

plasmids present in the intestinal tract of the animal or a change in the resistance spectrum of these organisms compared to those found in controls receiving no antibacterial drug. The resistance spectrum must be determined to ascertain whether or not there are determinants present for resistance to antibacterial drugs used in human clinical medicine.

b. If the resistance determinants indicated in a. are found, a sponsor may elect to conduct additional studies to determine if such multiple drug resistance is transferable to the indigenous coliforms in the intestinal tract of man.

In addition to the FDA Task Force, many other scientists were concerned that the use of antibiotics at subtherapeutic levels in feed might lead to the development of R-plasmid-bearing organisms in food animals, which might then spread to man. The normal enteric organisms that can serve as this reservoir are the coliforms, in particular *E. coli*. These *E. coli* can donate the R-plasmids to other bacteria, including pathogens, e.g., pathogenic *E. coli*, *Salmonella*, etc.

3. *Studies Relevant to Transfer of Drug Resistance*—(a) *R-plasmid-bearing E. coli develop in domestic animals that are fed subtherapeutic levels of antibiotics, including penicillin.* Many investigators have reported the presence of R-plasmid-bearing *E. coli* in domestic animals such as chickens, swine and cattle. The influence of antibiotic-supplemented feed in increasing the number of resistant organisms has been extensively documented. Mercer et al. (Ref. 1) showed that 394 of 491 isolates (80 percent) from animals exposed to antibiotics in feed, including penicillin, were resistant strains, and in contrast, only 14 of 64 isolates (21.9 percent) obtained from animals not exposed to antibiotics in feed were resistant strains. Mercer also reported that plasmid-mediated ampicillin resistance occurred more frequently in animals that were exposed to subtherapeutic levels of penicillin in their feed than in nonmedicated animals. Seigel et al. (Ref. 2) Smith and Tucker (Ref. 3), Katz et al. (Ref. 4), and others have also shown that the addition of penicillins to feed at subtherapeutic levels causes a significant increase in the R-plasmid-bearing coliform population of the intestinal flora of animals. Even the data submitted by the drug industry on the effect of subtherapeutic use of penicillin on the *E. coli* flora of poultry, which will be discussed in depth in part IV. B. 3. below, also show an increase in drug-resistant *E. coli*.

Accordingly, the Director has concluded that subtherapeutic use of penicillin in animal feed produces a high level of antibiotic resistant *E. coli* and that the subtherapeutic use of penicillin selects for R-plasmid-containing bacteria in animals (human health criteria 1.(a) set forth in II. B. above), i.e., the antibiotic pressure of subtherapeutic penicillin use allows microbial R-plasmid-containing populations to predominate. These populations appear to be stable and persistent, even in the absence of penicillin pressure. Once the reservoir of R-plasmids develops, the initial cause of the R-plasmid buildup, whether the subtherapeutic use of penicillin or another drug (or drug combinations), is irrelevant to the R-plasmids' transferability or movement from animals to humans. Therefore, all studies on the movement of R-plasmids and resistant bacteria are germane to this issue even though penicillin was not always used as the specific antibiotic.

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(b) *E. coli contribute their R-plasmids to man through several mechanisms.* There has been much debate over the extent to which *E. coli* in the animal community act as a source of R-plasmid-bearing strains for man. This is perhaps the most controversial and most difficult aspect of R-plasmid ecology to assess. Drug-resistant bacteria originating in animals may reach man (1) by direct contact with animals, (2) through the food chain, and (3) because of their widespread occurrence in the environment.

(i) Direct contact with animals: A number of studies have shown that humans in contact with animals receiving medicated feed, including subtherapeutic levels of penicillin, have a higher incidence of drug-resistant organisms in their flora than do control populations without this direct contact. Linton et al. (Ref. 1) found a higher incidence of drug-resistant *E. coli* in adults employed with livestock husbandry than other rural or urban adults. Wells and James (Ref. 2) found a higher incidence of drug-resistant *E. coli* in humans in contact with pigs given certain antibiotics than in humans in contact with pigs that had not been given antibiotics.

Seigel et al. (Ref. 3) compared the proportion of resistant organisms in fecal samples from: (*a*) people working on farms who were continuously in contact with the predominantly resistant flora of animals receiving subtherapeutic levels of penicillin; (*b*) people residing on the same farms with no direct exposure to the farm animals; (*c*) people treated with antibacterial drugs; (*d*) untreated people residing with treated individuals; (*e*) untreated people with no exposure to farm animals or treated individuals.

The data (Ref. 3) indicate that the enteric flora of individuals not directly exposed to the selective effects of antibiotics can be affected by contact with animals; furthermore, these individuals may be affected by contact with other people who have a predominantly resistant flora as a result of their exposure to subtherapeutic levels of antibacterials in feeds.

A study sponsored by the Animal Health Institute, Levy et al. (Ref. 4), examined the change in intestinal microflora of chickens, farm dwellers, and their neighbors before and after a tetracycline-supplemented feed was introduced on the farm. Within 1 week after introduction of this antibiotic in their diet, the *E. coli* of the chickens were almost entirely tetracycline resistant. Subsequently, at a slower rate, increased numbers of antibiotic-resistant bacteria appeared in the flora of the farm dwellers. No such increase was observed in the farm neighbors, who were not exposed to the animals fed subtherapeutic antibiotics. Within 5 to 6 months, 31.3 percent of weekly fecal samples from farm dwellers contained greater than 80 percent tetracycline-resistant bacteria compared to 6.8 percent of the samples from the neighbors. This is statistically significant ($P<0.001$). Using a specially marked resistance gene to identify a particular plasmid, Levy was also able to demonstrate the direct spread of resistant organisms from chickens to chickens and from chickens to man (Ref. 5).

Although penicillin was not used in this study, resistance to both penicillin and tetracycline is plasmid mediated; therefore, the study is germane to the question of the transfer of resistant organisms from animals to man. These studies demonstrate that the subtherapeutic use of certain antibiotics increases the pool of R-plasmid-bearing *E. coli*, and they define one route by which antibiotic-resistant strains can enter the human population. While this route is of great importance to farm dwellers, the majority of the population has no contact with live animals. For this segment of individuals, a more important route of exposure by which resistant bacteria can pass to man is by the handling and ingestion of meat and poultry products contaminated with R-plasmid-bearing *E. coli* of animal origin.

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(ii) Contact with *E. coli*-contaminated food: To assess adequately the significance of the problem of human food contaminated with *E. coli*, Howe and Linton (Ref. 1) described four factors that must be measured: (*a*) The incidence of R-plasmid-bearing *E. coli* in food-producing animals; (*b*) the load and frequency of excretion of *E. coli* from these animals; (*c*) the degree and source of contamination of carcasses at slaughter; and (*d*) the overlap of *E. coli* serotypes in various host animals with those commonly found in humans. A number of surveys have clearly documented that pigs, calves, and poultry carry a large reservoir of antibiotic-resistant *E. coli*. These include investigations by Anderson; Loken; Mercer; Smith; Howe, Linton and Osborne; Smith and Crabb (Refs. 2 through 8, and 15). In these surveys, animals excrete large numbers of *E. coli* organisms resistant to a wide range of clinically useful antibiotics, and these animals clearly constitute a reservoir "rich" in R-plasmids. Moreover, they excrete a large variety of distinct serotypes of *E. coli*.

During the slaughtering process, contamination of carcasses with intestinal microorganisms cannot be prevented. Meat and meat products are often contaminated with antibiotic-resistant *E. coli*, and these often reach the human consumer. Walton (Ref. 9) demonstrated that 52 percent of the bovine (beef) and 83 percent of porcine (pork) carcasses slaughtered at commercial abattoirs were contaminated with *E. coli*. Walton and Lewis (Ref. 10) isolated resistant *E. coli* from 21 of 50 specimens of fresh meat and from 4 of 50 specimens of cooked meat. Babcock et al. (Ref. 11) isolated multiresistant *E. coli* from 80 percent of 98 samples of dressed beef. Resistance in most cases was found to be transmissible.

Similar incidents of *E. coli* contamination occur with the slaughter of chickens. Kim and Stephens (Ref. 12) found a high incidence of R-plasmid-bearing *E. coli* in "ready to cook" broiler chickens. The greatest number of *E. coli* isolated were obtained from the fluid and abdominal cavity, suggesting that the principal source of these microorganisms is the intestines. Furthermore, poultry meat has been incriminated as a source of *E. coli* for patients in hospitals (Cooke et al., and Shooter et al. (Refs. 14 and 18)).

The presence of antibiotic-resistant (R-plasmid-bearing) *E. coli* in the animal intestinal tract and on the carcass does not conclusively prove that the *E. coli* are identical organisms. However, recent studies using serotyping methods have characterized resistant and sensitive *E. coli* isloated from the animal intestinal tract and carcass (Refs. 13, 15, 16, and 17) and have found that the resistant O-serotypes on the carcasses of pigs, calves, and poultry frequently are identical to those isolated from the fecal contents of the same animal. Moreover, Linton, Howe, et al. (Ref. 17) showed that a large number of *E. coli* found on table-ready thawed chickens were resistant to therapeutically important antibiotics. The organisms reaching the kitchen included a wide diversity of O-serotypes of antibiotic-resistant *E. coli*. Similarly, Shooter et al. (Ref. 13) described the distribution and serotype of strains of *E. coli* from a poultry packing station and an abattoir. Shooter concluded that "results in both the abattoir and the poultry packing station indiacte that there is transfer of strains from the faeces of the animals to the environment and that the strains of *E. coli* found on the carcasses of poultry, cattle and beef will originate from the feces of the animal and from the environment and will reffect the history of the carcass."

Foodborne *Salmonella* infections in man are a well-recognized and continuing problem. Animal meat products that serve as a primary source of *Salmonella* infections in humans also serve as a source of other bacteria for man including R-plasmid-bearing enteric bacteria (Ref. 19). Based on this evidence, the Director must conclude that man is exposed to R-plasmid-bearing intestinal bacteria through contact with contaminated food. Because the drug resistance of these bacteria is increased by feeding the animals subtherapeutic levels of antibiotics, such feeding enhances the likelihood of transmitting R-factor-bearing bacteria to man through contact with contaminated food.

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(iii) Widespread presence in the environment: Many studies (Ref. 1 through 6) have shown that intestinal bacteria (*e.g.*, *E. coli* and *Salmonella*) carrying R-plasmids are widespread in the environment. Resistant strains reach the environment from raw and treated municipal, hospital, and animal wastes. The number of R-plasmid-bearing bacteria reported in sewage and the effects of sewage treatment vary. Most surveys indicate that hospital sewage contains more drug-resistant coliforms, more R-plasmids, and a greater proportion of R-plasmids carrying multiple resistance than sewage from domestic and other sources. However, hospitals do not constitute a large proportion of total sewage. Therefore, Linton et al. (Ref. 4) compared the contributions of hospital and domestic sources to the total pooled sewage output of the city of Bristol, and they concluded that industrial and domestic sources, rather than the hospital population, appear to be by far the greatest contributors to the reservoir of R-plasmids in the community (Ref. 7).

R-plasmid-containing bacteria also occur in rivers and sea water, and some authors have urged stricter control of discharges to surface waters. Feary et al. (Ref. 2) examined the incidence of antibiotic-resistant *E. coli* present at sites along a fresh water river system and within the salt water bay into which it empties. Antibiotic-resistant coliforms were detected in nearly all the fresh water sites sampled and in about 50 percent of the salt water sites. Feary found that 20 percent of the 194 strains tested contained R-plasmids carrying multiple antibiotic resistance which could be transferred to sensitive *Salmonella typhimurium, Shigella dysenteriae,* and *E. coli.* They also isolated coliforms containing R-plasmid carrying resistance to chloramphenicol. Transferable chloramphenicol resistance is a significant health concern since chloramphenicol is often the antibiotic of choice for the treatment of typhoid fever. In Feary's study, the incidence of coliform organisms appeared higher around heavily populated areas, but coliforms were also recovered with ease from rural areas. In one case where particularly high counts were obtained, the sample was taken below a large cattle feedlot.

The high levels of resistant coliforms may be of more consequences in the salt water since certain sections are utilized heavily by fishermen in harvesting fish, shrimp, clams, and oysters. Oysters and clams are of primary concern because they continuously filter water and concentrate bacteria in their gut and they are often eaten uncooked.

Recent reports by Cooke (Ref. 1) have also described a high incidence of resistant coliforms in marine shellfish and freshwater mussels.

Therefore, the Director must conclude that the environment is heavily contaminated with bacteria containing transferable R-plasmids. Man is exposed to the danger of acquiring R-plasmid-bearing coliforms from the environment, and the relative number of R-plasmid-bearing bacteria is increased both by the subtherapeutic use of antibiotics in animal husbandry and the use of antibiotics in human medicine. Antibiotic-resistant bacteria are now so widely distributed in the general environment that it is difficult to relate their appearance to a particular use, but any unnecessary practice that results in the ineffectiveness of antibiotics for the treatment of disease should be eliminated.

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(c) *R-plasmid-bearing human and animal strains of bacteria overlap.* Typing of surface bacterial antigens is used as a means of identifying bacterial strains. Three types of specific surface antigens are associated with the *E. coli* cell: An "O" cell wall lipopolysaccharide antigen, a "K" capsular or envelope antigen, and an "H" flagellar protein antigen which occurs among mobile organisms. The antigens are characteristic of a specific organism, and they serve to identify distinct bacterial types (serotypes) within species. Their presence is detected by the ability of *E. coli* organisms to interact with specific antiserums.

(1) Epidemiological investigations—*E. coli* serotyping: (*a*) Despite the widespread occurrence of R-plasmids in the environment, some workers (Bettelheim et al., Ref. 1) suggested that human *E. coli* and animal *E. coli* were distinct. These workers argued that there were marked differences in serotype distribution in strains isolated from man and animals; they also suggested than animal strains of *E. coli* were not reaching the human population or were failing to implant in the bowel. More recently, however, this same group, Bettelheim et al. (Ref. 2), compared the serotypes of 13,139 strains of *E. coli* isolated from humans with the serotypes of 1,076 animal strains of *E. coli;* 708 different O/H serotype combinations were found. Of these, 520 were found in human strains only, 130 from animal strains only, and 58 O/H serotypes from humans and animals. The authors concluded:

> At first glance the results described in this paper would indeed support the view that human and animal strains of *E. coli* are largely distinct. Second thoughts, however, suggest a little caution in accepting the opinion too firmly.
>
> However thoroughly human or animal stools are examined, only a minute fraction of the total bacterial content is examined, and inevitably strains recorded as being isolated tend to be those that predominate. It is always probable that if examination is continued, further strains may be isolated but after an amount of work that is impracticable in any ordinary investigation. If this is so, it is possible that many of the strains recorded as coming from humans only or from animals only might, with more diligent examination, be recorded as present in both man and animals.

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(*b*) Linton, Howe, Richmond, and their collaborators (Refs. 1 through 4) also conducted extensive epidemiological investigations. They found a wide range of resistant and sensitive O-serotypes of *E. coli* in calves, pigs, and poultry, and they compared these serotypes with those found in the human intestine. The authors found that many O-serotypes common to man were also common to one or more of the three animal species examined. Thus, they concluded that it is impossible to make a clear distinction between "animal" and "human" intestinal strains of antibiotic-resistant *E. coli* based on O-serotyping alone. More importantly, the studies suggest a considerable overlap in the distribution of R-plasmid-bearing O-serotypes in man and in animals. Moreover, the same resistant serotypes, which predominate in the *E. coli* populations from healthy human and animal fecal sources, were also prevalent among R-plasmid-bearing strains from clinical material (Ref. 5).

Because the use of O-serotyping alone as an epidemiological tool has been criticized on the grounds that it is incomplete and inadequate, Howe and Linton (Ref. 2) examined *E. coli* for the K and H antigens as well as the O antigen. They studied 90 strains, 17 chosen at random from human urinary tract infections, 17 from human feces, and 56 from calf feces, all belonging to O-types 8, 9, and 101. The authors found the same K and H antigens in certain strains of the same O-types from each of the three *E. coli* sources. Additionally, K and H antigens associated with these O-serotypes were not specific to antigens associated with these O-serotypes were not specific to *E. coli* isolated from humans or from calves. Although further subdivision of the three O-serotypes was possible by this means, the authors concluded that O-serotyping alone provided a very useful means of distinguishing strains of *E. coli* in a general survey.

These studies show that a similar range of drug-resistant R-plasmid-bearing O-serotypes of *E. coli* have been found in man and the various animal species examined. Furthermore, the studies show that the ratio of drug-resistant to drug-sensitive isolates was much higher in animals than in man (Ref. 2 and 6). Thus the abundance and diversity of drug-resistant R-plasmid-bearing O-serotypes in animals are much greater than that currently found in man, and the serotypes overlap.

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(ii) Direct ingestion evidence: Direct ingestion experiments have also been conducted to show that R-plasmid-bearing *E. coli* of farm origin can colonize the human intestinal tract. In 1969, Smith (Ref. 1) concluded that animal *E. coli* strains were poorer at colonizing the intestine of man than were human *E. coli* strains. However, his observations were based on a single volunteer (himself) and a small number of *E. Coli* strains. Cooke in 1972 (Ref. 2), on the other hand, reported that it was relatively easy to produce temporary colonization of the intestine by *E. coli* strains from both human and animal sources. She reported the persistence of an *E. coli* infection of animal origin in a human volunteer for 120 days following the ingestion of a very large dose.

Other experimental studies (Refs. 3 and 4) confirm that temporary colonization occurs provided a large dose of the organisms is taken, but there is a great deal of biological variation between colonization for different strains and for different human individuals. In normal individuals the carriage of intestinal *E. coli* seems to follow a characteristic pattern. Each person carries one or two resident strains that establish themselves and multiply for months or years. In addition, four or more transient strains are present for a few days or weeks. Strains disappear and are replaced by others. Sometimes, under antibiotic pressure, a new strain suddenly takes over, later disappearing. Strains of *E. coli* thus differ in their ability to colonize man. Although some strains are not well adapted to colonize man, others are able to live in human as well as in animal intestines. The greater the diversity of R-plasmid-bearing O-serotypes that reach the consumer, the greater the probability that one more of these antibiotic-resistant strains will be capable of colonizing man.

Recently, Linton, Howe, Bennet, et al. (Ref. 5) demonstrated that antibiotic-resistant *E. coli* found on a commercially prepared chicken carcass colonized the intestinal tract of a human volunteer. Two strains present on the chicken carcass handled and eaten by the human volunteer were subsequently excreted by her. Both strains were undetectable in the human before contact with the chicken carcass. The strains were shown to be identical in chicken and man by comparing their serotypes (O, K, and H antigens) and R-plasmids. The plasmid complements were determined to be identical by electron microscopy and restriction endonuclease patterns. Restriction endonucleases are enzymes that cleave DNA at specific sites. Physiochemical techniques then visualize these plasmid fragments. The identity of these plasmids can be determined by a comparison of the DNA fragments generated using restriction enzymes with different recognition sequences. The Linton study also suggested that the handling of the uncooked carcass provided a greater opportunity for transmission than does eating cooked meat. The strains persisted for 10 days and the process occurred without feeding any antibiotics to the volunteer during the study. This is consistent with reports of Salmonella infections from animal sources.

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(iii) In vivo studies show that R-plasmids transfer from *E. coli* to pathogens: The ingestion of R-plasmid-containing bacteria can result in in vivo R-plasmid transfer to the normal intestinal flora. When this occurs, the *E. coli* constitute a reservoir of organisms capable of transferring R-plasmids to intestinal pathogens, e.g., Salmonella. The in vivo transfer of R-plasmids has been demonstrated in sheep, mice, calves, pigs, chickens, turkeys, and in the human alimentary tract (Refs. 1 through 8). Generally, in vivo transfer is not as readily detectable as in vitro transfer. In the absence of drug selection, the rate of in vivo R-factor transfer is generally low, and large numbers of resistant donors may be required for transfer (Refs. 1 and 6). Demonstrations of in vivo transfer have usually been achieved by first modifying the normal flora of the alimentary tract by feeding antibiotics, by starvation, or by using germ-free mice or newly hatched chicks, and these procedures probably counteract the inhibitory effects of bile salts, fatty acids, acid pH, and anaerobic conditions of the normal intestinal tract.

These experimental results may not be a true indication of the extent of R-plasmid transfer in natural populations since they often involve individuals who are exposed to restricted numbers and types of donor and recipient organisms. In some instances the methods were not suitable for the detection of low level transfer. However, Smith and Tucker (Ref. 9) studied the effect of antibiotic therapy on the fecal excretion of Salmonella by experimentally infected chickens. The authors found that R-plasmid resistance developed in the indigenous *E. coli* and that very similar resistance patterns then developed in the Salmonella. These results were duplicated in some of the studies submitted by the Animal Health Institute, which are also discussed in depth under Part IV, B. below.

Regardless of the frequency with which R-plasmid transfer occurs in the absence of modifying influences, it has occurred and given rise to antibiotic resistance in bacteria, including pathogens. The conditions of the Smith and Tucker studies mimic those brought about by the practice of feeding subtherapeutic levels of penicillin and other antibiotics to animals. That practice leads to an increase in and selection for R-plasmid-bearing organisms, and it therefore increases the probability of in vivo R-plasmid transfer to pathogens.

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(iv) R-plasmid compatibility studies: Another FDA study (Ref. 1) examined the compatibility properties of more than 100 R-plasmids from *E. coli* and *Salmonella* isolated from animals in or-

der to determine whether the plasmids are related to those isolated from man. The usual method of genetically classifying plasmids is based on their ability to exist with each other in the same bacterium. Genetically unrelated plasmids can exist in the same host, and they are called compatible. On the other hand, related plasmids cannot coexist, and they are called incompatible. Plasmids belonging to the same incompatability group are presumed to be related.

The FDA study showed that the R-plasmid incompatibility groups seen in animal isolates show the same distribution as those found in human isolates. This suggests that human and animal bacterial populations contain the same plasmids.

A more direct approach for examining the relationships between plasmids is to measure the proportion of DNA sequences (that is, the number of similar or identical genes) that are common to any two plasmids (DNA–DNA hybridization). R-plasmids belonging to the same incompatibility groups of human and animal origin are identical when examined by DNA–DNA hybridization techniques (Refs. 2 and 3). Restriction endonuclease activity has also confirmed the similarity of R-plasmids isolated from enteric organisms of human and animal sources (Ref 4). Therefore, the Director must conclude that R-plasmids of human origin are indistinguishable from those of animal origin.

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(v) Hazards: Although antibiotic-resistant *E. coli* in the intestinal tract of humans may generally cause no immediate problems to an individual, under proper circumstances their presence may lead to dangerous situations. For example, *E. coli* is the most common cause of urinary tract infections in man and commonly arises from a person's own intestinal flora. While sulfonamides are generally the drug of choice, a significant number of infections with sulfonamide-resistant strains are now reported, necessitating treatment with penicillin.

Resistant *E. coli* in the intestine of man also constitute a reservoir of organisms capable of transferring R-plasmids to intestinal pathogens. Perhaps the greatest hazard to human health arising from the use and misuse of antibiotics is the large reservoir of plasmid-mediated resistance genes in the normal flora of animals and man and present in the environment—resistance that can be transferred from nonpathogenic to pathogenic organisms.

In recent years the emergence of R-plasmid-mediated resistance in dangerous pathogens has been identified in epidemics around the world. A strain of *Salmonella typhi* carrying an R-plasmid-mediating resistance to chloramphenicol caused an epidemic of typhoid fever in Mexico. Transferable chloramphenicol resistance has also become common in *S. typhi* isolated in India, Vietnam, and Thailand (Ref. 1). The recent epidemic of drug-resistant *Shigella dysenteria* infection in Central America (Ref. 2) is another example of an epidemic disease that was no longer susceptible to treatment by the antibiotics that had previously been used for its treatment. Plasmid-mediated resistance has been reported in strains of *Bordetella bronchiseptica* (Ref. 3), and FDA scientists have demonstrated plasmid-mediated resistance to penicillin, tetracycline, streptomycin, and sulfonamide in strains of *Pasteurella multocida* and *P. haemolytica*, both of which cause serious diseases in animals (Refs. 3 and 4).

Recent studies (Refs. 5 through 12) have also shown that the genes specifying resistance to ampicillin, tetracycline, kanamycin, chloramphenicol, trimethoprim, and streptomycin reside on DNA sequences that are able to translate or move from plasmid to plasmid as a discrete unit, or from a plasmid to the bacterial chromosome. Therefore, in addition to movement of resistant bacteria from animals to man and the transfer of R-plasmids between bacteria, the genes that reside on the plasmids can themselves migrate from plasmid to plasmid by translocation. Furthermore, an R-plasmid does not have to be maintained stably within a cell to donate its resistant genes to a recipient chromosome or an indigenous plasmid.

Most bacterial species possess indigenous plasmid gene pools. In fact, plasmids have been found in all species of bacteria examined. The function of these plasmids is often unknown, but they could serve as effective recipients for the insertion of translocatable genes. The recent emergence of ampicillin-resistant strains of *Haemophilus influenzae* and penicillin-resistant strains of *Neisseria gonorrheae* represent alarming examples of the extension of the R-plasmid gene pool (Refs. 13 and 14). The resistance genes found in both species are identical to those previously found only in *E. coli* and other enteric organisms.

The World Health Organization prophetically warned (Ref. 15):

> The point will ultimately be reached at which the transfer of resistance to pathogens becomes inevitable and the larger the pool, the greater is this possibility. Moreover, the wide the distribution of R+ (R-factor) enterobacteria the greater the possibility that R-plasmids may emerge that can cross biological barriers so that they can perhaps enter bacterial species and genera apparently widely different from their original enterobacterial hosts.

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4. *Director's conclusions.* The holders of the approved NADA's for subtherapeutic penicillin-containing products were required to show that the subtherapeutic use of penicillin does not increase drug resistance (increase the pool of R-plasmid-bearing) organisms in animals. If they were unable to show that subtherapeutic penicillin use does not increase the pool of R-plasmid-bearing organisms in animals, the holders were then required to show that the R-plas-

mids are not transferable from animals to man. They failed to do any of this.

The evidence shows that the pool of R-plasmid-bearing organisms, particularly in *E. coli*, is increasing, and that the increase is due at least in part to the subtherapeutic use of penicillin in animal feed. Further evidence shows that *E. coli* contribute their R-plasmids to man through his direct contact with animals, through his direct contact with *E. coli*-contaminated food, and by widespread presence of the R-plasmids in bacteria in the environment. Studies also show that there is no strict distinction between the *E. coli* that colonize animals and those that infect man. On the contrary, there is considerable overlap in these strains, and there is also an overlap in the enteric bacterial R-plasmid population in humans and animals. This evidence is derived from epidemiology studies, bacterial ingestion studies, and compatibility studies of the normal intestinal flora of man and animals. These bacteria may donate their R-plasmid to pathogens in man and animals even when transient, and the NADA holders have submitted no evidence on the degree of colonization, if any, that is necessary for this transfer to occur. Accordingly, the Director concludes that the holders of the approvals for the subtherapeutic penicillin-containing products for use in animal feeds have failed to satisfy the requirements of § 558.15 and criterion 1 of this notice.

B. Shedding and Resistance Characteristics of Salmonella (Criterion 2)

1. *Background.* A second area of concern, related to the increase in the pool of R-plasmid-bearing bacteria, is the possibility that the subtherapeutic use of antibiotics in animal feeds may lead to an increase in the duration or quantity of live *Salmonella* excreted by the animal receiving the drug(s), which will increase contamination of the environment with pathogens. This concern was generated in part by reports that antibiotic therapy in human salmonellosis patients had resulted in prolonged *Salmonella* shedding and favored the acquisition of resistence in *Salmonella*.

Aserkoff and Bennett (Ref. below), for example, presented data on the effect of antibiotic therapy on the excretion of *Salmonella* in the feces of human infected with acute salmonellosis. Following a large *S. typhimurium* epidemic caused by eating contaminated chicken, feces of untreated patients and patients treated with tetracycline, ampicillin, and chloramphenicol were examined for *Salmonella*, and the antibiotic susceptibility of the *S. typhimurium* strains was determined. Patients generally received the recommended regimen of antibiotic therapy (1 gram per day). Fecal samples from 87 patients not receiving medication and 185 patients treated with antibiotics were examined. Of the patients treated with antibiotics, 65 percent were shedding *Salmonella* 12 days after infection, and 27 percent were positive 31 days after infection. In the untreated patients, however, *Salmonella* shedding was observed in 42.5 percent at day 12 and 11.5 percent at day 31.

Antibiotic therapy also favored the acquisition of drug resistance by the infecting strain of *Salmonella*, which was initially susceptible to antibiotics. Of the patients receiving antibotics, 18 excreted resistant *Salmonella*, while none of the 87 untreated patients excreted resistant *Salmonella* ($P<.05$). The antibiotic resistance acquired in the *Salmonella* strain was shown to be transferable. Because antibiotic treatment increased shedding in human salmonellosis, FDA became concerned that subtherapeutic antibiotic, penecillin) administration in animal feeds would prolong *Salmonella* shedding in animals, and for this reason the agency established criterion 2.

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Aserkoff, B., and J. V. Bennett, "(Effect of Antibiotic Therapy in Acute Salmonellosis on the Fecal Excretion of Salmonella," New England Journal of Medicine, 281:636-640, 1969.

2. *Criterion*—(a) *Shedding.* Controlled studies were to be designed to determine whether the administration of an antibacterial drug at subtherapeutic levels would result in an increase in the relative quantity, prevalence, or duration of shedding of *Salmonella* that are pathogens in animals. *Salmonella* are often found in the intestinal tract of man and animals, and the small intestine and colon are the primary sites of multiplication. After penetrating the epithelial lining, they multiply and elicit an inflammatory response. Most *Salmonella* infections are limited to the gastrointestinal tract, producing the clinical symptom termed "gastroenteritis." One of the more common strains, *Salmonella typhimurium*, causes diseases in both man and animals.

When an animal is infected with these bacteria, the live organisms are excreted in the feces ("shedding"). The quantity of *Salmonella* in the feces can be determined by a bacteriological procedure termed a "standard plate count." A specific amount of fecal material is diluted and spread on a semisolid bacterial growth medium which is selective for the growth of *Salmonella*. After a sufficient time for growth, individual colonies are counted and recorded as the number of *Salmonella* per gram of wet feces. The proportion of antibiotic resistant *Salmonella* in fecal specimens is independent of the quantity of Salmonella shed.

(b) *Resistance characteristics.* Controlled studies were to bedesigned to determine whether the administration of penicillin at subtherapeutic levels would result in an increase in the proportion of antibiotic resistant *Salmonella*. *Salmonella* isolated from feces can be tested for their susceptibility to various antibiotic drugs. *Escherichia coli*, a normal component of the intestinal flora, were also to be examined to determine their resistance spectrum sinffice oral administration of certain antibiotics, whether at therapeutic or subtherapeutic levels, has been shown to result in an increased proportion of indigenous *E. coli* that contains R-plasmids. These *E. coli* can serve as a reservoir of R-plasmids that can be transferable to other *E. coli* or to *Salmonella*.

3. *AHI Studies on the Effects of Subtherapeutic Levels of Penicillin in Animal Feed in Chickens.* On behalf of the NADA holders, the Animal Health Institute submitted the following study to address the criterion.

(a) *Experimental design.* The Animal Health Institute submitted an experiment in which the effects of subtherapeutic levels of procaine penicillin (with or without streptomycin) in feed were investigated. The duration, quantity and antibiotic susceptibility of a *Salmonella* strain inoculated into chickens were compared in medicated and nonmedicated chickens.

Also, FDA specified that prestudy (baseline) *E. coli* antibiotic resistance levels should be under 20 percent. This value was thought to provide a reasonable level for detecting any change in the amount of antibiotic resistance resulting from administration of subtherapeutic antibiotic levels since, if the initial R-plasmid level is too high, a small change in resistance is difficult to detect.

While others served as environmental controls, 1-day-old chicks were divided into six groups, artificially infected with *Salmonella*. Each group received medicated or nonmedicated diet, according to the following plan:

Room	Group	Inoculation of salmonella 1.6×10^{10}	Antibiotics and levels used in feed	Number of chickens in experimental group
1	A	Yes	None	10
2	B[1]	Yes	Procaine penicillin 50 g/ton	10
	B[2]	Yes	Procaine penicillin 12.5 g/ton, streptomycin 37.5 g/ton	10
3	C	No[1]	None	5
	D[1]	No[1]	Procaine penicillin 50 g/ton	5
	D[2]	No[1]	Procaine penicillin 12.5 g/ton, streptomycin 37.5 g/ton	5

[1] Environmental controls.

Groups A and B were used to determine the influence of penicillin or penicillin-streptomycin on shedding after experimental infection and the development of drug resistance by *Salmonella* and *E. coli*, with group A serving as a nonmedicated control group. Groups C and D were controls used to monitor the environment, and the effects of the drugs in the absence of experimental infection. To assure the absence of naturally occurring Salmonella prior to the study, the sponsors examined prestudy fecal samples. The samples were grown in a selective media, brilliant green agar, and serotyping was also done. By

this procedure, the birds were determined to be negative for Salmonella before the experiment began, and any bacteria suspected were further tested biochemically and serologically.

The infecting *Salmonella* (*S. typhimurium* 289–1, a poultry strain, chromosomally resistant to nalidixic acid and sulfonamides) was given by oral gavage. Fecal specimens from each chicken were diluted in phosphate buffered saline and appropriate dilutions were spread on growth medium selective for the nalidixic acid-resistant *S. typhimurium* used to infect the birds. The number of Salmonella growing on the medium was recorded as the number of *S. typhimurium* per gram of wet feces.

Presumptive *E. coli* isolates were obtained from EMB plates inoculated with diluted fecal material. The antibiotic resistance spectrum for *E. coli* isolates was also measured in accordance with the Standardized Disc Susceptibility Test set forth in § 460.1(c)(2) (21 CFR 460.1(c)(2)) for ampicillin, tetracycline, chloramphenicol, kanamycin, nitrofurantoin, streptomycin, sulfathiazole, and triple sulfa. The *E. coli* isolates were tested only twice prior to infections and once at the termination of the study (28 days), while the Salmonella isolates were tested nine times during the study.

Salmonella isolates were selected from the selective medium, brilliant green agar plates containing nalidixic acid, and were serotyped. Antibacterial susceptibility tests for ampicillin, tetracycline, chloramphenicol, kanamycin, nitrofurantoin, streptomycin, sulfathiazole, and triple sulfa were carried out in accordance with the Standardized Disc Susceptibility Test in § 460.1(c)(2). The isolates were tested on days 2, 4, 6, 8, 10, 13, 14, 21, and 28 of the experiment.

Clinical records were maintained on body weights, disease symptoms, mortality, and gross and microscopic pathology.

(b) *AHI's summary of the results.* (i) Shedding: Initially, on day 2, group B_1 (penicillin 50 grams/ton) shed a geometric mean number of 10^6 Salmonella per gram of feces; and during the remainder of the study, the geometric mean shed by the group decreased steadily. At the end of the study, the number shed was below the reliable limit of quantitation, less than 10^2 organisms per gram of feces. Group A, the nonmedicated control group, on the other hand, shed 10^7 organisms on day 2, and continued to shed a greater number of organisms than the treatment group ($P < .05$) throughout the remainder of the study. None of the environmental control groups, groups C and D_{1-2} shed detectable amounts of Salmonella.

The prevalence of *S. typhimurium* was estimated by comparing the fraction of Salmonella positive fecal samples in the penicillin treatment group (group B_1) to that for the nonmedicated control group (group A) from all samplings. Thus, 69 out of 90 specimens (77 percent) examined from nonmedicated (control) animals were positive for *S. typhimurium*, while only 36 of 81 specimens (41 percent) in the penicillin treatment group were positive for *S. typhimurium*. The results represent statistically significant differences ($P < .01$) between the incidence of Salmonella positive samples in the treatment group and in the nonmedicated control group.

Duration of shedding was measured by determining the length of time that fecal samples were positive for Salmonella, or analyzing the time required for quantities of Salmonella shed to reach a common value. At least three nonmedicated birds shed Salmonella in their feces throughout the experiment, and four were positive 28 days after infection. In contrast, by day 12, only one bird receiving penicillin was positive, and none were positive on day 28. The length of time positive counts persisted was significantly longer ($P = .05$) in nonmedicated controls than for the penicillin-treated group.

Liver, spleen, and cecal tissues from all animals were necropsied, and samples tested for Salmonella. All tissues were negative.

The AHI concluded that feeding a diet containing a subtherapeutic level (50 grams/ton) of penicillin to chickens that were experimentally infected with *S. typhimurim* did not increase the quantity, shedding, or prevalence of Salmonella in fecal specimens, nor did it increase the quantity of Salmonella isolated from liver, spleen, or cecal tissue. In the opinion of the AHI, the evidence from this study suggests that subtherapeutic use of penicillin in chickens reduced the quantity, shedding, and prevalence of Salmonella.

(ii) Resistance characteristics: (*a*) *E. coli.* According to the two pretreatment samples, the proportion of *E. coli* isolates that were drug resistant was low (below 6 percent), except for resistance to sulfonamides which was greater than 85 percent. But at the experiment's end, AHI found that the resistance to ampicillin, chloramphenicol, kanamycin, and nitrofurantoin was significantly higher ($P < .01$) in the penicillin environmental control groups (D_1) than the control birds (C). Ampicillin resistance also significantly increased in the infected birds that received penicillin. Resistance to sulfonamides remained at the pretreatment level of greater than 85 percent, although the figure in the environmental control groups decreased.

(*b*) *Salmonella.* Prior to inoculating the birds, the infecting strain of *S. typhimurium* was resistant only to sulfonamides and nalidixic acid, the nontransferable marker. *S. typhimurium* strains showed a significant increase in ampicillin resistance on days 12 ($P < .01$) and 14 ($P < .05$). No other significant increases were observed for the other antimicrobials in the test.

The AHI then concluded that the penicillin supplemented diets significantly increased the percentage of *E. coli* that were resistant to ampicillin. In the Salmonella, the AHI found no significant difference in drug-resistant isolates when all the chickens in the trial were considered. But among the animals shedding Salmonella, i.e., the medicated groups, the nonmedicated control, the birds exposed to subtherapeutic antibiotic pressure (both penicillin and penicillin-streptomycin), a significantly greater proportion shed Salmonella that were resistant to ampicillin than in the nonmedicated groups.

(c) *The Director's analysis.* (i) Shedding: (*a*) The Director does not disagree with some conclusions drawn by AHI about this study. Feeding a subtherapeutic level of penicillin did not apparently increase the quantity of Salmonella shed in fecal material; it did not appear to increase the number of Salmonella in liver, spleen, and cecal tissue; and it did not increase the number of positive chicken tissues.

The Director, however, disagrees with the conclusion of AHI that feeding penicillin at 50 grams/ton did not increase the duration or prevalence of Salmonella shedding because the procedures that were used to determine these parameters were inadequate. The information necessary to determine Salmonella duration and prevalence is whether Salmonella are present in the feces, not the quantity of Salmonella in the feces. After the animals were infected with Salmonella in this experiment, fecal specimens were processed by diluting them and then plating on the surface of agar plates. Clones growing on the plates were subsequently counted to provide information on number of Salmonella per gram of feces. As the study progressed, however, the number of Salmonella shed decreased in both groups, and this procedure is inadequately sensitive to detect small numbers of Salmonella. Good microbiological practice requires the use of an enrichment procedure for culturing. An enrichment procedure involves the incubation of a fecal sample in a selective broth to increase the number of Salmonella before plating on the agar. This increases the likelihood that Salmonella will be detected because other genera are being simultaneously inhibited. The enrichment procedure is recommended for examination of fecal specimens where small numbers of Salmonella may be present, as in the case of subjects in the carrier state. In its section about processing of specimens from the bacterial family, Enterobacteriaceae (Salmonella is a member of this family), the "Manual of Clinical Microbiology," 2d edition, American Society for Microbiology, Washington, D.C., p. 194 (1974) is clear:

> It always is advisable to employ enrichment media in the examination of various kinds of specimens, and their use is practically essential when dealing with fecal specimens from carriers of suspected carriers.

In an FDA experiment, the agency studiesd Salmonella shedding by swine (Ref. below). Through careful study, 28 percent more samples (136 rather than 94 from the 151 examined) were determined to be Salmonella positive when an enrichment procedure was used. In another similar study by FDA, 95 percent rather than 60 percent of 242 samples were found Salmonella positive by media enrichment. Enrichment procedures had been requested by FDA

during the protocol development stage; thus, the AHI determination of prevalence and duration for this study was considered inadequate.

REFERENCE

Rollins, L. D., FDA Project 108.

(b) The shedding study was conducted in three rooms. The chickens that were experimentally infected with *S. typhimurium* were maintained in two separate rooms, and the third room housed the noninfected environmental control animals. In one of the rooms containing infected birds, the chickens received only nonmedicated feed. However, all birds that were infected with Salmonella and receiving medication were placed in the same room. These birds received one of three different medicated diets, either penicillin, penicillin plus streptomycin, or sulfaquinoxaline. Although the chickens were maintained in separate cages within the same room, no birds were placed in this room to determine if bacteria from one study group were flowing to another study group within the room (environmental control). The rise in levels of resistance to antibiotics in noninfected, nonmedicated group A, as well as in the antibiotic-treated groups B_1 and B_2, suggests that some cross-contamination might have occurred or that contamination from the environment might have occurred. Such contamination of control groups makes it more difficult to detect differences in the increase of drug resistance between the experimental and control animals.

An FDA-sponsored contract (71-269) showed the relative ease by which cross-contamination occurs between various study groups. These groups were under similar or more adequate isolation conditions than the chickens in the AHI study.

Nevertheless, analysis of drug resistance data obtained from bacteria isolated from the various groups maintained in Room 2 of the AHI study indicates there are differences in drug resistance between groups. This suggests that when R-plasmids are present, regardless of their source, they may be transferred even in the absence of antibiotic pressure.

(c) When the shedding studies were initially requested, the optimum duration of such studies was unknown, although the 28-day duration appeared adequate. Data later generated under FDA sponsorship (contract 71-269) show that shedding patterns change after 30 to 50 days, longer than the length of the 28-day AHI experiment. Some studies have shown Salmonella shedding to be decreasing in both medicated and nonmedicated groups early in the experiment, with the shedding initially decreasing faster in the medicated group. In several of these experiments, approximately 55 days after initiating the experiment, the Salmonella shedding patterns reversed and shedding in the medicated birds increased, while shedding in the nonmedicated birds remained constant or continued to decrease. In the Director's opinion, the phenomenon is easily explained. Initially, the antibiotic attacks sensitive organisms and as these predominate, little shedding is observed. But, as the antibiotic-resistant organisms remain and become dominant in the population, shedding increases.

(d) The 28-day duration of the chicken studies should also be considered in relation to the life of a commercial broiler chicken, usually about 7 to 8 weeks. Although some changes in shedding pattern occurred beyond 6 weeks, in normal commercial production, groups of broilers are raised continuously with one group immediately following another. The production facilities may be cleaned between groups; however, the facilities are not sterilized. Bacteria left from a preceding group of birds are available to infect the birds that follow, and some of the microbiological changes that occur may be perpetuated in subsequent birds. Thus, if an antibiotic is used in the feed of each group of birds, it would have an opportunity to act over a long period of time. For these reasons, the Director now believes it is necessary to use an experimental design that allows sufficient evaluation of the effect of time of antibiotic usage on shedding.

(ii) Resistance characteristics: (a) *E. coli.* A major concern about occurrence of drug resistance in *E. coli* that are indigenous to the digestive tract is their potential for donating drug resistance to pathogens such as Salmonella. The Director agrees with the AHI analysis that feeding chickens the penicillin supplemented diet significantly increased ($P<.05$) the number of *E. coli* isolates that were resistant to ampicillin. But other aspects of the drug resistance characteristics of *E. coli* are also critical to an appropriate analysis of the data. Although the proportion of *E. coli* resistant to sulfonamides was high in all the groups before treatment and before inoculating the chickens with Salmonella, the bacteria were relatively susceptible to the other antibiotics tested. Results from one sample collected from each bird after penicillin treatment and inoculation with *S. typhimurium*, however, indicate that the proportion of *E. coli* resistant to streptomycin and tetracycline increased in all groups—environmental controls, nonmedicated controls, and treatment groups. This suggests bacteria that were resistant to tetracycline, streptomycin, and perhaps sulfonamides colonized the animals in the experimental facility.

(b) *Salmonella.* Although the total quantity of Salmonella shed decreased, the percentage of drug-resistant Salmonella shed increased, which is crucial. For birds that were shedding Salmonella, feeding penicillin resulted in a significantly greater proportion of Salmonella resistant to ampicillin ($P<.05$), which is consistent with the AHI analysis. The Director agrees with AHI that feeding subtherapeutic penicillin resulted in a significant increase in both the proportion of ampicillin-resistant *E. coli* and Salmonella.

For all of the foregoing reasons, the Director concludes that the study has failed to prove that the subtherapeutic use of penicillin in chickens satisfies the criterion and has failed to show that such use is safe.

4. *AHI Studies on the Effects of Subtherapeutic Penicillin in Animal Feed in Swine*—(a) *Experimental design.* To measure Salmonella shedding in swine and the transfer of drug resistance to Salmonella, AHI submitted a study that was similar in design to the previously described chicken study. This study was also subject to the same experimental conditions that FDA imposed on the chicken study, i.e., the base line incidence of resistance to drugs used in human clinical medicine in the indigenous flora of the test animals was not to exceed 20 percent.

Swine were divided into six groups, three of which were infected with Strain No. 58 DO 13C *Salmonella typhimurium* (swine) characterized as sulfonamide resistant. One noninfected and one infected group received diets containing either no medication, procaine penicillin, or procaine penicillin plus streptomycin according to the following design:

Room number	Group	Antibiotic and level used in feed	Inoculation of salmonella (1.3×10^{11} dose)	Number of pigs in experimental group
1	A	None	Yes	10
2	B_1	Procaine penicillin (50 g/ton)	Yes	10
	B_2	Procaine penicillin (12.5 g/ton), streptomycin (37.5 g/ton)	Yes	10
3	C	None	No	5
	D_1	Procaine penicillin (50 g/ton)	No	5
	D_2	Procaine penicillin (12.5 g/ton), streptomycin (37.5 g/ton)	No	5

(i) Shedding: Groups B_1 and B_2 were used to test the influence of penicillin on shedding and resistance of Salmonella in the test animals, with group A serving as a nonmedicated control group. Groups C, D_1 and D_2 were used as environmental controls to monitor whether swine administered the drug but not inoculated remained Salmonella free.

Orally via the diet, 6-week-old pigs were experimentally infected with an inoculation of 1.3×10^{11} Salmonella, 5 days after beginning their test diet. Preinfection fecal specimens were free of naturally occurring Salmonella for all test animals. For all pigs in each group, fecal samples were taken on days 2, 4, 6, 8, 10, 12, 14, 21, and 28 postinfection to quantitate the Salmonella. One-gram samples of fecal specimens from each test animal were diluted in phosphate-saline solution and plated in duplicate on brilliant green agar containing 0 and 20 micrograms/milliliter of streptomycin. After incubation, characteristic clones of Salmonella were recorded as total counts/

gram of wet feces. All pigs were killed and necropsied 28 days after the infection.

One-gram samples of aseptically collected liver, spleen, ileocecal lymph node, and cecum were minced and incubated in tetrathionate brillant green broth, and subsequently plated on brilliant green agar to determine the presence of Salmonella. Clinical records were maintained on body weights, mortality, and gross and microscopic pathology.

(ii) Resistance characteristics: (*a*) *E. coli*. Coliform counts were obtained from EMB plates inoculated with homogenized fecal samples. One gram of each sample was plated in duplicate on EMB agar containing 0 and 20 milligrams/milliliter of streptomycin. Antibiotic susceptibility tests were conducted on clones obtained from two prestudy samples and one poststudy sample from each animal in accordance with the Standardized Disc Susceptibility Tests in § 460.1(c)(2). Five cones from each specimen were selected from the streptomycin plates and were tested for susceptibility to ampicillin, tetracycline, chloramphenical, streptomycin, kanamycin sulfate, nitrofurantoin, and sulfathiazole.

(*b*) *Salmonella*. Five clones of *Salmonella* selected from the brilliant green fecal count plates were tested for antibacterial susceptibility to ampicillin, tetracycline, chloramphenicol, streptomycin, kanamycin sulfate, and nitrofurantoin, sulfathiazole, and triple sulfa, in accordance with the Standardized Disc Susceptibility Test in § 460.1(c)(2). When there were less than five clones of *Salmonella*, the number of clones picked corresponded to the actual number present on the plates.

(b) *AHI's summary of the results*. (i) *Shedding:* AHI reported that the number of *Salmonella* recovered per gram of wet feces diminished with time in all groups, and the number of organisms recovered from the medicated groups after day 2 was consistently less than the numbers recovered from the nonmedicated control group. These numbers represent average counts of clones growing on agar that did not contain streptomycin since no *Salmonella* grew on plates containing streptomycin. No *Salmonella* were isolated throughout the experiment from any of the environmental control animal (Groups C, D_1, and D_2). From this the AHI concluded that the presence of antibacterials in animal feeds reduces the quality and persistence of *S. typhimurium* in experimentally infected pigs.

(ii) Resistance characteristics: (*a*) *E. coli*. AHI concluded that penicillin supplemented diets significantly increased ($P<.01$) the number of *E. coli*. resistant to chloramphenicol. Similarly, penicillin/streptomycin supplemented diets significantly increased ($P<.05$) the number of *E. coli*. resistant to streptomycin.

(*b*) *Salmonella*. When the experimentally infected pigs in the medicated groups were compared to the nonmedicated control group, AHI concluded that feeding penicillin or penicillin/streptomycin at subtherapeutic levels did not increase the percent of pigs carrying resistant *Salmonella*. It also concluded that there were no significant differences in the percentage of resistant clones isolated from pigs in the penicillin group and the control group when all the pigs were considered (nonmedicated controls, environmental controls, and treatment groups).

(c) *Director's analysis*. (i) Shedding: The Director again does not totally disagree with AHI's conclusions concerning *Salmonella* shedding in swine. He agrees that, in this case, feeding a subtherapeutic level of penicillin apparently neither increased the quantity of *Salmonella* being shed in the pig's fecal material, nor increased the number of *Salmonella* in liver, spleen, ileocecal lymph node and cecum. Feeding penicillin also did not increase the number of swine tissues (liver, spleen, ileocecal lymph node and cecum) that were positive for *Salmonella*. However, the Director disagrees with the AHI conclusion that feeding swine penicillin at 50 grams/ton did not increase the duration or prevalence of *Salmonella* sheeding, because the procedures that were used to determine these parameters were inadequate. The information necessary to determine duration and prevalence of *Salmonella* shedding is whether feces contain any *Salmonella*, even in very low numbers, rather than the quantity of *Salmonella* present in the feces, which AHI measured. After the animals were infected with Salmonella, fecal specimens were processed by diluting and then plating the dilutions on the surface of agar plates. Enrichment procedures were not used.

(ii) Resistance characteristics: (*a*) *E. coli*. As in the chicken study, the data available on the occurrence of various drug resistances in *E. coli* are limited; nevertheless, they are sufficient to draw general conclusions. Susceptibility tests from streptomycin-containing plates show a high proportion of multiple-resistant *E. coli* in all groups prior to treatment, i.e., treatment groups, nonmedicated controls, and environmental controls. This is contrary to the recommendations of the FDA guidelines established for these studies. Data from post-treatment plate counts (one for each pig) indicate that the proportion of *E. coli* resistant to streptomycin remained high throughout the experiment and was similar for both the penicillin treatment group (group B_1) and the nonmedicated group (group A). The results are not unexpected because the high initial proportion of drug-resistant organisms makes it difficult to detect differences in the proportion of drug-resistant organisms caused by antibiotic administration.

A more acceptable procedure for determining the proportion of isolates resistant to a particular drug is to select clones from drug-free agar plates for susceptibility testing. A higher proportion of drug-resistant bacteria will be isolated on antibiotic-containing agar than with the random choice of a standard drug susceptibility test using normal agar.

Further, AHI has injected an element of bias in reporting the *E. coli* information. Only the clones that were growing on the streptomycin-containing agar plates were tested for susceptibility to multiple antibiotics. This procedure will reveal the drugs in addition to streptomycin to which the isolate was resistant, but a high proportion of the streptomycin-resistant isolates were also resistant to tetracycline and the sulfonamides.

Selecting clones from streptomycin-containing agar for further susceptibility testing is acceptable for determining what resistances, in addition to streptomycin, may be present. Only those cells resistant to streptomycin, alone or in a pattern with other antibiotics, will grow on agar containing streptomycin. However, cells may be present in the population that are susceptible to streptomycin but are resistant to one or more other drugs. For example, ampicillin-resistant bacteria might be missed. These cells would not grow on the agar containing streptomycin, and the procedures used by the AHI would not report them.

(*b*) *Salmonella*. *Salmonella* were isolated from both the nonmedicated control group (group A) and the penicillin treatment group (group B_1). Isolates that were singly and multiply drug resistant were observed, as well as isolates with resistance to ampicillin, tetracycline, chloramphenicol, nitrofurantoin, kanamycin, and stretomycin. The strain of *Salmonella* used to infect the animals was initially resistant only to sulfonamides when the animals were inoculated. In both the nonmedicated control group and the penicillin treatment group, the proportion of *Salmonella* isolates that were resistant to each drug tested was similar, and a significant proportion of *Salmonella* isolates were resistant to at least one of the following: ampicillin, tetracycline, and streptomycin.

The principal purpose of this experiment was to determine whether feeding of penicillin at subtherapeutic levels results in an increase of drug-resistant *Salmonella*. One way by which *Salmonella* become resistant is by transfer of drug resistance from the indigenous flora, e.g., *E. coli*, of the gut; therefore, the proportion of indigenous organisms in the gut carrying drug resistance directly affects the ability to detect differences due to antibiotic treatment. For this reason the effect that subtherapeutic penicillin has on increasing the proportion of drug-resistant *E. coli* was initially analyzed.

A high porportion of indigenous *E. coli* were drug resistant before treatment, which minimized or negated the observable effect that antibiotic treatment would have on the indigenous gut flora. Since the effect of antibiotic pressure on the indigenous flora was the initial step in the process under study, the study is invalid for demonstrating in a precise manner the effect of feeding subtherapeutic levels of penicillin on occurrence of resistance in *Salmonella*.

An unexplained inconsistency also invalidating the study is the fact that during the study no streptomycin-resistant *Salmonella* grew on the brilliant green agar (BGA) containing streptomycin. However, in subsequent sensitivity testing in the experiment it was determined that many of the *Salmonella* clones isolated at different times on plain BGA were indeed resistant to streptomycin as determined by the standard Kirby-Bauer disc susceptibility test.

A third deficiency undermines the validity of the study. The Director found that 70 to 100 percent of the indigenous *E. coli* in the test swine were resistant to tetracycline, streptomycin, and sulfonamide, and 20 to 50 percent were resistant to ampicillin and kanamycin. He also found that resistance to chloramphenicol and nitrofurantoin had occurred, but to a lesser extent. Nevertheless, in both the medicated animals and nonmedicated animals, the Director found that the resistance paterns corresponded.

Before the study began, the *Salmonella* were resistant only to the sulfonamides. On the basis of the disc susceptibility test, the Director found the following resistance pattern had evolved during the course of the study:

Percent resistant salmonella isolates

Drug	Non-medicated group A	Penicillin treatment group B
Streptomycin	53.0	48.0
Tetracycline	43.0	41.0
Ampicillin	60.0	58.0
Kanamycin	12.0	18.0
Chloramphenicol	3.6	5.6
Nitrofurantoin	8.0	3.6
Number of isolates	247.0	195.0

Resistance was transferred to *Salmonella* in the nonmedicated group at a rate at least equal to that of the medicated group. It is thus apparent that *Salmonella* readily became resistant to ampicillin, tetracycline, and streptomycin when exposed to the R-plasmids of *E. coli* present in the gut. This reaffirms the results obeerved in the chicken study, as well as the studies by Pocurull et al., Neu et al., and Smith and Tucker (Refs. 2, 3, and 6). Once a sufficient number of R-plasmid-bearing bacteria, principally *E. coli*, are present, the *E. coli* donate their R-plasmids in the absence of antibiotic pressure. Accordingly, the Director concludes that the presence and proportion of R-plasmid-bearing donors were responsible for the resistance in *Salmonella*.

Another safety question may be raised by the high *E. coli* resistance found in the swine used in this study; 70 to 100 percent of the *E. coli* were resistant to tetracycline, streptomycin, and sulfonamides, and 20 to 50 percent resistant to kanamycin and ampicillin. Yet, in the Gustafson study cited below (Ref. 7), in typical swine going to slaughter, there were no *E. coli* resistant to ampicillin, although 17 of 31 isolates were multiply resistant to other antibiotics.

For all of the foregoing reasons, the Director concludes that this study has failed to prove conclusively that subtherapeutic penicillin use in swin satisfies the criterion and has thus failed to show that such use is safe.

5. *Questions Raised by Other Studies of Salmonella*—(a) *CDC reports.* The Center for Disease Control (CDC) has maintained a national *Salmonella* surveillance program since 1963. The reported incidence of salmonellosis increased until approximately 1973, when it reached 27,000. The level of reported cases averaged 10.77 per 100,000 population from 1970 through 1974, and true incidence may be far higher because of underreporting. But the reported cases from antibiotic resistant *Salmonella* have continued to increase. *Salmonella typhimurium*, which is the most common *Salmonella* strain in animals, is the resistant strain most often reported in man and animals. More importantly, the number of antibiotic resistant strains of *S. typhimurium* isolated and reported almost doubled between 1967 and 1975, and the increase in antibiotic resistance in other *Salmonella* serotypes almost tripled during that period. Further, in addition to the fact that the number of *Salmonella* strains resistant to 6 or more antibiotics increased almost 10 times, the percentage of multiply resistant strains that are "super resistant" (containing resistance to 6 or more antibiotics) increased almost 7 times (Refs. 1 and 1a).

(b) *FDA survey.* Pocurull, Gaines, and Mercer (Ref. 2), in a 1971 survey, report that *Salmonella* strains isolated from outbreaks of salmonellosis in animals were bearing R-plasmid-mediated resistance to antibiotics. *Salmonella* isolates gathered in diagnostic laboratories of most States from outbreaks of salmonellosis in pigs, cows, chickens, and turkeys were tested for their susceptibility to ampicillin, tetracycline, dihydrostreptomycin, cephalothin, sulfamethoxypyridazine, colistin, chloramphenicol, furazolidone, neomycin, polymyxin, and nalidixic acid. Of the 1,251 strains studied, 75 percent were resistant to one or more antibacterial drugs, 40 percent were resistant to two or more antibacterials, and 21 percent were resistant to three or more antibacterials. But an even higher incidence of multiply resistant cultures was observed in *S. typhimurium*, which was again the most commonly isolated pathogen.

(c) *Neu, Cherubin, Longo, Flouton, and Winter studies.* Recently, Neu et al. (Ref. 3) examined the antimicrobial susceptibility of 718 *Salmonella* isolates from humans and 681 from animals. They compared the current prevalence of antibiotic resistance in *Salmonella* isolates from humans with their previous studies in 1968–1969 and with the resistance patterns of *Salmonella* isolates from animals.

Thirty percent of all human isolates were resistant to one or more antibiotic(s). Again, *S. typhimurium* was the most common pathogen and 58 percent were resistant to at least one antibiotic. More than 50 percent of the *S. typhimurium* were resistant to four to five antibacterials. The fraction of all *Salmonella* strains resistant to kanamycin rose from 3 percent to 12.5 percent. When these results were compared with a 1965 national survey conducted by Gill and Hook (Ref. 4), the authors found that the percentage of isolates of all serotypes resistant to ampicillin had increased fourfold by 1973, and the incidence of resistance to tetracycline and streptomycin had approximately doubled. Resistance in *S. typhimurium* had increased from 19 percent to 58 percent of isolates, and resistance to ampicillin has increased from 23 percent to 37 percent. Moreover, the resistance to ampicillin, tetracycline, chloramphenicol, streptomycin, sulfisoxazole, and kanamycin was transferable among the various *Salmonella* strains.

In animals, *S. typhimurium* accounted for 70 percent of the isolates, and 80 percent were resistant to one or more antimicrobial agents. R-plasmids were found in 86 percent of the *S. typhimurium*, and resistance to ampicillin, tetracycline, chloramphenicol, streptomycin, sulfisoxazole, and kanamycin was transferable. Generally, the resistance patterns were similar to those encountered in the *Salmonella* isolated from humans.

The authors conclude that the high incidence of transferable resistance in man and animals suggests that most resistant strains seen today contain complete R-plasmids, and that strains unable to mobilize resistance determinants are less common than was formerly thought. They further conclude that comparison of the resistance of *Salmonella* isolates from humans with that of *Salmonella* from animals shows that tetracycline resistance is greater among the strains from animals, as in the case with sulfonamide and streptomycin resistance. While the resistance to ampicillin is higher in *S. typhimurium* strains isolated from humans than those isolated from animals, the reverse is true for other serotypes. This difference may reflect the greater current use of tetracyclines, sulfonamides, and streptomycin in animals.

Finally, the authors conclude that the survey clearly demonstrates that resistance to antibiotics is increasing in *Salmonellae* isolated from both humans and animals, and since there are great similarities in the resistance patterns of human and animal isolates, it would be useful to know whether the R-plasmids are of a similar nature since this would suggest that animal strains have contributed to the human pool of resistant organisms.

(d) *Smith, H., and J. F. Tucker studies.* Smith and Tucker (Ref. 5) studied the effect of antibiotic therapy on the fecal excretion of *S. typhimurium* by experimentally infecting 3-day-old chicks. There were 3 different treatment regimens studied; 9 different antibiotics were used with experimental groups of 40 during each study. One or two groups in each experiment were fed nonmedicated feed throughout. The following antibacterials were tested: Ampicillin, oxytetracycline, chloramphenicol, furazolidone, neomycin, polymixin, spectinomy-

cin, streptomycin, and a mixture of trimethoprim and sulfadiazine. The regimens were: (1) continuous antibiotic administration in the diet for 61 days at 100 milligrams/kilogram of animal feed (subtherapeutic); (2) continuous antibiotic administration in the diet at 500 milligrams/kilogram of animal feed for 44 days (therapeutic); (3) continuous antibiotic administration in the diet for 9 or 18 days at 500 milligrams/kilogram of animal feed while observing for 65 days.

In each preceding experimental group, except the furazolidone group, when chickens were fed subtherapeutic drugs, the *E. coli* became multiply resistant with R-plasmids having the same pattern of resistance that developed shortly thereafter in the *Salmonella* of the same groups. No antibiotic resistant *Salmonella* were ever isolated from the fecal specimens taken from the chicks fed antibiotic-free diets, although high concentrations of antibiotic-resistant populations always developed in the *S. typhimurium* and *E. coli* from groups fed antibiotics.

Smith and Tucker found that although many of the antibiotics brought about a profound reduction in the concentration of fecal *E. coli*, it was usually short-lived because of the emergence of antibiotic-resistant populations of *E. coli*, even in the group receiving subtherapeutic levels of the antibacterials. Most of the resistance to ampicillin, oxytetracycline, chloramphenicol, streptomycin and spectinomycin are due to R-plasmids found initially in the entire chicken population, with the same patterns of antibiotic resistance (ampicillin, streptomycin, tetracycline, chloramphenicol) which were selected, transferred and subsequently appeared in the *S. typhimurium* populations of each different dietary regimen selected for any one drug.

Although penicillin was not used in the study, the principles that apply to the emergence of transferable drug resistance in this study apply to R-plasmids that emerge from use of penicillin. Further, ampicillin is a penicillin, which in sufficient quantity will produce the effects of penicillin G on drug resistance in Gram-negative bacteria.

Antibiotics have been used to such an extent in certain animal species that organisms that are well adapted to their digestive tract are now drug resistant. The selective pressure of antibiotics is one of the primary factors that results in an increase in the number of organisms carrying transferable drug resistance, and the selective pressure may be from either therapeutic or subtherapeutic antibiotic use. Although the procedures used to gather the information from the AHI chicken study were inadequate according to the current state of the art, nevertheless, the AHI chicken study exemplifies the interaction between the pool of R-plasmid donors and drug-susceptible pathogens in chickens; it also demonstrates the effect of subtherapeutic penicillin pressure on the development of resistance to ampicillin. Other recent literature such as the Smith and Tucker studies and contract studies confirm these findings. The Director concludes that there is no evidence to show that safety hazards do not exist as a consequence of the subtherapeutic use of penicillin in animal feed.

(e) *Kobland, Gustafson study.* Kobland, Gustafson et al. (Ref. 7) of American Cyanamid performed a survey of three major swine producing areas for the Animal Health Institute to determine the extent of the naturally occurring antibiotic-resistant Salmonella reservoir in hogs; subtherapeutic levels of antimicrobials were routinely used in animal feeds in the area. Fecal contents were sampled from market-age hogs obtained from slaughter houses in Pennsylvania, Iowa, and Georgia, and these samples returned to the laboratory for Salmonella isolation procedures. *E. coli* were also isolated to obtain information regarding antibiotic resistance status of indigenous coliforms.

The first survey was made in Lancaster County, Pennsylvania. Out of 151 animals sampled, 54 (35 percent) were positive for Salmonella, and all isolates tested (653) were sensitive to the 10 antimicrobial agents that were tested. Of 31 *E. coli* isolates, 17 were multiply resistant.

In the second study, in Iowa, 26 hogs (10 percent) were positive for Salmonella out of 251 sampled. Examination of 219 isolates yielded 10 (5 percent) resistant isolates, but all from 1 hog. Again, most of the coliforms (*E. coli*) were multiply resistant.

Finally, in the Georgia survey, Salmonella was isolated from 215 (84 percent) out of 256 animals sampled, i.e., 78 hogs (36 percent) carried drug-resistant Salmonella; and of 622 isolates, 145 (23 percent) carried tetracycline resistance singly or with streptomycin.

Four Salmonella serotypes were identified in Pennsylvania, eight in Iowa, and seven in Georgia. The Salmonella strains that were resistant to more than one antimicrobial were able to transfer resistance to an *E. coli* recipient. When the sponsors tested representative drug-sensitive Salmonella isolates for their ability to receive R-plasmids, four *S. worthington* and two *S. newington* isolates acquired resistance after a 24-hour mating. None of 28 other isolates as tested accepted an R-plasmid. Only two samples represented *S. typhimurium*, the most frequently isolated serotype from animal and human sources and a good donor of R-plasimds.

In summary, (i) 40 percent of ceca from animals in Pennsylvania, Iowa, and Georgia contained Salmonella; (ii) None were antibiotic-resistant in Pennsylvania, 4 percent in Iowa, and 23 percent in Georgia; and (iii) none of the Salmonellae from any of the three States were ampicillin-resistant. For *E. coli*, (i) 7 percent of the swine sampled from Pennsylvania were ampicillin-resistant, (ii) 31 percent from Iowa, and (iii) 39 percent from Georgia. Only certain Salmonella serotypes were shown to be good recipients for the *E. coli* R-plasmids in transfer studies done in conjunction with the surveys, and none acquired ampicillin resistance. On this basis, AHI concluded that naturally occurring Salmonella are neither R-plasmid-bearing nor willing R-plasmid recipients.

The survey alone, however, is inadequate to support a conclusion that the background level of drug-resistant Salmonella is not increasing because there is no documentation that the sites selected for sampling provide a random representative sample of the total swine population. The authors explained neither how they determined that the sampled swine had been exposed to antibiotic pressure nor which antibiotics were involved. Of 22 Georgia isolates that were resistant only to tetracycline, not one transferred its resistance, and for this reason, the authors assert that the gene coding for tetracycline resistance was probably located on the bacterial chromosome rather than on a plasmid. This assertion is contrary to current information which indicates that naturally occurring tetracycline resistance is invariably plasmid mediated (Ref. 8). Tetracycline resistance in a bacterial strain can be taken to indicate the presence of an R-plasmid because no evidence has ever shown tetracycline resistance to be chromosomally mediated in naturally occurring strains of enteric bacteria (Ref. 9). The plasmid may, however, be small and not self-transmissible, as was apparently the case in the Gustafson study.

American Cyanamid's in vitro tests for Salmonella R-plasmid recipient activity are also inadequate. Cyanamid tested only "representative" sensitive Salmonella isolates, and four *S. worthington* and two *S. newington* isolates acquired resistance. Although none of the other 28 isolates tested accepted an R-plasmid in these tests, only a single R-plasmid-bearing *E. coli* donor was used, and the compatability properties of the donor R-plasmid were never presented. It is well recognized that certain species of Salmonella are generally neither good donors nor recipients of R-plasmid in the laboratory. The ability of a particular Salmonella to act as a recipient is dependent on the compatability properties of the donor R-plasmid. For example, in recent years most R-plasmids isolated from naturally occurring Salmonella have been of incompatibility groups H and I, and many Salmonella are not good recipients for F II R-plasmids, a common type encountered in *E. coli*. Therefore, without data on incompatability groupings, the Director believes that this aspect of Gustafson's study is of little value.

(f) *Other studies.* Wilcock et al. (Ref. 10), found far greater levels of antibiotic resistance in clinical isolates of *Salmonella typhimurium* (95 percent were tetracycline-resistant) than in isolates of *S. choleraesuis* (18 percent). These strains accounted for 90 percent of the 63 isolates definitely associated with swine salmonellosis. The greater accessibility of *S. typhimurium* to intestinal *E. coli* in contrast to the systemic *S. choleraesuis* infection may explain this difference.

In a survey of 5 Canadian abattoirs by Groves and Barnum et al. (1970, Ref. 11), 20 percent of 462 hogs were Salmonella positive. Tetracycline-resistant Salmonella were found in isolates from 11 of the 94 (11.7 percent) mesenteric lymph node samples of marketed swine, in 2 of 15 (13.3 percent) isolates from the abattoir environment, and in only 1 of 25 (4.5 percent) isolates from a farm supplying the abattoir. Thus, 14 of 134 isolates (10.5 percent) were at least tetracycline resistant. Of the 14 resistant Salmonella, 5 were *S. typhimurium* and 8 were *S. schwarzengrud*. Single or multiple tetracycline resistance was present in all 14 resistant Salmonella. Out of 110 strains studied, 22 were *S. typhimurium*. Other prevalent serotypes included *S. heidelberg*, *S. muenster* and *S. anatum*. Voogd (1973, Ref. 12) charted various Salmonella serotypes, and a large percentage of resistance was seen in *S. typhimurium* (25 percent in 1971), *S. anatum* (29 percent) and *S. panama* (25 percent), although resistance in other serotypes such as *S. derby*, *S. infantis*, *S. dublin*, or *S. chloraesuis* was lower. As mentioned earlier, most surveys have clearly shown an increase in drug-resistant Salmonella in recent years, and the strains surveyed in those studies have obviously encountered R-plasmids which bacteria can accept and stably maintain. This is clearly demonstrated by the results of the AHI studies and the other evidence discussed earlier.

6. *Director's Conclusions.* Questions raised by the CDC reports, and the studies conducted by Ryder, Pocurull et al., Neu et al., and Smith and Tucker (Refs. 1 through 3, and 5) show precisely the same pattern of resistance and in the same sequence that was observed in the *E. coli* and Salmonella isolates from the AHI chicken and swine studies. Resistance occurred in the *E. coli*, and a corresponding pattern of resistance subsequently occurred in the Salmonella after exposure to the R-plasmid-bearing *E. coli*. Despite the absence of antibiotic pressure (in the nonmedicated animals), initially high numbers of resistant *E. coli* in all of the test animals did transfer R-plasmids to the antibiotic-sensitive Salmonella.

Furthermore, because most of the animals in the AHI studies were harboring drug-resistant R-plasmid-bearing *E. coli*, which was contrary to FDA criteria, the studies may be considered invalid for determining the effect of feeding subtherapeutic penicillin on the emergence of drug-resistant Salmonella. Moreover, the procedures used to gather the data on Salmonella prevalence and duration were inadequate. The studies nevertheless demonstrate that the reservoir of R-plasmid-bearing Salmonella increased in direct correlation with the resistance patterns observed in the drug-resistant *E. coli*. These results confirm the results observed in the literature. R-plasmid-bearing bacteria are widespread in the environment, and they can transfer their R-plasmids to pathogens, even in the absence of antibiotic pressure. Under § 558.15, the holders of approved NADA's were required to submit data to prove conclusively that the subtherapeutic use of penicillin in animal feed does not increase the duration and prevalence of Salmonella, and that such use does not contribute to the development of R-plasmid-bearing organisms. Because subtherapeutic use of penicillin contributes both to R-plasmid buildup and transfer, the data lead to the conclusion that the subtherapeutic use of penicillin has not been shown to be safe.

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C. *Compromise of Therapy (Criterion 2 (c))*

1. *Background and criterion.* The 1972 FDA Task Force was concerned that the continuous feeding of antibiotics to animals might compromise the treatment of certain animal diseases. It concluded that additional information was needed, and FDA accordingly determined that epidemiological and controlled challenge studies were to be carried out to determine the relationship of the use of antibiotics in animal feed to the effectiveness of subsequent treatment of animal disease, which is criterion 2(c) of this notice. To answer this criterion with regard to subtherapeutic use of penicillin, the Animal Health Institute submitted two studies. The first, carried out in chickens, involved treatment of a systemic *E. coli* infection by oxytetracycline after subtherapeutic use of penicillin in feed. The second study, in swine, dealt with treatment of a *Salmonella choleraesuis* infection by nitrofurazone, after subtherapeutic use of penicillin in feed.

2. *AHI Compromise of Therapy Study in Chickens.*—(a) *Experimental design.* Day-old-chicks were placed on subtherapeutic levels of penicillin (50 grams/ton) for 21 days. On day 21 the birds were infected by the intramuscular (I.M.) route with *E. coli* at 4.5×10^8 CFU (colony forming units). Subsequent treatment was with oxytetracycline (12.5 milligrams given I.M. for 3 days).

(b) *AHI's summary of the results.* The highest mortality (60 percent) occurred in the group of chickens receiving neither penicillin nor oxytetracycline treatment, as compared with no mortality in the group receiving penicillin in feed and subsequent oxytetracycline treatment. Penicillin-supplmented diets reduced mortality in chickens with systemic *E. coli* infections by 38 percent. The use of oxytetracycline treatment alone was enough to reduce mortality from 60 percent to 13 percent. The penicillin-fed groups showed better weight gain than the control groups.

Based upon the data presented, when mortality, feed consumption, weight gain, and feed efficiency are considered, AHI concluded that the subtherapeutic use of procaine penicillin at 50 grams/ton did not compromise subsequent therapy of artifically induced systemic *E. coli* in chickens, when oxytetracycline 12.5 milligrams I.M. was the therapeutic agent.

(c) *Director's analysis.* The experimental design used was inappropriate to address whether the subtherapeutic use of penicillin in animal feed will compromise therapy in diseased chickens. The establishment of a clinical infection by giving *E. coli* orally in chickens presents some practical problems, whereas challenge via intramuscular injection resulted in a more uniform clinical effect. However, infection by the intramuscular route prevented the interaction, on the intestines, of the infecting organism (*E. coli*) and resident *E. coli*, a combination that is known to be necessary for selection of drug resistance. Therefore, the Director must conclude that this work in chickens presented by AHI fails to address appropriately and to satisfy animal health criterion 2(c). The work provides no evidence that sheds any light on the compromise of therapy issue.

3. *AHI Compromise of Therapy Study in Swine.*—(a) *Experimental design.* Weanling swine were placed on a trial diet (penicillin 30 grams/ton) for 21 days. On day 21 the swine were orally infected with *Salmonella choleraesuis* (2.1×10^9 CFU) via stomach tube, following a 24-hour fast. Treatment was with nitrofurazone (110 parts per million in drinking water) when the first clinical signs of salmonellosis appeared.

(b) *AHI's summary of the results.* The highest mortality (30 percent) occurred in the group of swine receiving no penicillin feed and no subsequent treatment as compared with 10 percent in the group receiving penicillin in feed but no subsequent treatment. No mortality occurred in the groups receiving nitrofurazone treatment, regardless of whether penicillin was absent or present in the diet. The scouring index was higher in the negative control group receiving neither penicillin in the diet nor nitrofurazone treatment, while it was significantly lower in the remaining groups. Weight gain and feed efficiency were higher in the medicated groups than in the control groups.

Although differences in mortality between groups was not significant when other parameters, such as weight gain, feed efficiency, and scour index are observed, AHI concluded that the subtherapeutic feeding of procaine penicillin at 30 grams/ton will not compromise subsequent nitrofurazone therapy of artificially included *Salmonella choleraesuis* in swine.

(c) *Director's analysis.* Any study of compromise of therapy requires a determination of whether the subtherapeutic use of a drug results in an increase in the number of bacteria bearing R-plasmids that are capable of donating these R-plasmids to pathogens. The object of the AHI swine study was ostensibly to determine whether the subtherapeutic use of penicillin would compromise nitrofuran therapy. However, the resistances most commonly found to result from penicillin use in *E. coli* are resistance to ampicillin, tetracycline, sulfonamides, and streptomycin in various combinations. Rarely will the subtherapeutic use of penicillin result in an increased incidence of transferable resistance to nitrofurazone (Ref. 1). For this reason a study that attempts to measure compromise of therapy against nitrofurazone alone will be biased by design against showing a compromise. The nitrofurazone group is useful to show that the disease is treatable by an antibacterial. However, the study requires a group treated with a drug whose resistance is frequently mediated by R-plasmids to measure any compromise of therapy, particularly because penicillin would not be used to treat an *S. choleraesuis* infection. Even though nitrofurazone may be one drug of choice for treatment of *S. chloraesuis* infection in swine, it use alone in the study of compromise of therapy is inappropriate because nitrofurazone resistance is not one that would ordinarily become a problem from penicillin use; moreover, because of questions about carcinogenicity, the Director, in a notice published in the FEDERAL REGISTER of August 17, 1976 (41 FR 34899), proposed to withdraw approval of NADA's for the use of nitrofurazone on the grounds that it has not been shown to be safe.

The study should have been designed with treatment of the disease by a drug to which subtherapeutic use of penicillin may cause increased resistance, e.g., ampicillin or tetracycline, to provide a more accurate reflection of what may occur in the field. This study is of no value in showing that subtherapeutic penicillin feed does not compromise therapy by related drugs such as ampicillin or by drugs to which resistance would commonly occur along with that of resistance on an R-plasmid. For example, ampicillin, tetracycline, sulfonamide, and streptomycin resistance are commonly linked on R-plasmids.

4. *Questions Raised by FDA Funded Research.* Due to the complexity and importance of the compromise of therapy issue, FDA sponsored a study to develop a disease model with antibiotic susceptible organisms in a manner that would provide suspectible pathogenic *E. coli* with the opportunity to interact in the intestinal tract with R-plasmid-bearing organisms and develop drug resistance (Ref. 2). A University of Missouri survey for a tetracycline-susceptible pathogenic *E. coli*, however, failed to locate a susceptible strain in swine, and a compromise of therapy experiment using tetracycline-resistant pathogenic *E. coli* was performed according to the following design.

(a) *Experimental design.* Swine were fed an unmedicated diet and two diets containing subtherapeutic levels of the combination chlortetracycline, sulfamethazine, and penicillin; the investigators then measured the effectiveness of therapeutic levels of chloramphenicol and chlortetracycline.

	Number of animals	Infection with *E. coli*	Oral therapeutic agent (per kilogram of animal)
DIET 1—Unmedicated			
Group:			
1	18	No	None.
2	20	Yes	Do.
3	28	Yes	Chloramphenicol—50 mg.
4	30	Yes	Chlortetracycline—50 mg.
DIET 2—Chlortetracycline (20 g/ton of feed), sulfamethazine (20 g/ton of feed), and penicillin (10 g/ton of feed)			
Group:			
1	17	Yes	None.
2	21	Yes	Chloramphenicol—50 mg.
3	23	Yes	Chlortetracycline—50 mg.
DIET 3—Chlortetracycline (100 g/ton of feed), sulfamethazine (100 g/ton of feed), and penicillin (50 g/ton of feed)			
Group:			
1	14	Yes	None.
2	10	Yes	Chloramphenicol—50 mg.
3	12	Yes	Chlortetracycline—50 mg.

(b) *Director's analysis.* In each diet, chloramphenicol treatment was significantly more effective for the treatment of the disease than was treatment with chlortetracycline. In fact, the results show that chlortetracycline treatment was no more effective than either the untreated control group or the groups fed the combination of subtherapeutic antibiotics in the ration, i.e., the latter were ineffective.

The Missouri study indicates that animal therapy may be compromised where the pathogen is resistant to the antibiotic used for treatment.

5. *Director's Conclusion.* The potential for harm resulting from compromise of therapy is clear, and no evidence has been submitted that adequately addresses the basic issue, the potential for subtherapeutic penicillin use to compromise therapy, since the studies submitted contained design deficiencies. For these reasons, the Director concludes that the sponsors have failed to resolve the issue and thereby show that the subtherapeutic use of penicillin is safe in animal feed.

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6. Optimal Level of Effectiveness (Animal Health Criterion 4). This was originally stated as a separate criterion as follows:

> The optimum usage level for each indication of use of the antibacterial drug at subtherapeutic levels shall not increase significantly with continued use.
>
> Once the optimum level is established, a study shall continue over succeeding generations or populations of animals to determine if this same level continues to yield the same measurable effect.

No data were submitted on this issue for penicillin or penicillin-containing products. The failure to submit these data was in part due to the inability to design such studies that would be meaningful in the 2-year period designated for study. A study begun in 1972 was submitted by AHI which compares the effectiveness of four antibiotics (chlortetracycline, tylosin, bacitracin, and virginiamycin) to a nonmedicated group in swine (Ref. below). The study was conducted at only one location; tests at several locations are necessary to provide any evidence they may have general application to the swine industry. Moreover, the antibiotics were not fed to the swine at graded dosage levels (dosage titration), which is necessary to determine the optimal level of the drug's effectiveness. That is the first step in attempting to address the concerns. Without that evidence, the Director cannot make any determination about the role of R-plasmid-bearing organisms in the continuing effectiveness and safety of subtherapeutic use of any tested antibiotic in animals, including penicillin.

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D. *Pathogenicity (Criterion 3)*

1. *Background and Criterion.* It is clear that bacterial plasmids contribute significantly to an organism's capacity to produce disease and to survive within the host organism (Ref. 1). The production of enterotoxin, for example, is an essential factor in the pathogenicity of *E. coli* strains of porcine origin, and Smith and Halls (Ref. 2) demonstrated that this property was governed by a plasmid, termed ENT. Similarly, the genetic determinants for enterotoxin production in *E. coli* isolated from calves and lambs have also been shown to be controlled by transmissible plasmid (Ref. 3). Recent studies support the premise that enterotoxin-producing strains of *E. coli* are also responsible for a significant proportion of previously undiagnosed human diarrheal disease (Refs. 4 through 6). Corresponding to these studies in domestic animals, researchers have now shown that the ability of *E. coli* strains of human origin to elaborate enterotoxin is mediated by a transmissible plasmid (Refs. 7 and 8).

In addition to toxins, other plasmid-mediated virulence factors have been described. One of the characteristics of the diarrheal disease caused by enterotoxigenic *E. coli* in man or animals is the ability of large numbers of the bacteria to colonize the small bowel. There is evidence that a surface associated antigen K88, on *E. coli* toxigenic for pigs facilitates colonization since the antigen functions to overcome intestinal motility and other clearing mechanisms (Refs. 9 through 13). Further, Orskov et al. (Ref. 14) showed that K88 production is governed by a transmissible plasmid. A similar antigen, K99, has been described for calves (Refs. 15 through 17). Moreover, these K-antigens play a role in the host specificity of these pathogens. The K88 antigen from porcine isolates is unable to produce adhesion to the calf intestine, and the K99 calf antigen is unable to adhere to the pig intestine (Ref. 15). A similar plasmid-controlled surface antigen has recently been described in a strain of *E. coli*, causing severe human diarrheal disease (Ref. 18).

Another way plasmids can contribute to virulence is exemplified by the colicin V plasmid (Ref. 19). Colicin V is the most common colicin produced by *E. coli*, and pathogenic *E. coli* containing the colicin V plasmid have a greater ability to resist the host species' defense mechanism (Ref. 19). Such *E. coli* also tend to be more refractory to the bactericidal effects of undefined components in serum. In addition, Smith's experiments in chickens and in humans reveal that the colicin V R-plasmid confers on organisms an increased ability to survive in the alimentary tract as well as in the tissue (Ref. 20). On the basis of this evidence, the Director believes that other plasmid-mediated factors that enhance pathogenicity may well be found in the future.

Although pathogenicity is generally determined by more than one factor, the addition of a single specific character to a nonvirulent organism can endow that organism with virulence, and the potential dangers of this character being mediated by a transmissible element are apparent. Because R-plasmids and virulence plasmids can reside in the same bacterial cell, the possibility is increasing that plasmids that contribute to pathogenicity may become more widely disseminated among bacterial species due to the selection of the large reservoir of R-plasmids within enteric organisms.

For these reasons, FDA established Human and Animal Health Safety Criterion 3: "The use of low and/or intermediate levels of an antibacterial drug shall not enhance the pathogenicity of bacteria."

FDA's guidelines required a series of well designed studies to determine if the use of antibacterial drugs in animal feeds enhances pathogenicity of Gram-negative bacilli. First, the sponsors were to determine if plasmids coding for toxin production could become linked to an R-plasmid and be transferred in vitro. If this was demonstrated in germ-free animals, experiments were to be conducted in conventional animals.

Due to the progressional nature of the studies, the Director did not require the sponsors to complete the studies during the time alloted by § 558.15. The sponsors were committed to conduct such studies and to submit reports on the studies at regular intervals. The AHI did submit a study conducted by Dr. John Walton to examine the association of plasmid-mediated toxin production with R-plasmids, and data were also obtained from FDA contracts with Dr. Stanley Falkow and Dr. Carlton Gyles.

2. *Walton Study.* The Walton study (Ref. 21) reported in vitro transfer experiments using a donor organism bearing both the enterotoxin plasmid and R+ factors antibiotic resistance plasmids and a recipient organism that lacks an R-plasmid. Walton concluded that subsequent selection of R+ transconjugants does not select for enterotoxin production.

The Director finds that the study contained major shortcomings in the procedures used, and he rejects Walton's conclusions as inadequately supported. The enterotoxin-producing strains (containing plasmids termed ENT) used in the experiment were inadequately examined for the frequency of transfer of their ENT plasmids and the number of R+ transconjugants tested for ENT transfer (20) was insufficient since only a frequency of 5 percent or greater could be detected. From each mating, 20 transconjugant colonies were pooled and subcultured into 100 milliliters of nutrient broth; then they were grown overnight to obtain cells and supernatant fluid to test for toxin production. However, no positive control was included in the experiment to show that, in screening, 1 known ENT + colony, out of 20 colonies, would produce a positive reaction for toxin production. For these reasons, the Director concludes that the study neither conclusively resolves the issue nor even provides adequate evidence to support the conclusion that selection for R+ transconjugants does not select for enterotoxin production.

3. *Falkow Study*—(a) *In vitro transfer.* On the other hand, Falkow (FDA Contract 73-7210) unequivocally demonstrated that ENT and R-plasmids do cotransfer and that drug selection for the R-plasmid and subsequent clonal screening for ENT was an adequate laboratory tool for detection of cotransfer.

In an in vitro mating, *E. coli* K12 (containing a bovine ENT plasmid, a K-antigen-determining plasmid (K99), and an R-plasmid coding for tetracycline and streptomycin) was crossed to three drug-sensitive *E. coli* K12 recipient strains. The recipient strains were rifampicin resistant, and the donor was rifampicin sensitive. The rifampicin-resistant recipient that received the tetracycline-streptomycin plasmid were recovered on rifampicin-tetracycline drug plates; these recombinant clones were then scored for coinheritance of ENT and K99. Of 225 clones tested (75 from each of the 3 crosses), 2 clones (0.88 percent) received both ENT and K99+. Thus, cotransfer of K99 and ENT plasmid for pathogenicity with the tetracycline-streptomycin drug resistance plasmid was of a low but detectable incidence.

In another in vitro mating study, a bovine enterotoxigenic nonlactose-fermenting *E. coli* isolate (B44) (containing the following plasmids: ENT, K99, and an R-plasmid (R_4) containing genes coding for ampicillin, chloramphenicol, kanamycin, and streptomycin resistance) was crossed with a lactose fermenting strain of *E. coli*, K92 strain 1485. Lactose-fermenting and chloramphenicol-resistant transconjugants were scored for K99 and ENT.

The incidence of K99 plasmid transfer was 3/37 (8 percent) and the incidence of the ENT plasmid transfer was 9/37 (24.3 percent). Furthermore, the incidence of K99, ENT, and R_4 cotransfer was 3/37 (8 percent).

(b) *In vivo transfer.* Falkow fed B44 *E. coli* bearing resistance (R_4), ENT, and K99 plasmids to baby calves, and in vivo transfer of the (R_4) plasmid to indigenous microflora was monitored. In one experiment, ENT plasmid was cotransferred at an incidence of 3/39 (7.7 percent); however, K99 was not transferred. In another in vivo transfer experiment, the ENT was cotransferred at an incidence of 1/88 (1.1 percent) and cotransfer of K99 did not occur. But detection of K99 cotransfer was hampered by the autoagglutination of 50 percent of the transconjugants when slide agglutinations with K99 antisera were performed.

From these experiments, Falkow concluded that possession of an R-plasmid by an enteropathogenic strain does not guarantee cotransfer of ENT or K99; nevertheless, the implications of cotransfer at even a low incidence in the intesti-

nal tract of an animal, should the animal be exposed to the same antibiotics to which the enteropathogen is resistant, has potent public health consequences.

4. Questions raised by other studies. (a) Naturally occurring toxigenic strains of *E. coli* are often multiply resistant, and during a recent hospital outbreak of infantile diarrhea in Texas, Wachsmuth et al. (Ref. 23) reported that plasmid-mediated toxin production and multiple antibiotic resistance was demonstrated. Transfer of a 67 × 10^6 and 30 × 10^6 dalton plasmid was associated with the transfer of resistances and enterotoxin production, respectively. Moreover, when antibiotics were used to select *E. coli* K12 recipients from a one-step bacterial cross, all the resistances were concurrently transferred, and 36 percent of these drug-resistant recipient organisms also transferred their ENT plasmids and produced enterotoxin. Clearly, the Director must conclude that R-plasmid transfer can enhance the possibility of ENT transfer and the production of enterotoxin.

(b) Translocation is believed to be the primary mechanism for the dissemination of resistance genes in vivo. Under FDA Contract 223–73–7210, Falkow has been able to show the translocation of antibiotic resistance genes to ENT plasmids in vitro. He also demonstrated that ENT plasmids can acquire resistance genes from R-plasmids if they inhabit the same cell. Ampicillin, sulfonamide, and streptomycin plasmids constructed in vitro by translocation are indistinguishable from such ampicillin plasmids obtained from clinical isolates of *E. coli* and *Salmonella* (Ref. 24).

More recently, Gyles (FDA Contract 223–73–7219) demonstrated the in vivo transfer of ENT plasmids in the intestinal tract of pigs, using the selection of tetracycline-resistant recipient organisms as a basis for screening ENT+ recipient colonies. All of the 35 tetracycline-resistant recipient colonies obtained were shown to bear the ENT plasmid. Gyles also showed that tetracycline resistance and enterotoxin biosynthesis reside on the same plasmid.

5. Director's Conclusions. The evidence from both in vitro and in vivo experiments demonstrates that ENT plasmids and R-plasmids can become linked. Only Dr. Walton's study describes data to the contrary; however, his study is inadequate for the reasons discussed. Accordingly, the Director concludes that the existing evidence demonstrates that R-plasmids can increase the pathogenicity of organims, and inadequate evidence has been submitted to prove the contrary.

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E. *Tissue Residues (Criterion 4)*

1. *Background.* FDA has established zero tolerances in tissues of chickens, swine, pheasants, and quail, in milk and eggs for penicillin, its salts and residues. Negligible tolerances of 0.05 part per million exist for the uncooked edible tissues of cattle and turkeys. In all cases the tolerances are a function of the lowest limit that the penicillin assay methods can reliably measure; therefore, the agency in effect permits no residue of penicillin in human food. FDA established these "zero" tolerances because there is no scientific evidence to support a no-effect level for penicillin or its metabolites on the human or animal intestinal flora or on the induction of hypersensitivity. Violative, over tolerance, penicillin residues are regularly reported by the U.S. Department of Agriculture, Animal and Plant Health Inspection Service residue monitoring programs. The FDA followup investigations on the reported violations demonstrate that two routes of administration are primarily responsible for the violations, injection and feed use; and most of the violations are caused by the product misuse, including failure to follow the labeled withdrawal period.

2. *Criterion.* FDA's guidelines requested the following for antibiotics:

> Controlled studies * * * to determine whether or not an antibacterial drug used as subtherapeutic levels in the feed of animals results in residues of the parent compound, metabolites, or degradation products in the food ingested by man which are capable of causing (1) an increase in the prevalence of pathogenic bacteria; (2) an increase in the resistance of pathogenic bacteria to antibacterial drugs used in human clinical medicine.
>
> Controlled studies in appropriate test animals shall be conducted to determine whether the consumption of food produced by animals receiving antibacterial drugs will result in:
>
> (a) An increase in the intestinal flora of the prevalence of pathogenic bacteria;
>
> (b) An increase in the degree and spectrum of resistance of the intestinal flora to drugs used in human clinical medicine.

Experimental procedures shall include appropriate consideration of maximum use level, minimum withdrawal time and established tolerances.

In addition, a literature survey shall be conducted to determine the incidence of reports of hypersensitivity resulting from antibacterial drugs in food. The literature survey shall include information regarding hypersensitivity reactions occurring as a result of parenteral or topical exposure to antibacterial drugs as well as those ingested in food. When hypersensitivity has been shown, experiments in appropriate laboratory animals must be conducted to develop estimates of what level of antibacterial drugs in food will cause the production of hypersensitivity.

3. *Data submitted.* Because there is a "zero" tolerance for penicillin and no residues are expected when penicillin-containing products are used in accordance with their labeled withdrawal periods, the sponsors of penicillin were exempted by the Director from submitting the test data. Thus, no data have been provided by the sponsors to show whether the consumption of food produced by animals receiving subtherapeutic levels of penicillin will result in an increase of pathogenic bacteria in the intestinal flora of animals or an increase in the degree and spectrum of resistance of the intestinal flora to drugs used in human clinical medicine.

The firms were required and did, in fact, provide literature data on hypersensitivity reactions to penicillin. These documented the well known alergic and anaphylactic reactions occurring from the penicillins and their degradation products. Human reactions to milk residues after treatment of infections of mammary glands with penicillin was a frequent cause of allergic response; consequently, withdrawal periods from drug usage have been developed before edible products are marketed. One instance (Ref. 1) was cited of a severe hypersensitivity reaction to ingested pork containing penicillin residues.

4. *Director's Analysis and Conclusions.* A study carried out by Katz et al. (Ref. 2) examined the effect of feeding penicillin on the development of residues in edible tissues and the nature of the residues. Although no tissues contained detectable penicillin or its degradation products, penicillin and its degradation products were detected in the crop, proventriculus, gizzard, and duodenum, but not in the small intestine from where it might be absorbed into other body tissues. At the same time chicken feces contained high levels of antibiotic resistant Gram-negative lactose-fermenting organisms (presumably *E. coli*), although no penicillin was present in the feces.

The study, however, raises a question about the safety of penicillin. Although no tissue residues were detected, the feces of broilers fed growth promotant levels of penicillin in their diet exhibited a fairly high percentage of antibiotic-resistant, lactose-fermenting organisms. The resistance was found in spite of the fact that no antibiotic activity could be found in the duodenum of the birds. Accordingly, Katz undertook to investigate the ability of penicilloic acid, one of the major degradation products, to stimulate the development of resistant organisms in the intestinal tract. Groups of birds on three rations were studied, a basal ration, a ration of 50 grams penicillin per ton of feed, and a ration of 50 grams of penicilloic acid of feed. Two resistance markers, tetracycline and streptomycin, were separately incorporated in the agar to act as indicators of resistance.

The percentage of lactose-fermenting organisms in the feces of birds on the basal ration remained relatively low for the period of the experiment, but the birds on the penicillin and penicilloic acid diets showed a markedly higher level of such organisms in their feces. Although the results exhibit some variation due to several experimental factors, the resistance pattern of the lactose-fermenting organisms isolated showed a continuous rise in the percent resistance as reflected in the streptomycin marker. The resistance pattern reflected by the tetracycline marker was more variable, but definitely present. However, the levels of drug resistant lactose-fermenting organisms found in the feces of birds from both the penicillin and penicilloic acid supplemented feeds are at least four times greater than the levels found from birds fed the basal ration. Although not statistically proven, the marked increase in resistance reflected by the marker strongly supports the premise that penicilloic acid can stimulate the development of resistance.

Accordingly, the Director must conclude that feeding subtherapeutic levels of penicillin to chickens may cause an increase in resistant lactose-fermenting organisms. Since the principal lactose-fermenting organisms are *E. coli*, and antibiotic resistant *E. coli* have been demonstrated to transfer R-factors to pathogens, the Director must conclude that the subtherapeutic use of penicillin may contribute to an increase in the prevalence of pathogenic bacteria in the intestinal flora of chickens which is contrary to the criterion established. No data have been submitted to rebut this, and for this reason also the Director must conclude that penicillin has not been shown to be safe.

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V. EFFECTIVENESS

In the FEDERAL REGISTER of July 17 and 21, 1970 (35 FR 11533, 11647, 11650) FDA announced the conclusions of the National Academy of Sciences/National Research Council Drug Efficacy Study Group concerning the penicillin-containing premixes intended for subtherapeutic and therapeutic use in animal feeds. The NAS/NRC evaluated these preparations as probably effective for growth promotion and feed efficiency and concluded that for the remaining claims the products lack substantial evidence of effectiveness that each ingredient designated as active makes a contribution to the total effectiveness claimed for the drug.

The agency concurred with these evaluations, and it provided the manufacturers of these products 6 months to submit adequate documentation of the effectiveness.

Section 512 of the act (21 U.S.C. 360b) requires that a new animal drug have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. For fixed combination drugs, § 514.1(b)(8)(v) (21 CFR 514.1(b)(8)(v)) requires that each ingredient designated as active in any new animal drug combination must make a contribution to the effect in the manner claimed or suggested in the labeling. Furthermore, if in the absence of express labeling claims of advantages for the combination such a product purports to be better than either component alone, the sponsor must establish that the new animal drug has that purported effectiveness. The requirement of effectiveness includes the requirement that the most effective level for each compound be used. In the case of drug combinations for concurrent therapy, the requirement of effectiveness includes the requirement that the dosage of each component is such that the combination is safe and effective for a population of significant size specifically described in the labeling as requiring such concurrent therapy. Therefore, to demonstrate that the penicillin-containing premixes are effective for therapeutic use, the sponsors must submit, in accordance with section 512(d)(3) of the act, substantial evidence consisting of adequate and well controlled investigations, as defined by § 514.111(a)(5) 21 CFR 514.111(a)(5)), including field investigations, satisfying these requirements.

No interested person has ever submitted substantial evidence that the penicillin-containing premixes are effective for the claimed therapeutic uses. For this reason the Director concludes that there is a lack of substantial evidence that the products are effective for therapeutic use in animal feed. Moreover, this action will assure that these levels are not used illegally to replace the subtherapeutic uses that are also being withdrawn.

VI. CONCLUSION

Pursuant to § 558.15, the holders of approved NADA's for penicillin-containing drug products intended for subtherapeutic use in animal feeds have the burden of establishing that this use is safe in accordance with the criteria and guidelines established by that regulation in addition to the basic requirements imposed by the general safety provisions of the Federal Food, Drug, and Cosmetic Act. The Director in this notice has set forth in detail the basis for the criteria and guidelines implementing the regu-

lation and this action. The holders of the approved NADA's have failed to satisfy the legal requirements imposed by the regulations, and they have failed to resolve the basic safety questions that underlie the subtherapeutic use of penicillin in animal feed.

(a) The pool of R-plasmid-bearing organisms is widespread in the environment of man and animals, and antibiotic resistance is increasing in pathogenic and nonpathogenic *E. coli* and Salmonella. The resistance patterns observed in these *E. coli* and Salmonella isolated from animals are similar, and these patterns are similar to the resistance patterns observed in the strains isolated from man. The R-plasmids found in organisms isolated in man and animal are indistinguishable, and common serotypes of these organisms infect both man and animals.

The studies submitted by the holders of approved NADA's through the Animal Health Institute confirm the prevalence of R-plasmid-bearing organisms and the ability of these organisms to transfer R-plasmids to other strains, even in the absence of antibiotic pressure. The AHI studies were also inadequate to measure the duration and prevalance of the Salmonella infections because demonstrably inadequate measuring techniques were used to gather the information.

(b) The potential for harm arising from a compromise of therapy is well documented. None of the studies submitted on compromise of therapy address the fundamental issue—the ability of R-plasmid-bearing organisms to interact and donate these plasmids to other organisms in the intestinal tracts of animals and to acquire resistance to a drug related to the subtherapeutic drug given. Furthermore, no evidence was submitted to show that the effectiveness of subtherapeutic penicillin use over time is not being altered by the development of R-plasmid-bearing organisms.

(c) The evidence demonstrates that R-plasmids controlling pathogenicity, drug resistance, and intestinal motility can and do cotransfer in vitro and in vivo.

(d) Subtherapeutic doses of penicillin and penicillanic acid in chickens causes an increase in drug-resistant lactose-fermenting organisms, e.g., *E. coli*, in their feces. This phenomenon demonstrates a potential for harm, and adequate refuting evidence has not be submitted. In addition, inadequate evidence has been submitted to negate questions on the potential for harm associated with penicillin hypersensitivity and subtherapeutic penicillin use.

(e) Under § 558.15, the holders of approved NADA's were required both to file commitments to conduct studies that would conclusively resolve the safety of the subtherapeutic use of antibiotics in animal feeds and actually to conduct those studies. To ensure compliance with the letter requirement, the regulation required holders of the approved NADA to file periodic progress reports on the studies. The Director is proposing to withdraw approval of all NADA's for which evidence was submitted in accord with § 558.15 purporting to resolve the safety issues, and he is unaware of any sponsor that filed a commitment to conduct the requisite studies but that submitted no evidence. Nevertheless, the Director concludes that the approval of any NADA for which a commitment to conduct appropriate studies was filed but whose holder filed no evidence should be withdrawn on the grounds that the holder of the NADA has failed to establish and maintain records and make reports as required by appropriate regulation.

Additionally, under section 512 of the act, the holders of the approved NADA's have the burden of demonstrating that the products are effective for their indications of use. Based on the evidence now before him, the Director is unaware of any adequate and well controlled investigations demonstrating that the penicillin-containing premixes are effective for the therapeutic uses.

On the basis of the foregoing analysis, the Director is unaware of evidence that satisfies the requirements for the safety of penicillin-containing premixes as required by section 512 of the Federal Food, Drug, and Cosmetic Act and § 558.15 of the agency's regulations. Accordingly, he concludes, on the basis of new information before him with respect to these drug products, evaluated together with the evidence available to him when they were originally approved, that the drug products are not shown to be safe under the conditions of use prescribed, recommended, or suggested in their labeling. The evidence, in fact, indicates that such penicillin use may be unsafe, particularly if the higher or therapeutic levels of penicillin should be used as substitutes for the levels currently used subtherapeutically.

Therefore, the Director announces he is proposing to withdraw all approvals for penicillin-containing premix products intended for use in animal feed whether granted under section 512 of the act or section 108(b) of the Animal Drug Amendments of 1968 (Pub. L. 90-399) on the grounds that they have not been shown to be safe, and lack substantial evidence of effectiveness for therapeutic use. Notice is hereby given to holders of the approvals listed above and to all other interested parties. If a holder of an approval or any other interested person elects to avail himself of an opportunity for hearing pursuant to sections 512(e)(1)(B), 512(e)(1)(C), and 512(e)(2)(A) and § 514.200 (21 CFR 514.200), the party must file with the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, a written appearance requesting such a hearing by September 29, 1977, giving reasons why approval of the application should not be withdrawn and providing a well-organized and full-factual analysis of the scientific and other investigational data that such person is prepared to prove in support of its opposition to the Director's proposal within 60 days. Such analysis shall include all protocols and underlying raw data and should be submitted in accordance with the requirements of § 314.200 (c)(2) and (d) (21 CFR 314.200 (c)(2) and (d)).

The Director will soon issue a separate notice in the FEDERAL REGISTER proposing to withdraw approval of all tetracycline-containing new animal drug products intended for certain subtherapeutic uses in animal feeds on the grounds that they have not been shown to be safe under section 512(e)(1)(B) of the act and § 558.15. Data addressing the safety and effectiveness issues for the tetracycline component of those products should be submitted at that time.

The failure of a holder of an approval to file timely written appearance and request for hearing as required by § 514.200 constitutes an election not to avail himself of the opportunity for a hearing, and the Director of the Bureau of Veterinary Medicine will summarily enter a final order withdrawing the approvals.

A request for a hearing may not rest upon mere allegations of denials, but it must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person who requests a hearing, making findings and conclusions, denying a hearing.

Four copies of all submissions pursuant to this notice must be filed with the Hearing Clerk. Except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, responses to this notice and copies of published literature cited in this notice not appearing in journals designated by 21 CFR 310.9 and 510.95 may be seen in the office of the Hearing Clerk, Food and Drug Administration, between 9 a.m. and 4 p.m., Monday through Friday.

If a hearing is requested and is justified by the applicant's response to this notice of opportunity for hearing, the issues will be defined, an administrative law judge will be assigned, and a written notice of the time and place at which the hearing will commence will be issued as soon as practicable.

The Director has carefully considered the environmental effects of this action, and because it will not significantly affect the quality of the human environment, he has concluded that an environmental impact statement is not required for this notice. A copy of the environmental impact assessment is on file with the Hearing Clerk. Moreover, in a notice published in the FEDERAL REGISTER of May 27, 1977 (42 FR 2739) the Commissioner of Food and Drugs requested data concerning the potential environmental impact of a series of regulatory actions, including this one, designed to restrict

the subtherapeutic use of antibacterials in animal feeds. If the public discussion and information gathered warrant, a comprehensive environmental impact statement will be prepared, evaluating the impact of all the actions as a single program.

NOTE.—The Director has also carefully considered the inflation impact of the notice, and no major inflation impact, as defined in Executive Order 11821, OMB Circular A–107, and Guidelines issued by the Department of Health, Education, and Welfare, has been found. A copy of the FDA inflation impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

(Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343–361 (21 U.S.C. 360b)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Director of the Bureau of Veterinary Medicine (21 CFR 5.84).)

Dated: August 24, 1977.

C. D. VAN HOUWELING,
Director, Bureau of Veterinary Medicine.

[FR Doc.77-24971 Filed 8-29-77;8:45 am]

Mr. McLain. In the notice FDA proposed to withdraw approval for all animal feed uses of penicillin on three grounds. I would like to go briefly through those three grounds. One is that penicillin has not been shown to be safe for subtherapeutic uses. Briefly that is growth promotion and disease prevention. Second is that there is substantial evidence that it is not effective for therapeutic uses. Third is that the applicants had not maintained the appropriate records and filed the required reports.

My question, Mr. Ahart, is based on a statement made on page 30 of your report. That statement is:

> As of April 1, 1977, the effectiveness of subtherapeutic levels of penicillin for disease prevention has not been established. FDA regulations, however, permit the use of penicillin for subtherapeutic levels in the feed of chickens and turkeys for the prevention of several diseases.

My question is this. Could not FDA in its August 30 notice have also requested the withdrawal of approval of these drugs based on the lack of efficacy for disease prevention and other subtherapeutic uses?

Mr. Ahart. I think that you are correct on that, Mr. McLain. Mr. Linz is more familiar with that than I am. I think he has discussed with FDA why they utilized the safety aspect for the withdrawal of the subtherapeutic uses rather than the effectiveness aspect.

Mr. Linz. I think FDA believes that the safety issue is a more clear-cut route in this case. However, there has been no data submitted to FDA for the disease prevention uses of penicillin.

Mr. McLain. Your report also states, does it not, than an FDA official stated to you that lack of efficacy is an easier burden to meet from the agency's perspective in an action to withdraw approval of a drug? Is that not true?

Mr. Linz. Yes.

Mr. McLain. At the same time, you say in your report that the acting Director of the Division of Drugs for avian species at the Bureau of Veterinary Medicine stated that no data had been submitted to FDA to support the effectiveness of penicillin disease prevention in chickens and turkeys. Would that not seem like that is a prima facie case for withdrawal for lack of efficacy for disease prevention?

Mr. Linz. I think for those uses, yes.

I think you may be getting to a point where they are dividing their action into so many different pieces that it may become more difficult. For growth promotion they are going to have to proceed on lack of safety. They are generally recognized as effective for growth promotion. It is a matter of how fine they want to divide their action.

Mr. McLain. Your report further states that as early as 1968 the National Academy of Sciences questioned and found that penicillin was not effective for all the labeling claims for which it was marketed. I take that to mean that, this being 1977, FDA has allowed the continuous marketing of penicillin for disease prevention purposes without ever having made a finding as to the efficacy of that drug for the last 9 years. Is that correct?

Mr. Linz. That is correct.

Mr. McLain. FDA, as you know on April 15, announced that they also intended to take action relative to safety and efficacy of tetra-

cyclines. In your examination of the data available to FDA, what evidence as to efficacy, for whatever purpose, has been submitted with regard to tetracyclines?

Mr. LINZ. There are some data on the effectiveness of tetracyclines. We have not gone into great detail as far as specific uses. What we have done is look at the recommendations of FDA's drug efficacy study implementation task force. Several of the recommendations they have made are to switch from subtherapeutic uses to short-term therapeutic use for particular disease conditions. Many of the subtherapeutic disease prevention uses would be discontinued if that recommendation were implemented.

Mr. MCLAIN. To follow up on that, to talk about the recommendations of the people from the Bureau of Veterinary Medicine, you refer to the establishment in 1975 of the National Advisory Food and Drug Committee and then the subsequent establishment of a subcommittee. What was the stated purpose or the charge given to the subcommittee?

Mr. LINZ. To review the benefits and risks of a number of antibiotics and reach a conclusion as to their overall usefulness.

Mr. MCLAIN. That evidence that they reviewed was submitted by FDA to them, was it not?

Mr. LINZ. There were also some presentations from industry and some from university scientists.

Mr. MCLAIN. In the midst of their deliberations which began January of 1976 and carried on until their report of January of 1977, in April of 1976 the Bureau of Veterinary Medicine submitted to the subcommittee their recommendations regarding penicillin.

Is it or is it not the conclusion of the GAO that FDA had sufficient data available to them independently to initiate a regulatory action at that time as regards penicillin?

Mr. LINZ. I believe at that time they did have adequate data. If they reached their conclusions or recommendations without the specific input from the advisory committee, I think from that point they probably could have initiated action.

Mr. MCLAIN. I have the same question as regards tetracyclines. The BVM submitted to the subcommittee in June of 1976 their recommendations and conclusions as to what action they believed was appropriate regarding restriction of tetracyclines. Could not FDA have initiated regulatory action independently in June of 1976 regarding tetracyclines?

Mr. LINZ. Yes; I believe they could.

Mr. MCLAIN. I do not have any further questions at this time, Mr. Chairman.

Mr. MOSS. Mr. Wunder?

Mr. WUNDER. Thank you, Mr. Chairman.

I would like to follow up on some questions asked by Mr. McLain as to the burden of proof. With respect to tetracyclines and penicillin, and others, the other antibiotics that are used for subtherapeutic purposes, those drugs at one time or another were approved for use and were approved for that use. Is that not true?

Mr. AHART. I think that is correct, Mr. Wunder.

Mr. WUNDER. When FDA wants to remove a drug that has been approved from the market, who has the burden of proof then? Is it

the sponsor? Does he retain a continuing burden or does the burden shift to FDA?

Mr. AHART. I think under the law—I can refer to the specific language I believe—once questions have been raised, the burden is on the sponsor to bring forth evidence showing that the drug is safe and effective for the conditions of use specified on the labeling or FDA must withdraw the approval for those uses.

Mr. WUNDER. "Once questions have been raised" is the language that you used. How much has to be raised? Is there any level? Does there have to be substantial evidence, some evidence, or a scintilla of evidence? What is the standard?

Mr. AHART. Perhaps it would be better to refer to the specific language of the law, which I believe we have with us.

Let me ask Mr. Jojokian to read the language of the act itself.

Mr. JOJOKIAN. "The Secretary shall after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) with respect to any new animal drug if the Secretary finds (A) that experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; and (B) that new evidence not contained in such application and not available to the Secretary after such application was approved or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subsection (H) of paragraph (1) of subsection (d) applies to such drug, or (C), on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that such drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."

Mr. SANTINI. Mr. Chairman, may I have the citation of that authority?

Mr. Moss. Indeed, you may. Will you give the citation?

Mr. JOJOKIAN. I believe that is section 512(e)(1) of the law.

Mr. SANTINI. Section 512(e)?

Mr. JOJOKIAN. Section 512(e)(1).

Mr. SANTINI. Thank you.

Mr. WUNDER. The question becomes what under the statute is new evidence. Must the new evidence show clearly and convincingly, beyond a reasonable doubt, by preponderance? Is there a standard? Or is it some evidence?

As I understand it, there is dispute in the scientific community about the safety and efficacy of antibiotics on a subtherapeutic basis. Would that be true, Mr. Ahart, do you know?

Mr. AHART. On the question of degree of burden of proof and who has it, I think the burden is clearly with the manufacturers to show that it is, based on the language here. Whether it is preponderance or beyond a reasonable doubt or clear and convincing, I am really not prepared to answer you as to which of those three different tests it is.

It is a judgment of FDA and the Secretary on the question.

If you would like something more definitive on that, we would be happy to do some research or perhaps FDA would be in a better position to answer the question of what degree of evidence they feel is necessary to support the withdrawal of a drug for a previously approved use.

Mr. WUNDER. Thank you, Mr. Chairman.

Mr. Moss. Are there further questions?

If not, gentlemen, we want to thank you. I want to express my appreciation for another report by the General Accounting Office that reflects the professionalism that we have come to expect from your organization. We appreciate it.

Mr. AHART. Thank you, Mr. Chairman.

Mr. WAXMAN. Mr. Chairman, I would like to express to the gentlemen from GAO, particularly to Mr. Ahart, my concurrence with the chairman's review of this report.

Last Friday, Mr. Ahart and I had a disagreement over the quality of a report which I did not think met the traditional high standards of the General Accounting Office.

I want to congratulate them when they do a good job, just as I will criticize them when I am troubled by the quality of their work.

Mr. AHART. Thank you, Mr. Waxman.

Mr. Moss. Our next witness is Dr. Stanley Falkow, professor of microbiology and genetics, University of Washington.

Doctor, I wonder if I could ask you to stand and be sworn as a witness.

Do you solemnly swear that the testimony you are about to give to this subcommittee shall be the truth, the whole truth, and nothing but the truth, so help you God?

Dr. FALKOW. Yes; I do.

Mr. Moss. Would you identify yourself to the reporter for the hearing record?

TESTIMONY OF STANLEY FALKOW, PH. D., PROFESSOR OF MICROBIOLOGY AND GENETICS, UNIVERSITY OF WASHINGTON, SCHOOL OF MEDICINE

Dr. FALKOW. I am Prof. Stanley Falkow, University of Washington, School of Medicine, Seattle.

Mr. Moss. We are pleased to have you. We will be pleased to hear your statement.

Dr. FALKOW. Thank you, sir.

Chairman Moss and members of the subcommittee, I am pleased to have been invited to discuss with you the potential hazards to human health associated with antibiotics in animal feeds. I understand that this subcommittee for some time now has monitored the Food and Drug Administration's deliberations of this question.

Antibiotic use over the last 30 years has brought great benefits to us all—but these benefits have not been without cost. As antibiotic therapy has developed the number and type of antibiotic-resistant bacteria has increased. It is not so much that infections cannot be treated. Rather, it is often necessary to resort to secondary antibiotics that may be less effective, far more costly and, in some instances, more toxic.

The development of microbial antibiotic resistance due to human therapy is a difficult problem. Yet, the situation is incredibly complicated by the fact that virtually all food animals raised in the United States and other developed countries receive substantial amounts of antibiotic for growth promotion and disease prophylaxis. The antibiotics employed for use in animal husbandry and even for plant protection are very often the same agents used for therapy in man and for the treatment of overt disease in animals.

Since it is established that antibiotic use—for whatever purpose—selects for resistant bacterial populations, the desirability of the nontherapeutic use of antibiotics, such as growth promotion in animals, has been the cause of much controversy. Because of public health concerns, in 1969 Britain placed restrictions on the use of antibiotics in feeds. In 1970 our Food and Drug Administration organized a task force to study the human and animal health hazards associated with antibiotics in animal feeds.

The main recommendations of this FDA task force were published in 1972 and were basically similar to those adopted in England. As you know, the recommendations of the task force were not immediately implemented; and it is only within the past month that FDA has published a notice of proposed rulemaking which would in effect, one, discontinue use of penicillin in all animal species for purposes of growth promotion and/or feed efficiency and, two, discontinue use of penicillin for disease prevention when effective substitutes are available. Commissioner Donald Kennedy of FDA has indicated that a similar proposal to withdraw tetracycline will be forthcoming.

I think these proposed actions are sound. I found the documentation accompanying the notice of proposed rulemaking—Federal Register 42: 43770–43793—to be reasonably complete and, I think, compelling evidence in support of FDA's suggested action. In my judgment, it is a long overdue action; and it is perhaps a sad commentary that we are now only implementing regulations that have been in effect in Great Britain for almost 7 years and have also been adopted by the entire European Common Community and Japan.

But what is the evidence that leads to the conclusion that antibiotics in animal feeds may be deterimental to human health? The guidelines considered by FDA to establish the presence of a hazard to human and animal health were, in part:

One, an antibacterial drug fed to animals shall not have a significant effect on the ecology or the resistance characteristics of salmonella bacteria in food animals.

As you may know, salmonella organisms are one of the more common causes of food poisoning in man.

Two, an antibacterial drug fed to animals shall not increase the reservoir of enteric bacteria resistant to antimicrobic agents employed for therapy of human or animal disease.

Three, the use of antibacterial in feed should not enhance the pathogenicity of bacteria for animals and man.

Clearly, if one is to evaluate these criteria, it is necessary to understand something of the genetic and ecological basis of antibiotic resistance in bacteria. I will not bore the members of this committee with an academic lecture. Classes do not begin until next week.

I hope it will suffice to say that the bacteria possess molecular parasites called R-resistance-plasmids and that you will accept that: One, the vast majority of clinically significant bacterial antibiotic resistance is mediated by R-plasmids and, two, that R-plasmids are not stable entities but rather, under appropriate conditions, bacterial can share their plasmids in a most promiscuous fashion by means of a primitive sexual process.

The genetic makeup of R-plasmids make it inevitable that even occasional pressure by antimicrobial agents will result in some reservoir of resistant bacteria. Under most circumstances feeding an antibiotic rapidly results in the conversion of normal bacterial flora from being predominantly sensitive to predominantly resistant. Intially, the resistance will usually be directed against the antibiotic that is ingested. That is, if you were to take tetracycline to cure acne, initially most of your intestinal bacteria would be resistant only to tetracycline. But, if the selection with tetracycline was carried out for a long period of time, the genetic nature of R-plasmids dictate that multiple resistance will arise.

In other words, the longer antibiotic pressure is applied, the more likely it becomes that your normal bacteria will not only become resistant to tetracycline but the sulfonamide, streptomycin, chloramphenicol, and other antibiotics as well. Hence, the net result of a human taking tetracycline for an extended period of time is the selection of a multiply-resistant bacterial flora. Similarly, the net result of feeding our food animals subtherapeutic doses of antibiotics has been the development of a multiply antibiotic-resistant bacterial flora.

Most humans are treated with antibiotics only sporadically, but most food animals are currently dosed with broad spectrum antibiotics for most of their lives. Large numbers of resistant nonpathogenic bacteria may be carried for long periods of time without ill effects and in fact the normal bacterial flora of most healthy livestock is multiply resistant to antibiotics.

That means if one were to go out today and simply pick at random farm animals and culture their feces, one would find, as we have found in our studies in calves, that something like 60 percent of the normal intestinal flora are multiply resistant to bacterial agents. That is just in a general survey. The same is true in pigs. The same is true in poultry.

The hazard of this reservoir of drug-resistant nonpathogenic bacteria within our food animals is that if the reservoir becomes very extensive, reaches a critical ecological mass so to speak, then drug resistance will inevitably flow into known pathogenic bacteria. Moreover, R-plasmids may also become associated with other plasmids which carry toxins and other determinants of bacterial virulence and, hence, the pressure of antibiotics may act like a two-edged sword to select bacteria both antibiotic resistant and pathogenic.

This latter contention, incidentially, can be fully documented from field studies done very recently.

One of the major concerns of the 1970 FDA Task Force on Antibiotic in Animal Feed and the recent Subcommittee on Antibiotics and Animal Feeds of the National Advisory Food and Drug Committee was concerned with the possible increase of resistant salmonella bacteria.

I believe that Dr. John Bennett of the Center for Disease Control will appear before this subcommittee, and certainly he is far more knowledgeable on this subject than I. Yet, I cannot resist pointing out that antibiotic resistance has increased in salmonellae isolated from both humans and animals. And there are great similarities in the resistance patterns of salmonella from humans and animals. This is true throughout the world, I might add, gentlemen.

But the question that haunted the first FDA task force and is still raised to this day is whether the R-plasmids of animal bacteria directly or indirectly find their way into humans and hence present a real threat to our health.

Direct extension of animal bacteria to man is easy enough to envision via the food chain. This is amply documented in the Federal Register—42:43770–43793. The most cogent evidence is that rural residents having close contact with animals or with uncooked meat have significantly elevated populations of resistant enteric bacteria. Moreover, salmonella infection of man is most often contracted by exposure to contaminated food and, as noted, antimicrobic resistance in animal salmonellae has been unequivocally shown to have increased over the past decade.

I believe Dr. Bennett will indicate that the number of superresistant strains—strains resistant to more than six antimicrobial agents—has increased tenfold in the past 5 or 6 years.

But what is the evidence of indirect transfer or, to be more precise, that bacteria of animals and man draw upon the same reservoir of R-plasmids? Therein lies the critical point. For example, it is extraordinarily difficult for many individuals to discern how the R-plasmids of antibiotic-resistant typhoid or dysentery organisms, both of which exclusively affect man and not animals, can be in any way linked to the use of subtherapeutic levels of antibiotics fed to animals. Yet, advances in plasmid biology and molecular biology in the past 5 years let us now confidently say that the identical R-plasmid species determining penicillin resistance is found in salmonella isolated from man and animals in England. The identical plasmid type is found in a typhoid strain isolated in a Mexican epidemic. That, incidentally, was the largest typhoid epidemic in recorded history. The identical plasmid type is found in an epidemic strain of dysentery bacteria found in Mexico and Costa Rica. The identical plasmid type is found in salmonella in man and animals in France. The identical plasmid type is found in our studies in a common colon bacillus, *E. Coli*, in humans and calves in the United States and so on. These plasmids have a common origin.

I do not argue that we owe the bulk of our resistance problem to the use of antibiotics in animals feeds. Unquestionably most resistance is selected by therapeutic use of antibiotics in humans. Nor does the available data suggest that there is a torrent of resistant strains or their plasmids reaching the human population from animals. But there is likely a fine mist or even a constant drizzle. The point is that total community antibiotic usage selects for a pool of genetic elements that are common and available to an ever-growing list of bacterial species.

The most recent additions to the list are particularly disquieting since they involve two microorganisms previously considered to be universally susceptible to penicillin. One of these, *Haemophilus in-*

fluenzae, is the cause of meningitis and other serious infections of young children. The other, *Neisseria gonorrhoeae*, is the cause of the most commonly reported bacterial infection in the United States. Both these organisms are strict parasites of man so I would understand that many would scoff at the idea that resistance in these organisms is related to the use of subtherapeutic levels of antibiotics in animals. Yet, it is impossible to distinguish between the R-plasmid genes specifying penicillin resistance in *Haemophilus*, *Neisseria*, or penicillin resistant colon bacillis residing in farm animals.

The recent statement by the FDA in their proposed action on penicillin summarizes the point well:

> Antibiotic resistant bacteria are now so widely distributed in the general environment that it is difficult to relate their appearance to a particular use, but any unnecessary practice that results in the ineffectiveness of antibiotics for the treatment of disease should be eliminated.

It would be my sincere wish that this philosophy be adopted with respect to both human and agricultural use of chemotherapeutic agents.

In my judgment, any practice that increases the reservoir of antibiotic resistance genes is a hazard. And the greater the reservoir of resistance genes, the higher the probability of untoward effects. I believe that there are two concentrated reservoirs of resistance genes within the total U.S. community. One is our hospitals; the other is the enormous reservoir of resistance genes induced in our livestock by feeding animals subtherapeutic levels of antibiotics to promote growth.

It is impossible to eliminate R-plasmids. Even if antibiotic usage in animal feeds was discontinued tomorrow, the reservoir of drug resistance in animals would not quickly disappear. But the situation may be improved by the general adoption of the prudent and discriminating attitude toward antibiotic usage set forth in the Swann report and the original FDA task force.

I have avoided all mention of economic consideration since I am not an economist. The question may well boil down to whether the cost in resistant human and animal infection is worth the increase in achieved food conversion. This is essentially a political question since it balances one advantage for the community against the other, and it is difficult to answer since the available data on health risk are more descriptive than quantitative—though, in my judgment, certainly real. Perhaps we must accept a certain debt in human disease for the antibiotics used in legitimate animal disease prevention and animal therapy. But, in my judgment, the debt of human disease should not include the consequences of broad spectrum antibiotic use for animal growth promotion.

Can there really be any legitimate argument that antimicrobial agents used therapeutically to treat infectious diseases of man and animals be prohibited for use as growth promoting agents when nontherapeutic alternatives are available? I do not think so, since this was the view of the Swann committee, the first U.S. FDA task force, the World Health Organization, the recent NAFDC subcommittee, and every other objective scientific body that has examined this question.

Mr. Moss. Thank you.

Mr. Santini?

Mr. SANTINI. Thank you, Mr. Chairman.

Dr. Falkow, I hope you will indulge me by commencing your lecture series early this semester and assist this member, who is an enthusiastic consumer of beef and also an enthusiastic perpetuator of my own existence. If either represents a jeopardy, I would appreciate any enlightenment that you might share.

I have, in initial comments, expressed a reservation that I did not want to be the victim of a psychological hysteria, the Chicken Little syndrome, which sometimes attaches itself to health-related issues.

I appreciate that you come forward with authoritative commentary. I would like to ask you a few questions that have troubled me in this context.

You have suggested that there are alternatives for the purpose of promotion of growth and for feed efficiency to penicillin. Are there alternatives to tetracycline? Are there alternatives for the promotion of growth and feed efficiency to the use of tetracycline?

Dr. FALKOW. Yes, sir. There are alternatives to both penicillin and tetracycline for growth promotion and feed efficiency.

Mr. SANTINI. What are they for tetracycline?

Dr. FALKOW. The same ones they would be for penicillin. They usually mix penicillin, tetracycline, and sulfonamide together; that is one of the most popular growth promoting things.

There is bacitracin, flavomycin. Virginiamycin has not yet been approved in the United States, I believe. Oleandomycin, I believe, has been approved. There are a number of other alternatives that I am sure Commissioner Kennedy can tell you.

It has been determined by the NAFDC subcommittee and by the first FDA task force that there are some disease conditions for which there are not adequate substitutes. In fact, when the subcommittee reported to the main body, they recognized certain instances where, for disease prevention, tetracycline should remain for therapeutic use. I would be the last to argue that this is not necessary for liver abscess, foot rot, anaplasmosis, and some of the other diseases.

But, for growth promotion, there are suitable alternatives. I cannot see using penicillin or tetracycline any longer for growth promotion.

Mr. SANTINI. In regard to your testimony again, you have stated in part, "The available data on health risk are more descriptive than quantitative."

Could you clarify that for me please?

Dr. FALKOW. Yes, sir.

May I first preface by saying, sir, that I have been giving testimony like this since 1969; it has not changed very much during that time. Since 1969, when I first appeared before the Salmonella task force, the same question has been asked.

I cannot produce a body——

Mr. SANTINI. I am glad to be continuing that tradition.

Dr. FALKOW. I cannot produce bodies and say, "These people died because of R-factors that were in the salmonella or other bacteria that infected them." But it has been documented that resistant salmonella kill people and resistant salmonella have killed people in some cases because of treatment failure. I believe there is a definite health risk. I think we have seen increasing resistance in the human

population; we have certainly seen increasing resistance in the animal population. No one can convince me—and there is no data to show to the contrary—that the increased resistance in animal bacteria is not having a deleterious effect on animal disease.

Mr. SANTINI. Is there any division in the scientific or medical community on that conclusion?

Dr. FALKOW. Yes. There has been division that I am aware of. But, as I indicated in the last sentence of my statement, every objective scientific body that has examined this question has unanimously come out with the same conclusion, sir. That is that the use of antibiotics for subtherapeutic growth promotion should be eliminated. The World Health came to that conclusion. The Swann committee report came to that conclusion. The European Common Market came to that conclusion. Japan has come to that conclusion.

I mean, there must be some basis, sir.

Mr. SANTINI. And certainly your opinion reinforces that.

Dr. FALKOW. Yes, sir. I make no secret about that.

Mr. SANTINI. You have indcated, in part, in your statement: "I do not argue that we owe the bulk of our resistance problem to the use of antibiotics in animal feeds."

Could you summarize for me, sir, some of the sources? You have done that in part in your statement. Would you summarize for me the other causes?

Dr. FALKOW. Yes, sir. It is overuse and misuse of antibiotics in human medicine. That is it in great part.

There are many cases, sir, when one cannot avoid misusing antibiotics in human medicine. I could give you examples, but it doesn't matter. They are numerous. I can provide the committee with numerous citations in the medical literature where this subject has been discussed.

We do not get resistance just from misuse of these things in agriculture; they are misused in human medicine all the time.

Mr. SANTINI. Have there been, Dr. Falkow, any reported increases in the proportion of drug-resistant salmonella or other bacteria from farm animals fed subtherapeutic levels of antibacterial drugs?

Dr. FALKOW. Absolutely.

Salmonella resistance has increased—Is Dr. Bennett appearing befor the committee, sir?

Mr. Moss. He will be here on Friday.

Dr. FALKOW. I think Dr. Bennett can certainly answer that question. But, what I know of the information he has, there is no question. A report that recently was in the Journal of Infectious Diseases, showed that salmonella from both man and animals has increased dramatically in the past 5 or 6 years.

Mr. SANTINI. Are there contradictory studies suggesting that there have been decreases or declines in isolated population studies?

Dr. FALKOW. I do not honestly recall any indepth study of antibiotic resistance that has—most have shown an increase. Some have shown that the status quo was maintained. That is, if it were 30 percent resistant, the next time that they were sampled they were still 30 percent resistant. That's a lot of resistance.

Mr. SANTINI. So has there been a substantial increase in drug consumption by the American populace over that same time frame of 30 years?

Dr. FALKOW. Yes; although I think the increase in antibiotic usage has far outpaced the growth in population. As I remember the number, over one period when the population increased 5 percent, antibiotic resistance doubled.

Mr. SANTINI. Population increase would not be the issue; it would be percentage of drug consumption.

Dr. FALKOW. Percentage of consumption was much, much greater; yes.

Mr. SANTINI. Would that, then, be the primary cause, in your judgment?

Dr. FALKOW. The primary cause of resistance?

Mr. SANTINI. Of resistance reduction; yes.

Dr. FALKOW. There has been no reduction in resistance, sir. We have either maintained the status quo, we have increased it, or we find new species, the most recent of which is the report from South Africa of multiply-resistant pneumococci. That is the most common cause of bacterial pneumonia. It is the third organism in the past 5 years which has been considered universally susceptible to penicillin that has fallen by the wayside.

Mr. SANTINI. Then there has been a sort of serious decrease in resistance.

Dr. FALKOW. Increase in resistance.

Mr. SANTINI. Excuse me—increase.

Dr. FALKOW. Yes.

Mr. SANTINI. Then the issue remains as to the cause for the increase in resistance.

Dr. FALKOW. Yes, sir.

Mr. SANTINI. One of those causes certainly is the increased consumption of drugs.

Dr. FALKOW. Yes, sir.

Mr. SANTINI. The other cause, in your belief, would be the possibility of transmission—shedding, I guess, is the word—from the consumption of poultry, swine, or beef product.

Dr. FALKOW. Yes, sir. That has been documented.

Mr. SANTINI. That it is scientifically possible to shed.

Dr. FALKOW. It has been shown that poultry contaminated with resistant organisms, when consumed or handled by a consumer, will show the same resistant bacteria that were on the contaminated poultry are now in the consumers intestinal flora.

Of course, it is known that we get most of our salmonella from eating red meat and poultry. So, we ingest fairly good numbers of these things.

Mr. SANTINI. Then the link in the causal chain that has not yet been forged is the source.

Dr. FALKOW. The argument has been, at one time, that there were separate resistant bacteria in animals and separate resistant bacteria in humans and even separate reservoirs of R-plasmids.

That has been shown to be not correct. The point is that we cannot distinguish between many organisms of animal and human origin; they are the same. We cannot distinguish between the R-factors; they are the same.

So, there is an R-plasmid reservoir which is common to both animals and humans. If one reduces the reservoir of resistant organisms

in any one group, one will probably have a beneficial effect on health in all groups.

Mr. SANTINI. Thank you.

Thank you, Mr. Chairman.

Mr. Moss. The Chair recognizes the gentleman from California, Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. Falkow, you mentioned the recent pneumonia outbreaks in South Africa as one of three epidemics that may be related to new strains of antibiotic resistance bacteria. What are the other two?

Dr. FALKOW. We have had three organisms that have become resistant in the past 5 or 6 years which have been considered to be universally susceptible to penicillin. By that I mean, a physician did not really bother to get a sensitivity test on the organism; he simply knew it was going to be sensitive to penicillin or ampicillin.

The first one to drop by the wayside was *Haemophilus influenzae*. That was first detected here in Washington in the Children's Hospital with three fatal cases of meningitis. The organisms were found to be resistant to ampicillin and found to have R-plasmids. Our laboratory studied the R-plasmids and found that the plasmid genes in *Haemophilus* were the same as found in common enteric bacteria.

The next organism to go resistant was anticipated. In fact, it had been predicted that the gonococcus, the cause of gonorrhea, was going to become penicillin resistant; and it did. That happened roughly a year ago. We now find worldwide dissemination of penicillin resistant gonococci.

The next one has just been reported. It is the appearance of penicillin resistant pneumococci in South Africa. It is not clear how serious this is yet and whether or not there will be worldwide dissemination. But one interesting thing has consistently happened. It is interesting to me epidemiologically. When unique resistance appears in one place, it seems to appear almost around the world simultaneously. This happened with *Haemophilus*. No sooner was there a report made in Washington, D.C., than people were reporting it in England, Seattle, and all over the world.

People are now concerned, for example, that the organisms that cause streptococcal infection, common strep throat, now treated by penicillin, will next fall prey to resistance. Certainly, R-factors have been documented in some streptococcal species. Resistant streptococci have been shown to arise in feed animals, as a result of feeding subtherapuetic levels of antibiotics.

Mr. WAXMAN. Are you suggesting that, when a strain of resistant bacteria develops, it may spread to areas where there may not be widespread use of antibiotics in animal feed?

Dr. FALKOW. It is a subtle kind of thing, sir. If resistant, nonpathogenic bacteria build up to some extent it does not really make any difference; they are simply around us. They live, and they are happy. We get along fine with them. They do their thing; we do ours. But, if the nonpathogenic bacteria now transmit their R-plasmids to a pathogenic organism, it is a different story.

A pathogen has got its own thing going. It may pass from person to person or animal to animal and causing, not always disease, but certainly it has a good competitive advantage; it is more aggressive.

Once it gets drug resistant, its own aggressiveness will keep it going whether or not there is any more antibiotic selection applied.

Mr. WAXMAN. You have raised the specter of a return to the Middle Ages of medicine—before antibiotics were discovered.

Dr. FALKOW. No; I really do not think that. I would not want to be associated with that kind of a scare story.

There are cases in the hospital of people in intensive care units, burn units, where in fact you get organisms selected which are really untreatable.

But, no; we can still treat common infections. As I indicated in my testimony, however, resistance means that very often, one must go to secondary drugs that are more expensive or more toxic. For example, in the Philippines, as a result of the resistant gonococcus, penicillin can no longer be used. The cost per patient was something on the order of 50 cents before penicillin resistance. We would, in this country, go to something that costs on the order of $2 per patient when faced with a resistant strain. But, in the Philippines they could not, so they had to go to a substance which, it turns out, is toxic.

It is that kind of thing.

Mr. WAXMAN. As you know, the General Accounting Office believes the FDA utilized the National Advisory Committee improperly. With respect to their recommendations, are you aware of any information contained in the Committee's recommendations which were not contained in the recommendation of the 1972 task force?

Dr. FALKOW. No, sir. The 1972 recommendations were the same; in fact, perhaps a little more restrictive.

I was a member of the recent subcommittee.

Mr. WAXMAN. This is the three-person subcommittee?

Dr. FALKOW. I was not one of the three persons, but I was consultant to the three persons.

Mr. WAXMAN. Were you involved at all with the advisory committee? Was your involvement only indirect because the advisory committee acted on the subcommittee's recommendations?

Dr. FALKOW. The subcommittee made the report to the full advisory committee. I had input, certainly, on the report that was to be made; but was appalled when I found out what happened on January 24.

Mr. WAXMAN. Do you see any reason why a distinction should have been made between penicillin and tetracycline?

Dr. FALKOW. I am not sure I understand, sir.

Mr. WAXMAN. I understood from GAO's testimony that the full committee made a distinction between penicillin and tetracycline on the basis that there were alternative antibiotics for penicillin but more for tetracycline.

Dr. FALKOW. No; I did not understand that logic of the full committee.

I understand the logic that there is a distinction betwen penicillin and tetracycline in the sense that there are some disease-preventative uses for which tetracycline may be employed that penicillin would not be. In other words, as I understand it there are alternatives for virtually every use of penicillin. When it comes to tetracycline, they are clear alternatives for growth promotion. But in some instances, it was determined by the Bureau of Veterinary Medicine—and certainly we

heard testimony from a number of interested groups that appeared before the subcommittee—that for some disease conditions in animals, there were not appropriate therapeutic alternatives or disease-prevention alternatives for tetracycline.

That was reflected in the report of the subcommittee to the full body.

The decision of the full committee to accept the penicillin recommendations and reject tetracycline recommendations, to me indicated they could not have read anything very carefully.

Mr. WAXMAN. Perhaps they were influenced by some very active members?

Dr. FALKOW. I do not know about that.

I did write a letter to Congressman Moss at the time. I think it is on record. It was what my felings were.

Mr. WAXMAN. Under what circumstances should the FDA permit the subtherapeutic use of antibiotics in animal food?

Dr. FALKOW. I think, from what I understand, the economic advantages are clear. There have been economic studies done to the extent that, if you use no-growth promotion agent, then you take a fairly severe economic beating. But the plea has been, through any number of bodies, to try to use growth promotion agents that are not used in human or animal therapy; if at all possible, that does not induce cross-resistance to agents used in human and animal therapy. Some of these do exist. Others, there is some cross-resistance.

That has been the major thrust of recommendations ever since, well, at least 1970.

Mr. WAXMAN. FDA has certified bacitracin, flavomycin, and oleandomycin as safe and effective for subtherapeutic use. Do you agree with FDA's conclusions with respect to these antibiotics?

Dr. FALKOW. The data I saw suggest so. Certainly those are being used, along with other drugs, in Europe.

Mr. WAXMAN. These drugs are being used in Europe?

Dr. FALKOW. Yes; they are being used in Europe.

American Cyanamid has marketed a product in Europe which contains an alternative antibiotic for growth promotion.

Mr. WAXMAN. So, you think that it is appropriate, to permit their subtherapeutic use?

Dr. FALKOW. I read the literature that American Cyanamid distributed; they said it's very good.

Mr. WAXMAN. You do raise the specter of epidemics, if not the dire kinds of consequences I outlined in a previous question about the preantibiotic Middle Ages.

What kind of epidemics do you think we can anticipate, and what can we do about them?

Dr. FALKOW. There have been some outbreaks which have been very close to being epidemics. But it is very difficult for us to see an epidemic in this country and other developed countries of the world because we have good sanitation and very good health care; severe epidemics are spotted and stopped in most cases.

If one does indepth epidemiological analysis, however—and I just received a document from Professor Anderson, who is in charge of the enteric reference lab in Colandale in England, who looks at salmonella and other type infections throughout the world. He has

documented evidence of kind, of unseen epidemics where there is one kind of salmonella organism carrying one kind of R-factor that is found in a substantial number of porcine, bovine, and human cases. This is often a kind of an unseen epidemic. People usually are not going to die of these epidemics though. But there is going to be a good amount of time lost and perhaps suffering in some instances.

It is impossible to make the distinction—at least in my mind, any longer—between whether or not the appearance of these resistant human pathogens are or are not associated with antibiotics in feed. All we know is we have selected for an incredible reservoir of resistant organisms. We know we have done it in animals. It is increasing in man. And we know they are the same kind of resistance determinants.

That to me means that we have got to stop it or we are in trouble. Or else we are going to be in the same situation when we misused some insecticides. People were shocked to suddenly find that animals in the Arctic, which had never come into direct contact with insecticides, suddenly had traces of these substances in their flesh.

Well, resistance is like that. When you make an organism resistant, you are creating a biological agent. You cannot call it back and it may be widely disseminated.

I must say that I am a little puzzled. I served on the committee that help write guidelines for recombinant DNA experiments. I have felt like Alice in Wonderland. The whole thrust of the potential hazards of recombinant DNA revolves around the fact that you perform these experiments using R-plasmids. The potential dangers of recombinant DNA technology was seen in terms of the documented history of the spread of R-plasmid resistance.

I see the Congress of the United States getting ready to pass legislation on recombinant DNA. Yet, on the other hand, the issue of antibiotics in feeds is not seen in the same light. I do not see how they can tell the difference between the two.

Mr. WAXMAN. Would it be fair to say that the human health danger from R-plasmids coming from antibiotic use in feedstock is greater than the potential danger of recombinant DNA research?

Dr. FALKOW. That is my view; yes.

Mr. WAXMAN. That is not to say, however, that we should not establish safety standards for recombinant DNA research.

Dr. FALKOW. No, sir. I helped write the DNA recombinant molecule guidelines. I support the guidelines. I think they should be followed.

But the basis of reasoning of potential hazard of recombinant DNA, if you read the original letter by Paul Berg and his colleagues, was based on the historical precedence of antibiotic resistance disemination.

Mr. WAXMAN. I want to thank you. You are an excellent witness. I am sure you must be an excellent teacher as well, because I have learned a lot in the short time that I have been privileged to listen to you.

Dr. FALKOW. Thank you.

Mr. Moss. Mr. McLain?

Mr. MCLAIN. Thank you, Mr. Chairman.

Dr. Falkow, as you stated, you were a consultant to the subcommittee of the National Advisory Food and Drug Committee. You mentioned a letter that you wrote to Chairman Moss in February 1977. I would ask that that letter be included in the hearing record, Mr. Chairman.

Mr. Moss. Without objection, it will be included at this point.
[The letter referred to follows:]

UNIVERSITY OF WASHINGTON,
SCHOOL OF MEDICINE,
DEPARTMENT OF MICROBIOLOGY, SC–42,
Seattle, Wash., February 14, 1977.

JOHN E. MOSS,
Chairman, Subcommittee on Oversight and Investigations,
Washington, D.C.

DEAR CONGRESSMAN MOSS: I am writing in regard to your request for my considered response to the action taken by the full National Food and Drug Advisory Committee on the question of Antibiotics in Animal Feeds. As you know, I served as a consultant to the Subcommittee on Antibiotics in Animal Feeds. Consequently, I am fully aware of the deliberations and the reasons leading to the recommendations made to the full Advisory Committee. I was glad to learn that the Advisory Committee accepted most of the Subcommittee's recommendations. Nevertheless, the action to table the recommended action to restrict the use of tetracycline in animal feed was, in my judgment, irresponsible. It was an insult to the members of the Subcommittee on Antibiotics in Animal Feeds, its consultants and members of the Bureau of Veterinary Medicine who listened to many hours of testimony, read thousands of pages of scientific data and labored hard to reach a reasoned judgment. It is inconceivable to me that the Full Committee, many of whom I am told admitted that they had not taken the time to even read the relatively short Subcommittee report, could have possessed the insight or the background information to intelligently reach a judgment in less than one day to table action on the restriction of tetracycline. I understand the Advisory Committee, in effect, have advised the Commissioner not to change regulations on the use of tetracycline in animal feed until additional scientific information concerning the potential adverse effects of such use is forthcoming. Clearly, the Full Advisory Committee did not know of or could have read the full text of the Subcommittee's deliberations of April 26–28, 1976 which dealt in large part with tetracyclines. This report alone covered 491 pages and contained hundreds of scientific references as well as new data. Indeed, the most cogent data for the potential adverse effects of antibiotics in animal feeds came from the tetracycline studies. Without mincing words, to accept the reommendations on the restriction of penicillin and sulphonamide and to table the Subcommittee's recommendations on tetracycline simply reflects the ignorance of the Full Committee on the implications and rationale of the Subcommittee recommendations.

I was not present at the meeting of the Full Advisory Committee, although I have heard numerous reports of what occurred. It is my understanding that two of the three most outspoken critics of the Subcommittee's recommendations are directly associated with the pharmaceutical industry. Another outspoken critic, a clinician, is not generally recognized as an expert on matters of antimicrobial resistance. I earnestly hope that Commissioner Gardner will weigh the nature and source of the "advice" he received from the Full Committee against that of the Subcommittee. Good Lord, this matter has dragged on since April, 1970, when the FDA established a Task Force on Use of Antibiotics in Animal Feeds. In 1972, the task force made recommendations essentially identical to the present Subcommittee. This resulted in an FDA program which provided for a two year period of additional research. (Parenthetically, I should note that I presented testimony to the original Task Force and received FDA contract monies to provide further research information.) The two year period ended on April 20, 1975. On June 25, 1975 the full National Advisory Food and Drug Committee itself set up the Subcommittee whose recommendations it now, in part, rejects. Meanwhile, Great Britain has restricted the use of tetracycline (and other antibiotics) from animal feeds. The Common Market countries have followed suit. We still lag behind in the face of overwhelming evidence that what was considered a potential risk in 1970 has become a real threat in 1977. In not only my judgment, but in the judgment of many others who are actively engaged in research on antibiotic resistance, it is no exaggeration to say that the ecology of the enterobacteria, and recently other bacterial groups of the whole of mankind has been changed by the way in which the antibacterial drugs have been literally squandered in animals and man. It cannot be simply chance that many of us accurately predicted the emergence of specific resistant bacterial species based on our appraisal of the antibiotic resistance gene pool in man and his domestic animals.

Yet, our recomendations like that of the Subcommittee have had only limited success.

I hope that Commissioner Gardner will take decisive action. If not I hope your Subcommittee may act to investigate this sad state of affairs. As you know I have already provided Mr. Brown of your staff with copies of pertinent letters sent by me to the Subcommittee on Antibiotics in Animal Feeds. These may provide you with the background for the tone of my response to your request.

If I may be of any aid to you in providing your staff with scientific documentation of points or in providing you with any other relevant information, please let me know and I shall respond as quickly as possible.

Sincerely,

STANLEY FALKOW, Ph. D.,
Professor of Microbiology and Genetics.

Mr. MCLAIN. On page 2 of that letter, I would like to read one sentence. You state:

It is my understanding that two of the three most outspoken critics of the subcommittee's recommendations are directly associated with the pharmaceutical industry. Another outspoken critic, a clinician, is not generally recognized as an expert on matters of antimicrobial resistance.

Can you tell the committee who those members were, Dr. Falkow, and what is the significance of their interest as you see it?

Dr. FALKOW. At the time I wrote this, I did not know who they were. I was getting phone calls from a number of people. My honest response at the time was that I couldn't believe those turkeys had done it; that was my actual and true response when I learned they had rejected the subcommittee recommendations.

I was trying to find out who the individuals were.

Mr. MCLAIN. Do you know today who they are?

Dr. FALKOW. The clinician I was referring to was Dr. Ritz, who is at the Mayo Clinic. Apparently—at least that's who I think it was; he was on the committee. I did not consider him to be an expert in matters of antimicrobial resistance.

I should say that a number of clinicians do not agree with the contentions I have made. They have not seen any link between using antibiotics in animal feeds and the increasing resistance in human infection. They would, in fact, have two separate but equal populations.

My feeling on that is that they simply have not read the literature and are not aware of the epidemiological studies that have been done.

Now, the other person was the gentleman from the feedlot, Mr. Farr.

The other one, I was subsequently told, was the chairman of the board of a pharmaceutical house.

Mr. MCLAIN. What impact do you think that that interest might have had in the deliberations of the full committee?

Dr. FALKOW. I was not there, so I do not know. Clearly I—well, I don't know.

To me it seems such a clear-cut issue that it is hard for me to think of people that do not understand it. So, I am not really very—I am too subjective about it right now.

Mr. MCLAIN. When we discussed the possible conflict of interest issue with the General Accounting Office, the question was raised as to whether this committee was considering broad policy matters or specific regulatory actions.

How would you characterize the recommendations and conclusions of the full committee?

Dr. FALKOW. I thought that they were determining that this was going to be a matter of policy, I thought. I don't know. I have not thought in those terms, sir.

Mr. MCLAIN. Is that how it came out? Was that the outcome?

Dr. FALKOW. No; that is not how it came out. They said, "Don't do anything about tetracycline. Go ahead and do something about penicillin." I did not understand the logic.

Mr. MCLAIN. As we understand then, you were fully supportive of the recommendations of the subcommittee?

Dr. FALKOW. Yes, sir.

Mr. MCLAIN. And disagreed with the recommendations of the full committee as per their decision not to go ahead with tetracycline?

Dr. FALKOW. That is correct.

Mr. MCLAIN. You are also familiar with the activity of the first FDA task force on antibiotics in animal feeds?

Dr. FALKOW. Yes. I gave evidence to the task force.

Mr. MCLAIN. Could you briefly describe what their recommendations were?

Dr. FALKOW. Their recommendation was the withdrawal of penicillin, tetracycline, a number of other drugs from use for growth promotion. They recommended that—as I remember—streptomycin, neomycin, and several other drugs not be used unless absolutely necessary—chloramphenacol never used, as I recall. There were a number of far-reaching recommendations in the first task force.

Mr. MCLAIN. Part of that task force was developed to address the question of the human health hazard presented by the use of antibiotics in animal feeds. Dr. Bennett, who you mentioned, was a member of that group.

Dr. FALKOW. Yes.

Mr. MCLAIN. That group found that the hazard associated with the use of antibiotics in animal feeds presented an imminent hazard to human health. I realize this is a partly legal and partly scientific concept.

Has your data shown you that that was a proper evaluation of the hazard?

Dr. FALKOW. I felt it was. Because the indications were that there was going to be a sharp increase in resistance. At that time, salmonella resistance was hovering around 20 percent—as I remember my testimony before that task force, about 20 percent.

Mr. MOSS. We will suspend for 10 minutes to permit responding to a quorum call on the floor, and then we will resume.

[Brief recess.]

Mr. MOSS. The hearing will resume.

Mr. McLain?

Mr. MCLAIN. Dr. Falkow, let me just clear up one point that we made hastily before the committee took the brief recess.

Is it your statement that you agree with the findings of the task force group considering the human health hazards associated with antibiotics?

Dr. FALKOW. Yes; and I testified before the task force that that was my feeling.

Mr. MCLAIN. The history that we have seen develop, as presented primarily from the General Accounting Office this morning, and

traces FDA's concerns back until at least 1968 with the National Academy of Sciences study. Based upon your scientific background, at what point do you believe that there was data sufficient, as far as the safety and the efficacy of the use of antibiotics, for FDA to take some regulatory action?

Dr. FALKOW. That is a difficult question. The question was being raised very early. I recall going to the Department of Agriculture when I was teaching here at Georgetown University in 1965 and talking about it. I know that there was a body of people who were in R-plasmid research around the world who were raising this question beginning roughly in 1965. I think it came to a head with the Swann committee in England. They had a documented epidemic there with human deaths; that event spawned the Swann committee.

At that point in time, there was a lot of information that was accumulating worldwide. That is why the FDA task force was set up in 1970.

By the time they completed their task in 1972, I think that they had seen a good deal of data. There has been a lot more scientific information since 1972 which really confirms and reinforces the original conclusions of the task force.

The year following the task force report, 1973, the World Health Organization came to exactly the same conclusions as the FDA task force on much the same data. WHO quoted an additional 10 studies, as I remember.

This is just a reflection that, each year, there are 10, 12, perhaps 20 additional studies on this subject that are published. There is enormous literature now on this.

Mr. MCLAIN. So, you are saying that it is your feeling that FDA had sufficient data to act on the basis of the task force report back in 1972.

Dr. FALKOW. Yes. There was an initial order, in fact, saying that penicillin and tetracycline be out, I think, by December of 1973. They actually had a timetable. I thought that would be followed.

Mr. MCLAIN. Let me explore with you something you mentioned earlier; you stated that it is impossible for you to bring a body in to show what your feelings are on this matter.

One area that has been the subject of dispute is trying to correlate the nexus between the increasing incidence of drug resistance in animals and that increasing incidence of drug-resistant pathogens in human beings.

Does that nexus exist? How does it exist? How are these pathogens transferred if, in fact, they are?

Dr. FALKOW. They are transmitted both directly and indirectly. There is even a third mechanism which I really will not get into because it really is highly technical.

Mr. MCLAIN. Is it jumping genes?

Dr. FALKOW. Jumping genes.

Mr. MCLAIN. That is something I would like for you to discuss later.

Dr. FALKOW. All right.

It is easy enough, of course, to see the direct transmission by food. That has been known with certainty for salmonella. Professor Richmond and his colleagues at the University of Bristol have spent the

last 5 years in England studying the transmission of antibiotic-resistant common coliform bacteria from animals to man. They have shown the major danger really comes in the person who handles the meat. The meat usually is gotten frozen. It then thaws, perhaps at room temperature. The resistant organisms on the meat grow at room temperature. People handle it. The resistant organisms then are actually found in the food handlers' bowel.

Mr. McLain. Excuse me. Do I recall the FDA's notice of August 30 describing a higher incidence in the drug resistance in farmworkers as opposed to the normal population?

Dr. Falkow. Yes. There are also some studies that have been done by German workers. There is a very elegant study here that was in fact funded by the Animal Health Institute, an industry group. Professor Levy at Tufts set up an experiment in Massachusetts and was able to show that a family that was taking care of fowl on medicated feed got a significantly higher population of resistant organisms in their guts while this was not occurring in neighbors. Levy, infact, was able to document that the precise R-factor that was in the fowl could be later found in one of the family children.

So, as I said, it is not a torrent; but there certainly is a mist or drizzle of animal-related antimicrobic resistance that does not come into humans.

So, one gets direct extension of resistance.

Another means of resistance dissemination is based on the fact that the R-plasmids by their nature do mate and they exchange their genes; particularly under selection of antibiotics, this is more likely to be successful.

So, one sees the transfer of one R factor from one strain to another strain. It may be an animal strain to a human strain or even vice versa for that matter. This can occur in contaminated water. It can occur in any place where there is a meeting of ecology, so to speak.

When I was at Georgetown University, I sampled the Potomac for resistant organisms. At that time, 1967 or 1968, something on the order of 2 to 3 percent of the total coliform bacteria in the Potomac were carrying R factors. We could not tell if they were animal or human bacteria because of the varied kind of runoff and so on, but they were there. There is no question.

I understand that more recent surveys would indicate that probably the incidence of resistance is up around 8 percent of the total coliforms. So, there has been this kind of increase.

If the number of R factors in normal coliforms gets high enough, it becomes inevitable, as I said, that there is going to be a transfer into pathogens.

Then one has the idea of the "jumping genes." The jumping gene is a concept that has come up recently. It turns out that the plasmids carry their genes determining antibiotic resistance as kind of discreet packages. These packages can cut themselves out of one piece of DNA and insert themselves into another.

Now, R factors always just cannot enter where they want and get squatter's rights; it just doesn't work like that in biology. That is why all bacteria do not have R plasmids. Some bacteria have worked out very decisive ways of saying who shall come in and who shall not come in and whose genes they will carry and whose genes they won't.

But, if the R plasmid makes a forced entry into a drug-sensitive organism and can stay there long enough, one of these drug resistance genes may jump off—kind of abandon ship so to speak—and find a haven in the organism. Meanwhile, the organism may throw out the R factor, but the drug resistance gene kind of hides and just stays there. Now you have an extension of the gene.

That is why I say, when we look for these jumping genes—and we can do so very precisely at the molecular level—we find that it is the same gene determining penicillin resistance in enteric bacteria as there are in the organisms that causes gonorrhea. It is the same gene.

Mr. McLain. In your examinations, how prevalent is this?

Dr. Falkow. It is increasing daily. Ampicillin resistance or penicillin resistance has been one of the things that has increased the most in the past decade. There is no question about that.

Much of the increase has been due to the extension of jumping genes that were found initially in enteric bacteria. And now the jumping penicillin gene is in hemophilus. And that same gene is now in neisseria. I do not know if it is the same gene in pneumococcus.

Mr. McLain. Another point that has been raised by several people who question the action by FDA is whether the increased incidence we have seen in these diseases is attributable to the increase in drug resistance. Or is the emergence of these diseases attributable to some other factor?

Dr. Falkow. Well, I do not know, sir, if there has been an increase in the actual incidence of disease, since that is a reflection of a number of things. There certainly has been an increase in the number of antibiotic resistant infections.

I do not know—and Dr. Bennett would have the data—whether or not the actual number of cases of salmonella infection has increased each year. But the number of resistant cases, even if it has remained the same—let's say at 20,000 per year—the proportion of strains that are resistant to antibiotics has surely increased over the past 5 or 6 years.

Mr. McLain. How much of that increase would you attribute to indiscriminant use of antibiotics in either animal feeds or in human beings themselves?

Dr. Falkow. That is hard to say because, as I hope I was careful to say at the outset, antibiotic usage for any purpose will give you some resistance. I cannot really divide the pie up. I just know that, if there is anything at all that can be done to stop, slow down, make people aware of indiscriminate use of antibiotic uses, it will have an effect on the reservoir of resistance.

It has been indicated in a number of medical journals that there is antibiotic misuse in human therapy. I think any fair-minded person would also say it has been misused in agriculture. I think industry scientists would concur in that.

Mr. McLain. Would you care to characterize the significance of indiscriminant use and its effect as used in animal feed? Can that be done?

Dr. Falkow. The only kind of things I have seen is some breakdowns with regard to the amount of antibiotic that is used, say, in human medicine versus agricultural medicine; it was almost half and

half in 1970. I do not know. It is hard to get precise numbers on antibiotic usage except for how many grams have been certified.

Mr. McLain. To follow up on a couple of points that were made by Mr. Ahart in his previous testimony. FDA's August 30 notice does not question the efficacy of penicillin for subtherapeutic use.

To your knowledge, is there data available to question such efficacy, particularly as it relates to disease prophylaxis?

Dr. Falkow. I am not sure I understand the question.

Mr. McLain. Do you know of data available to show that penicillin is effective as a disease prophylaxis?

Dr. Falkow. In animals specifically?

Mr. McLain. Yes.

Dr. Falkow. I do not know. I am not conversant enough with animals to say that—not that I am aware of in penicillin.

For tetracycline I am aware of some things, but not for penicillin.

Mr. McLain. Is tetracycline effective?

Dr. Falkow. My reading of the literature indicates that it is, when used therapeutically.

Mr. McLain. When used therapeutically?

Dr. Falkow. Yes; well, for prophylaxis, for disease prevention, as I understand, it should be used in therapeutic doses for short periods of time, not at subtherapeutic levels.

Mr. McLain. What I have in mind is extended usage, continuous for subtherapeutic disease prevention. Is it effective?

Dr. Falkow. Not that I am aware of. But I am not an expert in that line.

Mr .McLain. Thank you, Mr. Chairman.

Mr. Moss. Mr. Wunder?

Mr. Wunder. Thank you, Mr. Chairman.

Dr. Falkow, you were talking about these organisms which are no longer responsive to penicillin treatment. You mentioned one in South Africa.

Do they use penicillin and tetracycline and other antibiotics on a subtherapeutic basis in South Africa?

Dr. Falkow. I honestly do not know, sir. I would not be surprised because they are a reasonably developed agricultural society. But I do not know.

Mr. Wunder. That leads to my second question then. Are there nations in the world which do not use antibiotics on a subtherapeutic basis?

Dr. Falkow. Many.

Mr. Wunder. Are they mostly the underdeveloped?

Dr. Falkow. Yes.

The actual amount of antibiotic use for animals there is not fully clear, however. I simply used to accept on faith that antibiotics were not used in animals. But the antibiotics are, in fact, freely available. I have been told by some people who visit developing nations that, very often, an animal can be considered more valuable than a person. The antibiotics being available, are fed to sick animals.

Mr. Wunder. These are in the underdeveloped nations?

Dr. Falkow. That is correct. But certainly there is no program of subtherapeutic feeding in any developing country that I know of.

Mr. WUNDER. A second one of these organisms that you mentioned was this gonorrhea strain. You mentioned specifically the Philippines. I was wondering if the same question with respect to the Philippines as was with South Africa: Do they use it on a subtherapeutic basis?

Dr. FALKOW. Not that I am aware of; no.

Mr. WUNDER. If they do not use it on a subtherapeutic basis, does that not militate against the argument that there is a link between the subtherapeutic use and the buildup in resistance?

Dr. FALKOW. No; not in my view.

My view is that we have one ecosystem in terms of resistance.

Mr. WUNDER. For the whole world, you mean?

Dr. FALKOW. Yes. Bacteria in no way respect international boundaries.

The point is that there has been a buildup of resistance throughout the world, both from misuse in animals and humans. There is a great accumulation of a resistance reservoir that is freely available to both animal and human strains. The plasmids which are involved are the same.

At the same time gonococcal resistance was first detected was in U.S. military personnel in the Philippines, it was also being detected in London, with an apparent tie-in to importation from Africa.

In other words, the same event is happening concurrently throughout the world. I think I indicated that earlier. The increase in resistance in Haemophilus showed up around the world almost simultaneously.

It is impossible to say where the resistance gene came from. All we can do is look back retrospectively—which a good deal of epidemiology is—and say, all right, all we know is that the genes are the same and the R-plasmids are the same in both animals and humans; and it must be some common reservoir feeding R-plasmids to them both. If we can reduce the R-plasmid reservior in any way, then we may be able to reduce these untoward effects.

So, I am not pointing and saying the subtherapy in animals caused the emergence of antibiotic resistance in the gonococcus in any direct sense. But I am saying that the total usage of antibiotics in the community has an effect. And this is one of them and an important one.

Mr. WUNDER. In the Philippines can you purchase antibiotics over the counter?

Dr. FALKOW. Yes.

It is the same way some farmers in this country can purchase antibiotics over the counter.

It always seemed to me to be rather an interesting observation that, if I have a prescription for tetracycline, I have to go to the pharmacist and have it filled. But, if I want to buy them for my tropical fish, I just go to the pet counter and pick them up.

Mr. WUNDER. Thank you, Mr. Chairman.

Mr. Moss. Are there any further questions?

Mr. Waxman?

Mr. WAXMAN. The last comment you made is surprising.

Dr. FALKOW. I think it is true; I believe that is true.

Mr. Moss. That is quite correct; I can assure you.

Mr. WAXMAN. Do you think we ought to restrict the sale of antibiotics for those kinds of other purposes?

Dr. FALKOW. Yes, sir. I think antibiotics are like a natural resource. I do not think they can be squandered. We cannot keep depending on these things working if we are going to use them irresponsibly. And I think they have been used irresponsibly.

Mr. Santini in his question earlier mentioned that people say that these things have been used for 27 years and there have been no untoward effects. Now people say to me, "Why is it, after all these years, suddenly there is resistance?" Well, I don't know why there is. But I do know that, if we keep pushing and pushing on the biological ecosystem, it is not a static thing, things will happen.

Microorganisms have been around a very long time. They have some very nice genetic mechanisms that they have evolved. You put pressure on them, and it is the survival of the fittest. The fit have come out. Lately, to be a successful microorganism in the world, you have to be resistant to antibiotics.

Mr. WAXMAN. Thank you.

Perhaps this is another area for the subcommittee to look into as we deal with this whole question.

Mr. Moss. Doctor, I thank you for your appearance, for both excellent testimony and a most informative response to the questions that have been put to you.

Dr. FALKOW. Thank you, sir.

Mr. Moss. I know it is going to be very helpful to the committee. We are most appreciative.

The committee will now stand in recess until 10 on Friday, September 23.

[Whereupon, at 12:50 p.m., the hearing was adjourned to reconvene at 10 a.m. Friday, September 23, 1977.]

ANTIBIOTICS IN ANIMAL FEEDS

FRIDAY, SEPTEMBER 23, 1977

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 2212, Rayburn House Office Building, Hon. John E. Moss, chairman, presiding.

Mr. Moss. The subcommittee will be in order.

Today the subcommittee continues its hearings on the potential adverse human health effects associated with the use of antibiotics in animal feeds. Since the introduction of antibiotics decades ago, the American people have taken for granted the effectiveness of such antibiotics as penicillin and tetracyclines as a treatment for disease including salmonella poisoning, gonorrhea, and others. Now, serious questions have been raised as to how effective these antibiotics might be in the future to combat numerous diseases which afflict Americans.

At the hearings conducted by this subcommittee on Monday, testimony was presented recounting episodes of outbreaks of several diseases around the world which were resistant to antibiotics.

The issue to be addressed is whether the indiscriminate use of antibiotics in animal feeds over an extended period has contributed to this increase in the resistance to those same antibiotics when used as a cure for human disease.

This question is not a new one to the scientific community. As early as 1968 the National Academy of Science issued a report challenging both the safety and the efficacy of use of antibiotics in animal feeds. In 1971, England, followed by the other common market countries, severely restricted the use of antibiotics in animal feeds. The Food and Drug Administration as early as 1970 established its first expert panel to examine this question. The opinion of scientific bodies has been a consistent one, an opinion that questions both the safety and efficacy of the use of these antibiotics.

During Monday's hearing, representatives of the General Accounting Office described their findings in a report entitled "Need To Establish Safety and Effectiveness of Antibiotics Used in Animal Feeds." That testimony and report described a long history of the failure of the Food and Drug Administration to act in light of the evidence that had been before it for many years. Further, that testimony questioned FDA's use of advisory committees and their enforcement of their own conflict-of-interest regulations. These areas will be pursued today with FDA Commissioner Donald Kennedy. We will seek to determine

whether FDA's actions in this particular case have been in pursuit of its primary mission to protect the health and safety of American consumers.

Our first witness this morning will be Dr. Kennedy. He is accompanied by Gerld Meyer, Dr. Van Houweling, Edward Allera, and Gerald Guest.

Commissioner Kennedy, we are very pleased to have you here and happy to receive your statement.

Dr. KENNEDY. Thank you, Mr. Chairman.

I will not read my entire prepared statement.

Mr. Moss. It will be inserted in the record, without objection [see p. 73.]

STATEMENT OF HON. DONALD KENNEDY, PH. D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ACCOMPANIED BY GERALD F. MEYER, ASSOCIATE COMMISSIONER FOR ADMINISTRATION, FDA; C. D. VAN HOUWELING, D.V.M., DIRECTOR, BUREAU OF VETERINARY MEDICINE, FWDA; EDWARD ALLERA, ASSOCIATE CHIEF COUNSEL FOR VETERINARY MEDICINE, OFFICE OF GENERA LCOUNSEL, FDA; AN DGERALD B. GUEST, D.V.M., ACTING DEPUTY ASSOCIATE DIRECTOR FOR SCIENTIFIC EVALUATION, BUREAU OF VETERINARY MEDICINE, FDA

Dr. KENNEDY. Mr. Chairman, we have been concerned at FDA for some time about the potential health hazard—as your introductory statement said—that is posed by the use of antibiotics in animal feeds. As we see it, the safety issue involves the emergence of drug resistant bacteria in animals, the availability of routes of transfer of these resistant bacteria to man, and the clear potential that this drug resistance can be transferred to those bacteria responsible for human diseases.

I know that the members of the subcommittee are aware of our intentions to restrict the addition to animal feed of low levels of certain antibiotic drugs. Affected by the restrictions that we are proposing will be penicillin, several tetracyclines, and combination products containing these antibiotics. Penicillin and tetracycline were chosen as the initial subjects of regulation because of their critical importance in the treatment of human disease.

Our conclusion that this action is necessary rests on the potential risks associated with the unrestricted use of these compounds, and it is based on this sequence of logical steps:

First, the long-term, low-level feeding of antibiotics to animals promotes, by natural selection from the pool of resident, enteric bacteria, the intestinal flora—as it is often called—those coliform bacteria that contain R plasmids. R plasmids are lengths of extra chromosomal material not incorporated into the bacterial chromosome that confer antibiotic resistance to the bacteria that contain them.

These plasmids can be transferred among various kinds of bacteria by cell-to-cell contact. So, in effect, they hop around from bacterium to bacterium in the gut of man or in animals. Simultaneous resistance

to several antibiotics is commonly carried on a single plasmid, and therefore these resistances to several antibiotics are simultaneously transferred together as though they were on the same piece, which in fact they are.

Second, we know that *E. coli* strains bearing R plasmids can be transferred from animals to man, and under the proper circumstances organisms of animal can colonize the human gut.

Parenthetically, Mr. Chairman, that used not to be thought to be so. Formerly, microbiologists believed that the strains of *E. coli* and the other common enteric bacteria in livestock animals and man were very distinct populations that never, as it were, crossed over and exchanged hosts. Now it is known that that sort of transfer is much more likely.

Third, R plasmids can be transferred from normally nonpathogenic *E. coli* in the intestinal tract of humans to certain pathogenic strains of bacteria with which they may come in contact in man.

That transfer from primarily digestive tract resident bacteria to the kinds of micro organisms that are associated with disease and generally do not live in the digestive tract is not a common event. But we know that it has occurred. Our knowledge that it has occurred repeatedly depends primarily upon new techniques of looking at the homology of the nucleic acids that are the genetic materials of the two kinds of bacteria. What we know is that the DNA sequences in the plasmids match up between the enterics and the pathogens. That provides evidence that they have a common origin.

This results in the creation of pathogenic strains of bacteria that are resistant to antibiotic therapy in humans. The serious health consequences of such an event, I think, are obvious.

There is recent evidence that such a series of events may have already occurred. It is, furthermore, certain that the origin of resistant pathogens has happened through R plasmid transfer in the past. The only uncertainty is in deciding whether the event of resistance selection occurred through the overuse of antibiotics in animal feeds or whether it occurred through the overdosing of antibiotics in hospitals. That uncertainty makes it difficult to trace particular cases to particular sources. But it does not change our estimate of the seriousness associated with both kinds of overuse.

We think that continued unrestricted use of the antibiotics will continue to exert a selective pressure that will increase the pool of drug-resistant bacteria in the environment.

In short, Mr. Chairman, the evidence indicates that enteric microorganisms—those that live in the digestive tract—in food animals and man, their R plasmids, and human pathogens form a linked ecosystem in which action at any one point can affect every other. If you view them in this way, the vulnerability of microorganisms to antibiotics is a kind of "common"—a resource which, if exhausted by the use of antibiotics for nonmedical purposes in animals, will be diminished in man. Experts on infectious disease and public health on the FDA task force on the use of antibiotics in feed, and others whom I consulted in connection with this action, I think are in overwhelming agreement with this view. I know you will be hearing from other witnesses more expert than I in these fields. I believe they will underscore that.

To summarize matters, Mr. Chairman, I would be less than candid with you and your colleagues on the subcommittee if I left the impression that the scientific and public health issues involved in this series of proposed actions will run a smooth and quiet course. The implications for both the public health and the economics of the agricultural community are significant, and there is already considerable debate—as you well know—about the merits of our proposed action.

Our proposal, as will subsequent ones, provide an opportunity for affected parties to object to the withdrawal of the new animal drug applications affected and to request an administrative hearing. If those requests, which I am sure will be filed with the agency, provide a showing that disputed issues of fact exist, then the agency must grant an administrative hearing.

In the normal course of events in FDA, the review of requests for hearing and determination on the merits of those requests can take anywhere from 2 to 6 months of additional time following the close of the original comment period. If a hearing is granted, I would estimate that, given the complexity of the issues and the science involved, an administrative hearing, once commenced, will probably require an additional 8 to 12 months to complete.

I can assure you that it will be neither brief nor tranquil. The importance of the public health issues at stake in this process just cannot be overestimated. I think that, given that importance, a public health agency just cannot take any other course than the one we have taken.

These proceedings are conducted according to regulations prescribing the internal operation of the agency, which require that we adhere to the principle of separation of functions whenever we publish a proposal which provides an opportunity for a formal evidentiary public hearing. Under the current proposal, the Bureau of Veterinary Medicine acts as the proponent for the proposed action, and the affected parties have the opportunity to present evidence in opposition to the bureau position.

As the Commissioner, I am the ultimate decisionmaker in that proceeding. So, the minute a notice of hearing gets published, Mr. Chairman, I go into a telephone booth and change uniforms: I put on a red shirt. After I do that, I am separated from the merits of that argument until I hear it as the final decisionmaker.

I am in that position now with respect to penicillin. So, my observations are restricted to the historical. I am also in that position, as you know from previous testimony, with respect to nitrofurans, a related matter.

In summary, Mr. Chairman, the actions we have proposed are controversial: but I think they are necessary to protect the emergence of a serious future public health problem. The process by which we will arrive at a final decision is one of openness. It involves wide public participation and has assurances that all affected parties will be given a full opportunity to present their views.

At this point, Mr. Chairman, I will conclude my statement and ask if you or members of the subcommittee have questions.

[Dr. Kennedy's prepared statement follows:]

STATEMENT OF HON. DONALD KENNEDY, PH. D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I welcome this opportunity to appear before your subcommittee to discuss the use of antibiotics in animal feed.

The Food and Drug Administration (FDA) has been concerned for some time with the potential health hazard posed by the use of antibiotics in animal feed. The safety issue involves the emergence of drug resistant bacteria in animals, the availability of routes of transfer of these resistant bacteria to man, and the clear potential that this drug resistance can be transferred to those bacteria responsible for human diseases.

I am sure the members of the subcommittee are aware of our intentions to restrict the addition to animal feed of low levels of certain antibiotic drugs. Affected by the proposed restriction would be penicillin, several tetracyline drugs, and combination products containing these antbiotics. Penicillin and tetracycline were chosen as the initial subjects of regulation because of their importance in the treatment of human disease.

Why is this action necessary? Our conclusion that the potential risks outweigh the benefits of continued unrestricted use of the antibiotics is based upon this logic:

1. Long-term, low-level feeding of antibiotics to animals promotes, by natural selection from the pool of normal intestinal flora, those E. coli which contain R-plasmids. R-plasmids are lengths of extra chromosomal material which confer antibiotic resistance to host bacteria. These plasmids can be transferred among various kinds of bacteria by cell-to-cell contact (conjugation). Simultaneous resistance to several antibiotics is commonly carried on a single plasmid and therefore is simultaneously transferred from one bacterium to another.

2. E. coli strains bearing R-plasmids can be transfered from animal to man and under the proper circumstances organisms of animal origin can colonize the human gut.

3. R-plasmids can be transferred from normally nonpathogenic E. coli to certain pathogenic strains of bacteria with which they may come in contact in man (or in animals).

4. This will result in the creation of pathogenic strains of bacteria which are resistant to antibiotic therapy. The serious consequences of such a series of events are obvious.

5. There is recent evidence that such a series of events may have already occurred. It is, furthermore, certain that the origin of resistant pathogens has happened through R-plasmid transfer in the past; the only uncertainty is in deciding whether the resistance was selected through overuse of antibiotics in animal feeds or in hospitals.

Continued unrestricted use of the antibiotics will continue to exert a selective pressure that will increase the pool of drug-resistant bacteria in our environment. The possibility that drug-resistant pathogens can be produced by antibiotic selecton has become a real threat with the recent emergence of human diseases (typhoid, childhood meningitis, gonorrhea, pneumonia) caused by antibiotic resistant bacteria.

In short, the evidence indicates that enteric microorganisms in food animals and man, their R-plasmids, and human pathogens form a linked ecosystem in which action at any one point can affect every other. Viewed in this light, the vulnerability of microorganisms to antibiotics is a kind of "commons"—a resource which, if exhausted by the use of antibiotics for nonmedical purposes in animals, will be diminished in man. Experts on infectious disease and public health on the FDA task force on the use of antibiotics in feed, the subcommittees, and others whom I consulted in connection with this action, are overwhelmingly of this view.

BACKGROUND

The practice of using antibiotics in animal feeds to improve growth and feed efficiency became widespread in the early 1950's and has increased steadily since that time, particularly in the feeding of beef cattle, poultry and swine.

FDA scientists, as well as those in other countries, have been studying the effects of low-level feeding of antibiotics to animals over a rather long period of time. In 1956 and again in 1965 and 1967, FDA held symposia and consulted outside experts to review the nonmedical uses of antibiotics in animal feeds. The

results of these studies and other documentation provided the background for deliberations of the FDA Task Force on the use of Antibiotics in Animal Feeds established in 1970.

In April 1970, the Commissioner of the FDA established this task force of scientists to undertake a comprehensive review of the use of antibiotics in animal feeds. The scientists included ten specialists on infectious diseases and animal science from FDA, the National Institutes of Health (NIH), the United States Department of Agriculture (USDA), the Center for Disease Control (CDC), and five consultants from universities and industry.

FDA established the group on the recommendation of its Science Advisory Committee, after the committee had reviewed a report issued by the Government of Great Britain on the use of antibiotics in veterinary medicine and animal husbandry. The British study, known as the Swann Committee Report (1969), recommended that antibiotics should be divided into "feed" antibiotics and "therapeutic" antibiotics and that only those antibiotics not used for treatment of diseases in many should be allowed in animal feeds at the so-called growth promotion level.

FDA's Task Force report, issued in January 1972 concluded that: (1) The use of antibiotics, especially in subtherapeutic amounts, favors the selection and development of single and multiple antibiotic resistant and R-factor bearing bacteria. (2) Animals which have received either subtherapeutic and/or therapeutic amounts of antibiotics in feeds may serve as a reservoir of antibiotic resistant pathogens and nonpathogens. These reservoirs of pathogens can produce human infections. (3) The prevalence of multiresistant R-factor bearing pathogenic and nonpathogenic bacteria in animals has increased and has been related to the use of antibiotics. (4) Organisms resistant to antibacterial agents have been found on meat and meat products. (5) There has been an increase in the prevalence of antibiotic resistant bacteria in man.

These conclusions were published in a notice of proposed rulemaking on February 1, 1972 in the Federal Register. Following our review of the comments received on the proposal, a final order was published in the Federal Register of April 20, 1973, which made the requirements imposed by the regulation legally binding on al firms marketing antibacterial drugs used at subtherapeutic levels in feed. In August of 1974, the Commissioner proposed withdrawal of all approvals held by persons who had not complied with the initial requirements. Final action on this proposal was published in the Federal Register of February 25, 1976.

In early 1974 the Bureau of Veterinary Medicine began a review of the data required by the regulation which was applicable to the principal antibiotics used subtherapeutically in animal feeds (penicillin and tetracycline), and by April 1975, data concerning the safety and efficacy criteria for all antibiotic and sulfonamide drugs had been received.

NATIONAL ADVISORY FOOD AND DRUG COMMITTEE ACTIONS

To assist the Agency, the Commissioner asked the Agency's National Advisory Food and Drug Committee (NAFDC) to review the data and issues involved and to make recommendations to him on the future uses of subtherapeutic antibiotics in animal feeds. A subcommittee of three members, the Antibiotics in Animal Feeds Subcommittee (AAFS), was appointed to work in conjunction with four expert consultants from disciplines related to the issue. The Bureau prepared two day' presentations concerning penicillin and the tetracyclines during which comments were heard from the drug industry, animal scientists, and other interested parties. The Bureau also prepared a comprehensive summary report with tentative recommendations for the subcommittee. Two additional meetings were held during which subcommittee deliberations were conducted and other statements given.

In September 1976, the AAFS presented its preliminary recommendations to the parent NAFDC, and in January 1977, the subcommittee's final report was submitted to the NAFDC. The parent committee reviewed the recommendations on penicillin and accepted them. NAFDC recommended the FDA immediately withdraw approval for the subtherapeutic uses of penicillin, i.e., growth promotion/feed efficiency, and disease control.

On April 15, 1977, the Agency, having again reviewed the data and the committee's recommendations, announced its decision.

PENICILLIN RECOMMENDATIONS

The Agency concurred with the National Advisory Food and Drug Committee and its subcommittee's recommendations concerning penicillin and sulfaquinoxaline. Implementation of the penicillin recommendations will for all practical purposes eliminate the use of this drug in animal feeds. Penicillin, however, will be made available by other means of administration for therapeutic use. A Notice of Opportunity for Hearing and a proposal to withdraw approval of new animal drug applications (NADA) for all penicillin-containing premixes intended for use in animal feeds was published in the August 30, 1977 Federal Register. In addition, the proposal would delete those regulations that provide for the use of penicillin in animal feeds. I would like to submit a copy of this proposal for the record.

This action is being taken for the following reasons:

New evidence shows that the penicillin-containing products have not been shown to be safe for subtherapeutic use as required by the Federal Food, Drug, and Cosmetic Act;

The applicants have failed to establish and maintain records and make reports as required by the Act;

New evidence shows that there is a lack of substantial evidence that penicillin-containing premixes are effective for therapeutic uses as required by the Act.

Our proposal originally provided 30 days for public review and comment. Since its publication, we have received several requests for additional time for comments. We recognize the complexity of the issues involved and that there is widespread interest in them. We too, are anxious that this proposal receive very careful review by the various publics affected by it, so the comment period has been extended for an additional 60 days.

TETRACYCLINE RECOMMENDATIONS

The Agency did not concur with the National Advisory Food and Drug Committee's recommendation to continue marketing tetracyclines as these drugs are currently being used in feeds. However, we did concur with the basic recommendations of the expert Subcommittee. We intend to eliminate certain subtherapeutic uses of the tetracyclines (oxytetracycline and chlortetracycline) from animal feed use. The subtherapeutic uses of those antibiotics intended to be eliminated are uses for which there are effective alternative drugs. Nontherapeutic uses of the tetracyclines for which there are no alternative drugs available will be retained for use by the livestock industry, where those uses are supported by adequate safety and effectiveness data. Several effective alternative drugs are available for the uses of the tetracyclines.

We believe it is essential to restrict the use of tetracyclines in animal feeds at this time. We recognize the benefit of the use of these drugs in certain animal disease situations. We further recognize that in at least some disease situations, substitutes—either other drugs or other methods of control—are not currently available for these diseases. By limiting claims to those for which there are no substitutes, and by placing these drugs under regulations that require a veterinarian's order, our intention is to: (1) insure, to the extent possible, that the drug will be placed in the hands of individuals who, by training and background, are best able to determine when drugs should be used; (2) that the most appropriate antibiotic is used at the most effective level for the shortest time necessary to achieve the desired result(s); and (3) to insure that a valuable management tool (i.e., the tetracyclines) continues to be available to the animal industry, when needed.

These actions on the tetracyclines will be published as proposals in the Federal Register in the near future and will provide sixty days for consumers, the scientific community and the affected industries to review and comment on our proposed actions. The proposal will also provide holders of the new animal applications affected to object to the proposed action and request a hearing.

ROLE OF THE VETERINARIAN

In addition to eliminating many of the current label indications for these drugs, we intend to impose further restrictions in the marketing of these drugs by proposing that the waiver from requiring medicated feed application approval be revoked, thereby making such applications required and assuring that they

will only be used in animal feed following the written order of a licensed veterinarian.

We realize that we are placing a burden of responsibility on the practicing veterinarian in this country. Food animal medicine has come to be more than the already complicated business of curing disease and improving animal health. The veterinarian is and will increasingly be, a guardian of the public health both from a drug residue and a bacterial drug resistance standpoint. We have already begun to meet with various veterinary medical specialty groups and associations. In the coming months we will continue to work with the veterinary medical colleges, the veterinary medical profession, and the food animal producing industries to establish the educational programs necessary to implement the kinds of changes that I have discussed with you today.

FUTURE EVENTS

Mr. Chairman, I would be less than candid with you and the other members of the Subcommittee if I would leave the impression that the scientific and public health issues involved in this series of proposed actions by FDA will run a smooth and quiet course. The implications from both the public health and the economics of the agricultural community are profound and there is already considerable debate on the merits of our proposed action.

Our proposal, as well as subsequent ones, provided an opportunity for affected parties to object to the withdrawal of the new animal drug applications affected and to request an administrative hearing. If those requests for hearings, which I am sure will be filed with the Agency, provide a showing that disputed issues of fact exist, the Agency must grant an administrative hearing. In the normal course of events in FDA, the review of requests for hearing and determination of the merits of those requests, can take anywhere from two to six months of additional time following the close of the original comment period. If a hearing is granted I estimate that given the complexity of the issues and the science involved, an administrative hearing, once commenced, will probably require an additional eight to twelve months to complete. The hearings will, I can assure you, be neither brief or tranquil. The importance of the public health issues at stake in this process cannot be underestimated. Given that importance, I believe that a public health agency could take no other course than the one I have just outlined here today.

Mr. Chairman, the Agency proceedings such as these I have just described are conducted according to regulations prescribing the internal operation of the Agency, which requires that we adhere to the principle of separation of functions whenever we publish a proposal which provides an opportunity for a formal evidentiary public hearing. Under the current proposal the Bureau of Veterinary Medicine acts as the proponent for the proposed action and the affected parties have the opportunity to present evidence in opposition to the Bureau position. I, as Commissioner, am the ultimate decisionmaker for the Agency on this matter, and must make my decision solely on the basis of the evidence in the public record of the Administrative hearing. Therefore, it is inappropriate for me at this time to speculate on the resolution of facts yet to be presented at any such public hearing or on what my final decision will be. This separation of function also will be initiated at the time we prepare our proposal on the use to tetracyclines in animal feeds.

In summary, Mr. Chairman, the actions we have proposed are controversial but are necessary to prevent the emergence of future public health problems. The process by which we will arrive at a final decision is one of openness with wide public participation and with the assurance that all affected parties will be given full opportunity to air their views. This concludes my statement. If you or members of the Subcommittee have any questions, my staff and I will be pleased to try and answer them .

Mr. Moss. Mr. Waxman?

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Kennedy, I am pleased to see that the FDA is moving forward to restrict the use of antibiotics in animal feed.

But was not the evidence available to FDA in 1972, concerning the relationship between antibiotics and the development of antibiotic-

resistant bacteria sufficient to justify the decision that is now being taken?

Dr. KENNEDY. Mr. Waxman, it is hard for me to say whether it was adequate. In the first place, I have not deliberately done the exercise of projecting myself back to 1972 to second-guess that question. I am not sure it would be a wise expenditure of my time to do it. If I did, I think what I would find is that the evidence suggested reasons for the deep concern which FDA had. But, at that time, we did not know what we now know about the DNA homology of the R plasmids in human pathogens and enterics. I think that is an important piece of the puzzle—at least it is for me.

I also think that the data were less complete on the proportion of resistant bacteria in the digestive tract of humans who have close association with livestock producing operations in which antibiotics in feeds were used.

So, I guess all I can tell you is that the evidence is stronger now. Whether it was strong enough then to have suggested that the agency ought to have moved faster, I honestly do not know.

In defense of my colleagues, I would like to say that one of the real important questions here is if the evidence is good enough for us to write a document that will stand up? We know we are going to be challenged on actions like this. If we cannot make a strong case, it is often a poor expenditure of our resources. I have to watch that; I know my predecessors did, too.

Mr. WAXMAN. I can understand your personal reluctance to retrospectively look at the 1972 evidence to determine it if was sufficient to justify the action FDA is now proposing. FDA is a continuing organization, however, and I think it is part of our responsibility to look at FDA, not just with respect to each new Commissioner, but to evaluate the agency's role in protecting the public health.

I am concerned that in 1972 we knew pretty much what we know now. You pointed out some other factors, but I believe that there was reason enough for FDA to take action as did Western Europe around that time, based upon the evidence available to the scientific community at the time.

I will not ask you to comment about it. I think we have to be concerned about the future, but I do not think we can ignore the past experience of the FDA.

Dr. KENNEDY. I understand.

Mr. WAXMAN. The action that FDA is taking now consists of publishing a notice in the Federal Register requesting public comment. You point out that completion of this regulatory route could result in an 8- to 12-month delay. Some people estimate the delay, before final implementation of antibiotic use restrictions, may taken even longer.

During this public comment period antibiotics will be permitted to be used in animal feed; is that correct?

Dr. KENNEDY. That is correct.

Mr. WAXMAN. If the danger from animal feed use of antibiotics exists, as both Dr. Falkow, yourself, and others seem to believe, isn't the public going to be exposed to the risk during the months required of the FDA's chosen regulatory action?

Dr. KENNEDY. I think there will continue to be some risk.

Mr. WAXMAN. Why couldn't the FDA act under imminent hazard procedure rather than just file a notice in the Federal Register?

Dr. KENNEDY. It could in principle.

Our view of that process, Mr. Waxman, is that it is to be used only when an extremely serious level of demonstrated adverse reaction is present and going on right now. As you know, we have employed that power only once since the law was made. I can understand your concentration on it since the one happened to be just a couple of months ago. But, in that case, one had at least a fairly well bracketed fatal adverse reaction rate associated with the human drug.

In this case, the hazard is, I think, cumulative and ongoing but not of such a character that we can associate explicit events with the continued use. I do not think that there is, in the present hazard, an adequate indication of imminence to justify our using that route. It has been considered. I do not think it is justified in this case.

Mr. WAXMAN. If a direct correlation can be established between the alleged hazard and human illness, isn't that sufficient for invocation of the imminent hazard procedure?

Dr. KENNEDY. Well, I would take the position that it is not. I think that a cumulative developing risk is exactly the kind of risk—particularly where there are other potential sources of that same risk—that ought to be dealt with by the somewhat slower but more conventional procedures that provide an adequate opportunity to air the scientific issues fully. I think that can be done by our present procedures.

Invoking the imminent hazard for the use of these drugs in animal feeds would not, I think, get at the whole problem because there would still be a much more difficult to control use of antibiotics in hospitals. In other words, I am suggesting to you that the risk has accumulative and developing character that does not accord with our criteria—at least the ones we have applied in the past—for imminence of hazard.

Mr. WAXMAN. Salmonella is becoming increasingly resistant to conventional antibiotics. The FDA is willing to concede that the present regulatory process will take over a year to complete. If you move under imminent hazard, I gather that would mean there would be a court test of your decision; I gather you are going to have a court test anyway. Would not it be appropriate to move this issue into the courts and test the use of the imminent hazard provision as an effective and expeditious way to protect the public health, particularly in cases where there is such a clear danger?

Dr. KENNEDY. I think that whenever you adopt quickness, Mr. Waxman, you also give something away. I think what you give away in that case is the opportunity for more careful preparation of our position and more careful analysis in connection with the responses to the notice of opportunity for hearing.

Mr. WAXMAN. I find that point somewhat unconvincing; FDA has had the whole matter since the task force completed their 1972 report on the danger of antibiotic uses in animal feeds. If anything, over the 5-year period since the task force report we have developed a stronger case for regulatory action.

Dr. KENNEDY. I think——

Mr. WAXMAN. How much are you going to learn between the time you file that notice in the Register and the time you have to fight it out on a notice of proposed regulations?

Dr. KENNEDY. I do not think it is a question of what we are going to learn, Mr. Waxman, by new experiments or anything of that sort. I think, rather, it has to do with the very extensive task of marshaling evidence that is already there; but not, by the way, evidence which was there in 1972. It really is not right that we have had the whole story. If you examine our Notice of Opportunity for Hearing for penicillin and you look at the literature references in that very substantial document, you will discover that a great many of them are post-1972 literature references.

This is a case that has been building, and much of the buttressing for that action is recent.

Mr. Moss. We will suspend for 10 minutes in order to vote on the pending appropriation bill.

[Brief recess.]

Mr. Moss. The hearing will resume.

Mr. Waxman is recognized.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Kennedy, the 1972 task force concluded—and I want to quote from that report:

> The use of low-level antibiotics in animal feed for growth promotion and/or disease prophylaxis poses a potential danger to man. We feel, further, that this conclusion is consistent with the intent of the recent FDA statement of general policy on an imminent hazard to public health.

It would seem that they were recommending that the imminent hazard authority was a proper basis for proceeding. Is that your understanding of the intent of the 1972 task force when they used that phrase?

Dr. KENNEDY. I doubt it was, Mr. Waxman. At that time in particular, before a history of recent case law in connection with the Environmental Protection Agency statute, I think it was regarded in the Agency as necessary that there be demonstrated cases of people whose deaths or injuries could be directly associated with the procedure in question.

Even now, with the benefit of some case law that I think we can consider as somewhat liberalizing in the application of the imminent hazard provision, the Secretary, in declaring phenformin to be an imminent hazard, set out a list of criteria for suspension that he would require in order to suspend a drug. I do not think those criteria could be met by the antibiotics today.

Mr. WAXMAN. One of the notes from the *Environmental Defense Fund* v. *EPA* case cites the court as saying,

> We have cautioned that the term "imminent hazard" is not limited to a concept of crisis. It is enough that there is a substantial likelihood that serious harm will be experienced during the year or two required in any realistic projection of the administrative process.

I believe that is the same case to which you were referring.

Dr. KENNEDY. Yes; that is right.

Mr. WAXMAN. Do you feel that you do not have enough evidence under that concept of imminent hazard to proceed? Or, is it your fear that, if you proceeded under imminent hazard, it would drag out the regulatory proceedings even further due to court litigation?

Dr. KENNEDY. I do not know whether it would drag it out or not, Mr. Waxman. I have three feelings about it. In the first place, I think

that the imminent hazard provision is one that has to be used sparingly, for the most imminent and serious of cases.

The criteria that the Secretary laid out in the phenformin decision seemed to me to require—and we will submit those for the record—that there be demonstration of presently demonstrable hazards associated with the use. I tend to regard this problem a little differently; perhaps you disagree. My view of it is that it is a little bit like the chlorofluoroalcane accumulation in the atmosphere. It represents an unacceptable accumulation of risk.

[The following information was received for the record:]

CRITERIA FOR DETERMINING WHETHER CONTINUED USE OF A DRUG CONSTITUTES AN IMMINENT HAZARD

A. The severity and likelihood of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drug permanently from the general market.

B. The likelihood that, after the customary administrative process is completed, the drug will be withdrawn from the general market.

C. The risks to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the general market, taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.

D. The availability of other approaches to protect the public health.

Dr. KENNEDY. The continued attenuation of the vulnerability of pathogenic bacteria to human antibiotics use is a problem. I regard it as more of a long-range problem. I think that our conventional mechanisms are capable of dealing with it. Therefore, I do not consider it to be the kind of case in which I would want to recommend to the Secretary that he use a provision that our law clearly intended him to invoke sparingly.

Let me say just one other thing about it. I think that the process may get a little speeding up. For one of our Federal Register notices involving the requirement for a written order of the veterinarian and so forth, we are using informal rulemaking procedures for that. We may be able to manage very substantial curtailment before the formal evidentiary hearing process on the tetracyclines and on penicillin is brought to a close.

Let me emphasize that this is a process that we can continually monitor in time. If new evidence that increases our fear of these risks arises, if unacceptable delays that we do not anticipate seem to be thrown into the proceedings, then we can reconsider that question. We are not dropping it forever.

But at this point, I repeat, I am not persuaded that it is a case on which we ought to ask the Secretary to invoke the provision that only he can invoke.

Mr. WAXMAN. Another concern about the notice of opportunity route is FDA's past experience dealing with nitrofurans. As of this date, 7 years have passed since the FDA promised to hold a hearing on the carcinogenic qualities of nitrofurans.

I do not know if you are familiar with the recent history but this subcommittee held a hearing during the 94th Congress which, in my opinion, produced an action by FDA, the day before our hearings convened, to file a notice of opportunity.

I would like to get from you an update on nitrofurans as an example of how that case is proceeding and perhaps to use it as an example of how effective FDA's use of the notice of opportunity route is in protecting the public health.

Dr. KENNEDY. Well, I will have to get exact dates for you. That is a matter that I am separated from, Mr. Waxman.

[The following information was received for the record:]

NITROFURANS

The class of nitrofurans includes four chemical compounds with antimicrobial and antiparasitic activity (furaltadone (NF-260), furazolidone (NF-180), nitrofurazone (NF-7), nihydrazone (NF-64)). These compounds have found use in the prevention, treatment, and cure of, a variety of diseases of chickens, turkeys, swine and cattle, including dairy animals. The most widespread uses are for NF-180, added in the drinking water or feed for the treatment of poultry and swine, and the use of NF-260 to treat mastitis in dairy cattle.

BACKGROUND

When nitrofurans originally were approved for use as animal drugs from 1948 through 1963, FDA had no reason to believe they might be carcinogens.

After approvals, the drug sponsors submitted additional toxicity data in a drug experience report which indicated that the nitrofurans were potential carcinogens. Based upon these data, the Bureau of Foods recommended in 1969 that more sensitive tissue residue assay methodology was needed for the nitrofurans to assume human safety if these products continued to be used as animal drugs. The Bureau recommended the development of methodology having the capability of a lower unit of detection of 2.0 parts per billion (ppb).

Problems in the design of these early chronic toxicity studies submitted by the firms marketing the drugs made interpretation of the data relating to carcinogenesis scientifically difficult. FDA engaged experts through the National Cancer Institute to review the evidence. All of the reviewers agreed that there was a tumorigenic response related to the drug treatments and that the drugs might be carcinogenic. However, they could not all agree that the data available supported the positive classification of these animal drugs as carcinogens.

On the basis of these opinions and all data then available, the Food and Drug Administration issued a notice of proposed withdrawal and opportunity for a hearing for NF–7 and NF–64 in March 1971 and for NF–180 and NF–260 in August 1971. The stated basis for the proposed actions was: (a) that the drugs were tumorigens and suspect carcinogens, and (b) that assay methods for monitoring residues were not available with a sufficient sensitivity to assure continued safe use.

The drug sponsors objected to the proposed withdrawals of approval and demanded a hearing pursuant to section 512 of the Federal Food, Drug, and Cosmetic Act. The major factual contentions which they made were that:

a. The tumorigenic effects were a secondary response due to hormonal interference, and that at low levels of exposure there was no carcinogenic risk;

b. A residue assay for tissue monitoring for NF–180 had been developed with a sensitivity of 2.0 ppb, and this procedure could be adapted for use in tissue assay for NF–7 and NF–64;

c. A residue assay method for 6F–260 in milk had been developed with a sensitivity of 0.2 ppb;

d. Methods of such rigorous sensitivity were not necessary because there was no reason to believe that under the approved conditions of use, residues would occur at levels sufficient to affect human health.

The sponsors, upon request, supplied the methods of analysis which they claimed were available at the lower levels of sensitivity. The assay procedures were reviewed by FDA and preliminary laboratory trials were conducted. Various problems arose in applying these methods, which we attempted to resolve, one firm continued over an extended period of time to supply modifications which it felt would improve the procedure. Finally, in 1972, the Agency decided that no new methodology data would be accepted for review and that the most recent procedure "in hand" from the sponsors would be subjected to interlaboratory trials and stand or fall on the basis of the results.

The trial for NF–180 and NF–260 was completed in late 1972. From the results FDA concluded that the method for NF–180 in tissue was not satisfactory. This also meant that there was no satisfactory method for NF–7 and NF–64 since the drug sponsors had planned to adapt the methodology for NF—180 to NF–7 and NF–64, contingent upon the acceptability of the procedure for NF–180.

The Agency found the method for NF–260 in milk acceptable at a sensitivity of 0.2 ppb, provided a confirmatory test was developed by the drug sponsors to assure the specificity of the procedure. Other data also were needed to bring the quality of the safety data base for NF–260 up to current standards.

These facts were brought before the Chief Counsel of the Food and Drug Administration on March 30, 1973, to determine an appropriate course of action. It was the opinion of the Chief Counsel that the notices of intended withdrawal were legally deficient under prevailing case law. He concluded that before further action could be taken, it would be necessary to present a clear, detailed discussion of the available evidence, of the basis for our safety data requirements, of how we determined the necessary sensitivity required for the regulatory assay method for drug residues, and to set forth a detailed statement of the deficiencies in the data presented by the sponsors.

As a first step in this process all data on nitrofurans available in the Agency, including supporting data in the new animal drug applications as well as all relevant safety data available in the investigational and new human drug applications, were assembled for review. Concurrently, two new FDA pathologists reviewed all of the slides from the chronic studies involving the tumors and a consultant at the National Institutes of Health and a specialist in the Bureau of Drugs reviewed the evidence claimed by the sponsors to support the hormonal hypothesis for tumor response.

The review and consolidation of information was completed in October 1973. The conclusions were that the compounds were highly suspect carcinogens and that there was not substantial evidence to support the hormonal hypothesis.

During this period the drug sponsors completed more adequate chronic toxicity/carcinogenicity studies for NF–180 (three studies in rats and one study in mice) and submitted the final reports in December 1973. FDA's review of the four new chronic studies was completed in late December 1974. FDA concluded that the studies showed a definite carcinogenic effect at the higher dose levels and further supported the earlier opinions of the Bureau of Foods. The finding of bronchial adenocarcinomas in the mice added supporting evidence of carcinogenicity, which previously was tied only to the occurrence of mammary gland tumors in rats.

Additionally, in the fall of 1974, the drug sponsors had submitted new methodology for assaying for tissue residues. The supporting data for the assay were inadequate at the 2.0 ppb sensitivity for a new method validation trial.

In February 1975, a summary of the most pertinent information was reviewed by the Chief Counsel and representatives of the Bureaus of Foods and Veterinary Medicine in a policy meeting to determine appropriate action. The participants decided that the new evidence from the lifetime studies gave adequate evidence that NF–180 is a carcinogen. They also agreed that the other nitrofuran compounds should be treated as carcinogens based on the evidence from the early studies and their close structural relationship to NF–180. No additional carcinogenesis studies had been undertaken for the other compounds.

The difficult remaining issue was establishing a basis for the required level of sensitivity for the regulatory assay method. This had been raised by the drug sponsors in the request for hearing as an "issue of fact," and is almost certain to be a major point of controversy in any subsequent legal action.

It was therefore concluded in the February 1975 meeting that:

a. Efforts should be continued at high priority to finalize a regulation on the sensitivity of the method for carcinogenic compounds used in food animals. (A new regulation published in the Federal Register of February 22, 1977, prescribes steps for using carcinogenic data from animal tests in a conservative statistical extrapolation procedure so that a required assay sensitivity can be determined that is related to carcinogenic potency.)

b. Concurrently, new notices of intended withdrawal and opportunity for hearing, complying with current legal standards, would be drafted for NF–180, NF–7, and NF–64.

c. A letter would be prepared to the drug sponsors notifying them that the assay method for NF–260 in milk is acceptable and outlining additional data requirements which are necessary to complete the reaffirmation of safety for NF–260 under current criteria.

SUBSEQUENT FDA ACTIONS

In the Federal Register of May 13, 1976, the FDA issued a notice of opportunity for hearing proposing to withdraw approval of new animal drug applications (NADA) for the use of furazolidone (NF–180) in food-producing animals.

In the Federal Register of August 17, 1976, FDA issued notices of opportunity for hearing proposing to withdraw approval of NADA's for furaltadone (NF–260) and nitrofurazone (NF–7).

In response to these notices, some manufacturers of the drug requested hearings on the above drugs. They offered new data and substantive comments which have required further evaluation of existing data.

The Commissioner concluded that it is in the public interest to hold evidentiary public hearing on the proposal to withdraw approval of new animal drug applications (NADA's) for NF–180, NF–7 and NF–260.

A notice of hearing will be published in the Federal Register later this summer or in early fall. Because of the complexity of the issues, the Bureau of Foods' staff has found it necessary to work with consultants to complete the evaluation of comments and new data, and to prepare the notice of hearing. The forthcoming evidentiary hearing will be open to the public.

Also in the August 1976 Federal Register publication, the Director of the Bureau of Veterinary Medicine offered an opportunity for hearing on a proposal to withdraw approval of certain NADA's for the use of nihydrazone (NF–64) in food-producing animals. Neither the holders of the NADA's nor any other persons requested a hearing on this action. Therefore, the Director of the Bureau of Veterinary Medicine issued an order in the Federal Register of April 8, 1977, withdrawing approval of the NADA's for NF–64. In this same issue of the Federal Register the Commissioner of Food and Drugs issued an order revoking certain regulations that provide for the use of animal drugs containing nihydrazone alone or in combinations.

Mr. Moss. Mr. Waxman, would you yield at that point?

Mr. WAXMAN. Certainly.

Mr. Moss. I am troubled by that matter of your being separated from it.

Why? It is not judicial. This is legislative.

Dr. KENNEDY. Mr. Chairman, our rulemaking procedures provide that the Commissioner, once a "Notice of Opportunity for Hearing" is published—because he is the final decisionmaker in an evidentiary hearing—must separate himself from the substance of the matter.

I did not mean to imply by my answer to Congressman Waxman's question that I did not consider myself responsible for maintaining a reasonable schedule; I do. But, if it is substance you want to know about, then I am going to have some difficulties.

Mr. Moss. I would like to pursue this for a moment, Mr. Waxman, if I may.

I may well be interested in substance. Don't you concede that I have a right to be and to be able to get the answer from the best source and the most responsible course in the Agency: the Commissioner?

Dr. KENNEDY. Well, Mr. Chairman, I agree that you have the right to get it from the best and most responsible source in the Agency; but we have found no other way to maintain the Commissioner's status as a decisionmaker in such cases, other than temporarily in time to vest that best knowledge status in the bureau Director instead of in the Commissioner. That is all.

Mr. Moss. I have been around here now for 25 years. I do not think that, in the exercise of oversight, I have had this kind of a philosophy state for me before. And I have been dealing with all of these agencies.

I do not want something to creep in here that, in my judgment, has no place.

Dr. KENNEDY. I understand that, Mr. Chairman.

With your permission, let me suggest that we supply for the record the relevant part of our procedure regulations and a——

Mr. MOSS. Let me make this very clear, Commissioner. I do not feel that we are bound by your regulations. You are by ours, but we are not by yours.

Dr. KENNEDY. I understand that, Mr. Chairman; I am not suggesting that. I was merely trying to explain why I was unable——

Mr. MOSS. I think what I would prefer to have is a legal opinion from your counsel giving the basis for this unusual assertion before a committee of the Congress.

Dr. KENNEDY. Mr. Chairman, let me try to clarify the kind of assertion I have made.

Mr. MOSS. I am very familiar with it, Mr. Commissioner.

Dr. KENNEDY. I want to be sure that there is not any misunderstanding.

Mr. MOSS. Be very certain, sir, that I am quite familiar with it. That is why I asked the question.

Dr. KENNEDY. Well, we will certainly supply that for the record.

Mr. MOSS. Without objection, we will hold the record open at this point to receive it; and I thank the gentleman from California for yielding to me.

[See tab A to letter dated November 6, 1977, from Dr. Kennedy to Chairman Moss, p. 109, this hearing.]

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Kennedy, the reason I raised the issue of nitrofurans is that, if FDA insists on following a slower regulatory route, the public should somehow be assured that the agency will follow the process through to completion. The nitrofurans situation seems to have run into a tremendous amount of delay.

I would like to get assurances from you that the notice that has been filed by FDA is going to move along at least within the timeframe that you suggested and certainly no longer.

What assurances can you give us that this regulatory action will move along at a rapid pace?

Dr. KENNEDY. I can assure you, Mr. Waxman, that I have communicated my own sense of urgency about this to our staff and to our Office of General Counsel. It is receiving all the priority attention that I believe it can receive, stretching our resources as far as they will go. I think we can keep the schedule that I have set for you. I regard myself as accountable to you if we don't.

Mr. WAXMAN. I would like a clarification on one point. Tetracycline was treated differently than penicillin. What does FDA intend to do to regulate tetracycline in animal feed? Is that part of the Notice of Opportunity that has been filed by FDA?

Dr. KENNEDY. The Notice of Opportunity that has been filed by FDA already is on penicillin. The order that is shortly to be filed deals with the three tetracycline compounds. They had to be handled differently because of some issues relating to the availability of substitutes for certain uses and other technical problems. We would have preferred to handle them all together but could not.

Mr. WAXMAN. You are ready to move on tetracycline?

Dr. KENNEDY. Yes. The Notice of Opportunity for hearing will issue in just 2 or 3 weeks.

Mr. WAXMAN. How long a period of time after issuance of the Notice of Opportunity can we expect the question of tetracycline to be resolved?

Dr. KENNEDY. The schedule that I read in my testimony, Mr. Waxman, actually applies to both. There will be a comment period; it is 60 days. That is the period in which those who wish to have a hearing can state their case for one; then we evaluate that case and either grant the evidentiary hearing, if there are material facts in dispute that are surfaced by the application for hearing, or deny it.

Mr. WAXMAN. Were you satisfied by the advisory committee's decision to separate tetracyclines from penicillin? Do you think that the decision made any sense?

Dr. KENNEDY. I believe that the people in our Bureau agreed with it. And, to the extent that I can appreciate the issues involved in the necessity to treat the substitution problem separately, I do agree with it.

I also agree with it in that I think it has been possible to move ahead with the documents a little faster. We have used the penicillin document as a way of breaking open some of the problems we had with it, and yet we could allocate a different set of people and a different set of resources to the responsibility for the other.

So, I think it has worked out reasonably well.

Mr. WAXMAN. Dr. Kennedy, I appreciate what you have to say about the FDA moving swiftly on both tetracycline and penicillin. I have been critical of FDA in the past for not having moved as rapidly as I thought it should. I accept your assurances that FDA is going to move vigorously on these two drugs. I am pleased to see FDA taking a proper role in advocating protection of the public health in a way that I think it has not been fulfilled by that agency in the past.

Thank you for your testimony. I hope, when you are accountable to us for the work of FDA in removing these two antibiotics from the marketplace, that that accountability will be to your credit. Thank you for your testimony.

Dr. KENNEDY. Thank you.

Mr. Moss. Mr. Santini?

Mr. SANTINI. Thank you, Mr. Chairman.

Dr. Kennedy, I would like to share with you some different perspectives on the issue that you are examining. It is a troublesome issue to me because a principal industry in my district is affected by it—livestock. Approximately 60 percent of the livestock are reliant for either growth inducement or for health purposes on either penicillin or tetracycline.

Yet, I suppose the undisputed evidence—because, simply, there has been no effort to countermand this evidence—suggests it is going to cost the poultry, swine, and livestock industry $2.1 billion. It is going to cost an awful lot of money.

In the context of health, cost can be considered an irrelevancy; or cost can be considered a legitimate concern.

The issues I would share with you this morning, Dr. Kennedy, include examinations on do we in fact have a health hazard situation.

Other countries appear to have come down emphatically, yes we do. And that is a consideration that I cannot ignore.

I would like to pose some considerations and invite your response thereto. In the context of alternatives to tetracycline, tetracycline was separated from penicillin because further examination was necessary to determine if there are alternatives to tetracycline. I gather you have come down on the affirmative side, yes there are alternative drug substances to tetracycline?

Dr. KENNEDY. There are three drugs at issue here among the tetracyclines. They have several different applications. So, the difficulty there was to discover which applications there were for which there were adequate substitutes and which ones there were not so that we could permit some exceptions. That is why the analysis of the tetracycline problem was more difficult than the analysis of the penicillin problem.

There was also an issue with respect to penicillin about its effectiveness. For that reason, they had to be treated as separate documents and developed independently.

Mr. SANTINI. In regard to the tetracyclines, what are the substitutes or alternatives that can be used to eliminate the necessity of relying on those?

Dr. KENNEDY. That is a very complicated question. There is a long list of uses and a matrix of substitutes which we will be publishing as a part of our notice of opportunity for hearing on the tetracyclines.

I am going to have to ask for Dr. Van Houweling's help, with the chairman's permission, if you really want to get into that level of technicality.

Mr. SANTINI. Let's approach it from a different way. I assume the drugs would have a name or a combination of drugs would have a name, and those alternative drugs would be identified in the record.

Dr. KENNEDY. They will be in our notice of opportunity for hearing which will be issued in a couple of weeks.

Mr. SANTINI. Are you satisfied, based on your evidence and evaluation of that evidence, that the alternative drugs to tetracycline do not themselves pose a possible health hazard because of the prospect of shedding and the prospect of possible transference of resistance?

Dr. KENNEDY. No; I cannot completely reassure you on that point, Mr. Santini. The evidence that we have about multiple antibiotic resistance is that it is selected for most strongly by the same antibiotic to which one is measuring the resistance. In other words, tetracycline induces tetracycline resistance primarily. But, because of the multiplicity of the resistance factors and because of their genetic association, there is a tendency for them to come on together.

Some of the substitute antibiotics do also select, although we think somewhat more weakly, for multiple antibiotic resistance.

So, we will not completely free ourselves of the kind of problems that we think exist with the present antibiotics. We do think that we will reduce the problem very substantially.

Mr. SANTINI. That is encouraging. That, of course, is the kind of alternative solutions that I am hoping to probe through the murky mass of evidence as I perceive at this point. Perhaps that is the viable and rational alternative.

The distressing state of the industry is just not a matter that I can ignore. The livestock industry has been staggering about on its knees—or is flat on its face, as the case may be—for the last 2 or 3 years. This is just another sort of aggravating possibility for further deterioration of that industry.

You, of course, need not concern yourself with mundane matters of economics because your goal is legislatively mandated and perfectly clear. Safety and effectiveness must be your standard—not economic consequence. I recognize that.

In your statement, Dr. Kennedy, you state that the only uncertainty in deciding whether the resistance was selected through overuse of antibiotics in animal feed or in the hospital. I think that is a very important difference. For example, if the evidence came down to resolve that whatever resistance transmission has occurred has occurred as a consequence of overuse of drugs, we may be looking for false solutions in expecting that, by eliminating the transmission potentiality of penicillin or tetracyclines in poultry, swine, and livestock, we are thereby going to solve the problem; and we can thereby be content that whatever resistance deterioration has occurred over recent years will not now occur in the future.

Dr. KENNEDY. I agree that that is a problem. But let me make it plain that I think that hazard of antibiotic use in animal feeds is a significant one. We have, I think, very unmistakable evidence that there is transfer of resistant microorganisms from the guts of livestock animals to the intestinal tract of those persons who work with them in raising operations, feedlot operations, or in slaughtering and meat handling operations. The route of transmission really exists. It is bona fide. There is not any doubt about it on the grounds of the evidence.

So, you are in this peculiar position of not being able to tell when we encounter a tetracycline resistant gonococcus or meningococcus in man. As you know, there have been numerous recent instances of persistent pesky human diseases tha just cannot be treated with conventional antibiotics. We cannot say for a particular case:

Aha, the history of this one traces to use in livestock, and the history of this one traces to overdosages in some particular hospital.

All we know is that both routes are possible. All we know is that the sum total of the routes is being used. I think that a prudent approach to the public health dictates that we must shut them down if they are patent and real.

I am not sure we will ever know securely and quantitatively what the relative contribution of these two sources is, although perhaps the CDC folks can help with that.

Mr. SANTINI. I understand, Dr. Kennedy. I believe the acknowledgment was made by an earlier witness that there is no one instance that can be proven of human resistance to penicillin or of human resistance to medical treatment caused as the result of ingestion of meat, fish, swine, or poultry substances which were the cause.

I am sure that I fail to perceive some of the medical complexities with which you are grappling. It was also asserted that, in the situation, for example, where a farm worker or a person who admits to have consumed a large amount of either poultry, swine, or beef prod-

ucts and who never had occasion or necessity of any ingestion of any medical substance, then that would seem to me to offer a test group that would enable you to determine if there is or is not a causal relationship between this resistance.

Is that an impossible kind of empirical or field test?

Dr. KENNEDY. I think not impossible, Mr. Santini, but surely difficult. The epidemiology of drug resistance is a complicated matter. Routes of infection are complicated, and sometimes improbable ones are used.

Whether a large scale epidemiological study comparing disease incidence and incidence of resistant pathogens in human populations that had very close and very distant contact with uses of antibiotics in feeds might be a way to get at the problem—I know of no study of adequate scale that has yet been done or is now planned. I would have to yield to my colleagues from the Center for Disease Control on the question whether such a study is, in principle, possible.

Mr. SANTINI. It is contemplated, at least in terms of one alternative solution, that the veterinarians would make recommendations on use or nonuse. You perhaps are aware that the American Veterinary Medical Association recommends the continued use of subtherapeutic antibiotics in animals. In your judgment, is this a realistic solution possibility to the problem that you are probing and seeking to resolve?

Dr. KENNEDY. I think that the solution is realistic. I think veterinarians are a responsible professional group and that they are the appropriate place to vest the responsibility for the wise use of drugs. They have an excellent postgraduate education that is as intensive and as prolonged as that of medical students.

I see no reason why they should not be exerting their share of responsibility over the public health.

I do not see anything inconsistent between that position on our part and the position of the American Veterinary Medical Association. There are some things about the practice of medicine in this country that the American Medical Association disagrees with but which doctors still fill their responsibilities on anyway. I think that veterinarians, even though they may in the beginning disagree in the majority with the judgments on which we have based that decision, will carry out their responsibilities for the public health.

Mr. SANTINI. Dr. Kennedy, it seems that, if they have the qualifications and the capabilities of fulfilling this significant responsibility that you wish to share with them, perhaps their recommendation is deserving of additional consideration on your part.

Dr. KENNEDY. I think it is. It will be given that kind of consideration as a part of the notice of opportunity for hearing. Public comment on these issues has been invited. The process of scientific balancing and evaluation is only beginning. We expect veterinarians to contribute significantly to it.

Mr. SANTINI. Are there any human health benefits from limiting disease in animals?

Dr. KENNEDY. Well, yes. First of all, of course, success of all phases of the animal production and plant production enterprise in this country is important to human health because nutrition is a terribly important health benefit.

Additionally, there are aspects of animals disease that affect the status of certain routes of infection to man. Some animal diseases certainly affect the degree of shedding of salmonella and things of that sort. There are, I suppose, a small number of animal diseases that are even transmissible to man.

Mr. SANTINI. What are some animal diseases that are transmissible to man?

Dr. KENNEDY. Dr. VanHouweling can help me out here. Salmonella, of course, is the obvious one. One of the chief issues in the antibiotics in feeds matter to begin with was salmonella shedding and salmonella infections in man. Brucellosis and tuberculosis are animal diseases that are transferred to man, although I think that particular transfer is not the most important health aspect of this question.

Mr. SANTINI. But I think it is an issue that deserves consideration as this evidence-finding process proceeds.

Are penicillin and tetracycline useful in eliminating or reducing the potential for shedding of these animal disease potentials?

Dr. KENNEDY. I do not know of any evidence that suggests that these antibiotics are more effective than the substitutes that our proposal will allow in affecting the degree of shedding of salmonella or, indeed, the transmissibility of any of these others.

Mr. SANTINI. So, it is your professional conclusion that the alternatives that you have determined with regard to penicillin, tetracycline will be just as effective in preventing the transmission of the animal disease elements as penicillin and tetracycline?

Dr. KENNEDY. That is our view; yes, Mr. Santini. But I remind you that it is, of course, subject to challenge through the procedures we have outlined.

Mr. SANTINI. I thank you, Mr. Chairman, for your indulgence.

I thank you, Dr. Kennedy, for your responses.

Dr. KENNEDY. Thank you, sir.

Mr. MOSS. The Chair is going to ask the cooperation of the witnesses from the Food and Drug Adminstration. Congresswoman Smith of Nebraska is here and has been waiting for some time. She is scheduled at meetings. I would ask that you stand aside long enough for her to deliver her statement to the committee, and then we will resume.

Dr. KENNEDY. Yes. Mr. Chairman.

Mr. MOSS. Mrs. Smith, I apologize for the delay in hearing from you.

STATEMENT OF HON. VIRGINIA SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEBRASKA

Mrs. SMITH. Mr. Chairman, I understand this; and I appreciate the opportunity to appear before this committee.

I have six typewritten pages here; but do not fear, I will not read them. I will just comment.

Mr. MOSS. The entire statement will be placed in the record, without objection [see p. 90].

Mrs. SMITH. Thank you, Mr. Chairman.

It is my privilege to represent one of the few agricultural districts that are left in this Nation. I believe that my district is second in the

Nation in the production of cattle, and also we have a great deal of swine and turkey products. So, this is a very big issue with us.

Our livestock producers, for some 27 years, have been using low-level antibiotics. They have had no case of damage to anyone who handles the product, anyone who eats it, or to any animal from using these products. They have tried to market healthy, top-flight animals. Because of these antibiotics, they have been able to make greater use of our feed, get faster growth, and to have more disease-free animals.

I would like briefly to quote from our Livestock Feeders Association in Nebraska, which describes the advantages this way:

> When livestock are concentrated in large numbers in pens or buildings, it is only natural that diseases become harder to combat. We have found by experience that when we use antibiotics as feed additives we can hold down the incidence of disease which in turn will, one, save precious grain; two, allow more animals to live and become feed for human consumption; three, produce meat at a more reasonable cost; and, four, maintain a more healthy herd.

I come from the middle of the cattle country. I do not know of any of my friends that have ever known of any damage that has come from using these low-level antibiotics. In addition, you know, there have been hundreds of research projects on this subject; and we do not have any sources that show that there is any problem with resistance transfer.

I think it is most unfortunate, both for our producers and for our consumers, to take away these low-level antibiotics—which is going to cost livestock producers some $2 billion more a year to produce beef for America—and the consumer is going to have to pay the added cost. Moreover, when we have more healthful animals, we have more healthful people. So, we think it is good all around.

I understand that right now there is a study underway from the Office of Technological Assessment and another by the Council on Agricultural Science and Technology. I think we should wait until those studies are completed before any action is taken.

So, I am here to urge that Commissioner Kennedy back off and wait before any action is taken and that you, in your wisdom, permit us to continue using the low-level antibiotics until and unless there should be real proof that there is any damage.

Thank you very much for permitting me to come.

[Congresswoman Smith's statement follows:]

STATEMENT OF HON. VIRGINIA SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEBRASKA

Mr. Chairman, members of the subcommittee, I welcome this opportunity to come before you today to register my views on the proposal of the Food and Drug Administration to limit the use of low-level antibiotics—particularly penicillin and the tetracyclines—in livestock feed.

I have the honor of representing one of the few truly agricultural districts in the United States. The production and sale of farm products and commodities is our No. 1 industry. The raising and feeding of cattle, swine, and poultry accounts for a major part of the income of the farmers and ranchers in the 61 counties of the Third District of Nebraska. Livestock production in our part of the State contributes to the high ranking Nebraska has in the Nation in the categories of commercial cattle slaughter, feed cattle and calves marketed, commercial livestock slaughter—all species, commercial hog slaughter and others.

Our livestock producers make use of established production techniques which enable them to send to market healthy, wholesome and top flight animals. They have been fortifying the feed for their livestock and poultry with low-level anti-

biotics for over a quarter of a century. In doing so, they have benefitted from feed efficiency, faster growth and more disease-free animals.

The Nebraska Livestock Feeders Association describes the advantages this way: "When livestock are concentrated in large numbers in pens or buildings, it is only natural that diseases become harder to combat. We have found by experience that when we use antibiotics as feed additives we can hold down the incidence of disease which in turn will: (1) save precious grain; (2) allow more animals to live and become feed for human consumption; (3) produce meat at a more reasonable cost; and (4) maintain a more healthy herd."

During all of the time this practice has been followed, these producers have not been aware of any harmful effects or health hazards to the animals consuming the feed, to the feeders working with the livestock, or to the people consuming the meat and poultry products. If there has been any evidence of the transfer of antibiotics resistance from animal to man, it has not come to the attention of these people who make the widest use of using animal feed containing low-level antibiotics. Besides, Mr. Chairman, I understand there are hundreds of research reports from universities, hospitals and from industry sources on the whole question of antibiotic resistance transfer. They do not indicate any health hazards to humans or animals.

The livestock producers I know want to stay in business and meet the demand for their product. They would be hard pressed to continue a profitable and satisfying operation if the slightest doubt existed about the quality of their product. They have no reservations about this wholesomeness for themselves and their families. They have seen no evidence that the practices they are following are endangering the health of the meat-consuming public.

The use of antibiotics in animal feed represents a $2-billion annual savings to the livestock industry. To do away with the practice is to add this much more to the retail price of meat and poultry. An unwarranted economic burden is placed on the producer and consumer alike. I do not need to tell you that the plight of the livestock producer has been no bed of roses over the past five years. He has suffered one blow after another.

Mr. Chairman, I realize that in the hearings of your subcommittee held last year, and in your ongoing effort this year, you have tried to "build a fire," so to speak, under the Food and Drug Administration to be more diligent in determining the safety and effectiveness of drugs, and especially to take prompt action in the area of antibiotics in animal feed which has been under study for several years.

Apparently Commissioner Donald Kennedy felt the heat right away after he assumed office. He came out immediately with a notice that he intended to "* * * severely restrict the addition to animal feed of low levels of certain antibiotic drugs."

His decision to act so precipitously is disturbing because in one respect he was flying in the face of the recommendation of the National Advisory Food and Drug Committee, and in another, by his own admission, he lacked the scientific evidence upon which to base a decision of this kind. Permit me to quote his own words: "Although we can point to no specific disease in people that cannot be treated because of resistance due to drugs in animals, we are concerned about the threat it may pose in the future. It is even possible that such problems now exist but have gone unnoticed."

The question immediately comes to mind: "How could any health problems resulting from the use of antibiotics in this manner go unnoticed over the past 27 years?" It is inconceivable that any health problem this serious would not have come to the attention of American physicians or the practitioners in our advanced medical sciences.

Extensive studies have been made since 1973 to research the theoretical concerns about the potential danger of using antibiotics in animal feed. These studies did not demonstrate that low-level antibiotics compromised the health of man or animals. It is evident then that the antibiotic resistance link between food-producing animals and man has not been shown.

Mr. Chairman, in addition to the abundance of scientific data already available on the subject of antibiotic resistance, I understand that other studies are underway—one by the Office of Technological Assessment and another by the Council of Agricultural Science and Technology, plus additional research by the drug manufacturing firms themselves.

May I suggest that lacking sufficient scientific evidence to the contrary, that Commissioner Kennedy back off from his proposed bans until it can be documented beyond a reasonable doubt that this threat to health exists and that

the kind of limitation proposed by the Food and Drug Administration is absolutely necessary.

I wish to add that I have voiced my own objections to the Hearing Clerk at FDA during the present comment period for the proposed limitation on the use of penicillin in animal feed. When the document on tetracyclines is published, I will file similar objections. I am encouraging livestock and poultry producers, as well as all other interested parties, to do likewise on the premise that the weight of reasoned comment from people with first-hand knowledge may cause the Food and Drug Administration to delay implementation of these proposals until further substantiating evidence is forthcoming. I have no doubt that ongoing and future studies will verify what we already know, but all of it should have an influence in steering Commissioner Kennedy away from his tendency to proceed on a theoretical basis and get him back to using factual data and incontrovertible evidence in making his proposals.

Mr. Chairman, and Members of the Subcommittee, I am grateful for this opportunity to come before you and express again my seirous concern about the implication of these proposed limitations on the use of low-level antibiotics in animal and poultry feed.

The limitations are not warranted on the basis of scientific fact. They will place an additional economic burden on the livestock producers and on the consumers without any compensating benefits to either.

I trust the testimony in this and other hearings will result in an about-face by the Food and Drug Administration and that the limitations will not go into effect.

Thank you.

Mr. Moss. Thank you very much.

As you recognize, we are the oversight rather than the legislative part of the Commerce Committee. So, all we are going to do is look at the way they are operating and try to make a judgment whether they are proceeding effectively, efficiently, and fairly, or whether there are deficiencies in the procedures. That is why I had my little dialog here with the Commissioner of the FDA as to the right of the Congress to inquire most broadly into substantive matters, if need be, in order to gather all facts relevant to a legislative purpose.

We do thank you.

Mrs. SMITH. I appreciate this opportunity. Thank you very much.

Mr. Moss. Gentlemen, please return to the table now.

STATEMENT OF HON. DONALD KENNEDY, PH. D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ET AL.—Resumed

Mr. Moss. Mr. McLain?

Mr. MCLAIN. Thank you, Mr. Chairman

Mr Commissioner, you mentioned earlier the notice published by the Administration on August 3 relative to penicillin. As you stated, there are basically three bases upon which you are acting. One is that it has not been shown to be safe for subtherapeutic use: growth promotion, disease prevention. Two is that there has been substantial evidence presented that they are not effective for therapeutic uses. Three is that the sponsors have not maintained adequate records or filed the requisite reports.

In 1968, as was discussed in the chairman's opening statement, the National Academy of Sciences questioned the safety and efficacy of penicillin, among other drugs. Again, in 1970, the task force was created by the Food and Drug Administration to examine the safety and efficacy of antibiotics.

GAO testified on Monday—and this has been confirmed by an Assistant Director of DVM—that no evidence has ever been submitted to the Food and Drug Administration to support a finding of efficacy for penicillin as a disease preventant for poultry. Is that correct, Dr. Kennedy?

Dr. KENNEDY. I do not know.

Can I get some help on that one, Mr. Chairman?

Mr. MOSS. Certainly.

Dr. GUEST. I do not know precisely the answer to that question.

When you say "disease prevention in poultry," that is a pretty broad statement. I am not trying to avoid answering; I am just not sure.

I think what we found is, at this time, that we question the efficacy of both the subtherapeutic and the therapeutic uses of penicillin in feeds. I think in the notice of August 30 we dealt with the therapeutic side of that.

Mr. MCLAIN. That is my question. Why did you not deal with the subtherapeutic side of the efficacy question?

Dr. GUEST. There are a couple of reasons for that. One is that we felt the safety issue was substantial enough to carry that argument that we put forth there. We were anticipating that persons asking for hearings would be asking on the basis of safety and that we need not address the efficacy in that particular document.

The other reason was—and I think the better reason—that, for disease prevention, penicillin is most ofen used in combination with other drugs. We have taken action on efficacy for the penicillin-streptomycin combination, which is a popular drug used in swine and poultry, as far as penicillin is concerned. This was done on June 10, I believe, Mr. McLain. We proposed to remove the use of pen-strep on the basis of lack of efficacy.

We have also underway another document with the combination use in penicillin which is used in swine. It has a tetracycline, a sulfonamide, and a penicillin in it. We will propose to withdraw that combination on the basis of efficacy.

So, the administrative determination was made to attack efficacy in different areas rather than in this particular document you are talking about when you talk about subtherapeutic levels of the drug.

Mr. MCLAIN. It has also been stated by the GAO in their testimony Monday that representatives from the Food and Drug Administration have stated that the burden is easier to carry on the question of efficacy than it is on safety. Is that a correct statement?

Dr. KENNEDY. I think there is not universal agreement on that. When you are trying to predict what is going to be the most effective strategy, it is difficult to decide.

I think the decision was that the efficacy route was the best route to take on the double and triple combinations that Dr. Guest has referred to. But, on the single-use drugs, it seemed to us that, because a single set of scientific issues involving the safety was involved, that probably that was the way to go. But not everybody agrees with that, by the way. You might be interested to known that the Canadian Government has decided to proceed one by one on efficacy grounds.

Mr. MCLAIN. Are you stating to us then that you have accepted the original claims, the NADA's, as to the efficacy for subtherapeutic uses of single-use penicillin?

Dr. KENNEDY. No. I do not know whether we have done that or not. I will have to ask.

Mr. MCLAIN. Do you have any evidence available to you that they are efficacious?

Dr. KENNEDY. The single drug uses of penicillin?

Mr. MCLAIN. Yes.

Dr. KENNEDY. I will have to ask Dr. Guest the status of those.

Dr. GUEST. On the single drug penicillin use for growth promotion, we had some very clear direction from the National Academy of Science. By changing the claim as it was presently being presented on the labeling to a claim which says, "as an aid in weight gain and feed efficiency," that we could move these to the effective category. So, we had pretty clear direction that at least the lowest growth promotion level was in fact accepted by experts as being effective.

Where you get into the questions comes in this middle category of disease control agents. That becomes a matter of sorting out the science. We are in the process of doing that.

If this particular document and the combination documents are not successful in taking penicillin—period—out of feeds, then of course we have that recourse to go to. We just made the judgment not to attack that right now.

Mr. MCLAIN. You are talking about something that might take place in the future. If I could refer to something that happened in the past that directly bears on this.

I ask that two letters be inserted in the record at this time, Mr. Chairman.

Mr. MOSS. Without objection, they will be placed in the record at this point.

[The letters referred to follow:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
CENTER FOR DISEASE CONTROL,
Atlanta, Ga., May 10, 1971.

RICHARD P. LEHMAN, Ph. D.,
Acting Director, Division of Nutritional Sciences, Bureau of Veterinary Medicine, Rockville, Md.

DEAR DR. LEHMAN: Thank you for forwarding the material on the efficacy of ASP 250 as a growth promotant that was requested at the time of our last Task Force meeting in Washington. I have finally had the opportunity to review this material at length. I was surprised to find that the latest studies included in this group were apparently conducted in 1963 (if I interpret the codes appropriately). Obviously, more up-to-date information would be desirable.

After careful review of these 11 studies, I must conclude that, in at least eight of them, the results may well reflect the efficacy of AS 250 for disease prophylaxis and treatment. I cannot confidently separate the "growth promotion" effects from the former effects in the following studies:

P–60–22–FT	Atrophic rhinitis and pneumonia were present in controls. No morbidity rates presented for the various groups.
P–60–23–FT	"Scouring" said to have affected all groups, but the morbidity rates in the different groups are not documented.
P–60–24–FT	Control pigs had enteritis. No morbidity rates among the groups were given.
P–61– 9–FT	Enteritis occurred in the first 2 weeks of the trial and a leptospiral problem was also acknowledged in the herd. No morbidity rates for different groups were presented.
P–62– 7–FT	Scouring was said to have occurred in the controls throughout the test. No morbidity rates presented for the various groups.

P–62– 8–FT No statement about disease appears in the text, but the appendix indicates that pig #91, a control, died of "enteritis." A skeptic must presume that additional cases also occurred; however, no morbidity rates are presented.

P–62–10–FT Enteritis said to be present during this study, but no morbidity rates are presented.

P–63– 3–FT Scouring in all groups was said to have occurred during the first 2 weeks of the trial. It was alleged to be "equally severe" in all groups, however, morbidity rates to solidly document this are not given.

I would have preferred the study design of the three remaining studies to have avoided the use of antibiotics in the controls during the time prior to the start of the experimental runs. This practice could conceivably have had an effect, one way or the other, upon the results during the study period. Such usage was noted in the remaining three studies, namely, study P–62–9–FT, study P–63–4–FT, and study P–63–5–FT.

I have checked the statistics on the latter three studies and would agree that the ASP 250 treated animals gained significantly more weight than the controls, and that the feed efficiency was higher among the treated animals. It is ill advised, I feel, to conclude from these three studies that ASP 250 is of general benefit as a growth promotant since a critical denominator is missing; namely, the number of trials of similar nature that failed to show a significant difference or that may have actually showed a significantly superior performance of the controls. The number sequence on the studies you sent indicates that a large number of additional studies were probably conducted. Presumably they did not show growth promotant effects. In a large series of trials, one might expect to observe disproportionate results such as seen in the above three studies by chance alone, i.e., he who throws the dice often will sometimes have a lucky hit.

In addition there remains the rather important question concerning the relevance of "growth promotant" effects during the weaning period to the market weight of an animal. There seems to be a rather strong likelihood that the market weight of treated and untreated animals may be quite comparable, in which event the only benefits accruing from the use of growth promotants would presumably relate to the saving of feed during the several weeks immediately post weaning.

I cannot conclude from a review of this information that ASP 250 is, or is not, effective as a growth promotant. More data on this issue, in my opinion, needs to be collected. Especially critical in this regard is the necessity to insure that the results reflect a true growth promotant effect, in distinction to disease prophylaxis and treatment effects.

Sincerely yours,

JOHN V. BENNETT, M.D.,
Chief, Bacterial Diseases Branch,
Epidemiology Program.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., May 25, 1971.

JOHN V. BENNETT, M.D.,
Chief, Bacterial Diseases Branch, Epidemiology Program, HSMHA, PHS, DHEW, Center for Disease Control, Atlanta, Ga.

DEAR DR. BENNETT: We obviously agree with your conclusions; in fact, we have several reviews of this material by our staff that contain conclusions equivalent to yours. We have notified the firm of the lack of data to support the growth claims, and have given them in writing, 30 days to delete these claims from their labeling.

There are several additional points, as you recall during our last task force meeting, the basic question of whether or not CTC was active as a growth promotant in swine, was under consideration. I maintain that it is; there are many references on this point that so indicate. See, for example, references numbered 10, 14, 16, 17 and 19, cited in the most recent version of Dr. Howard Teague's paper. Also, the data that I sent also indicates and supports this contention of growth stimulation by CTC. I have not maintained, nor do I maintain, that ASP 250 used as a growth promotant is valid from a biological point of view.

With respect to the deletion of negative trials, you must understand that such a deletion of material is specifically pointed to in the Federal Statutes. Such an offense is felonious, and is so prosecuted. The whole FDA premarket clearance program is based on these statutes, and we assume, with assumption validation completed through our field inspectional program, that all of the data, both positive and negative, are submitted with each application.

With respect to a growth promotion claim, it must be shown that over a fixed time period the treated animals must be significantly heavier than those not treated after an adjustment for initial weight is made. If the non-treated and treated groups were comparable at market, then no growth claim would be permitted. This is pointed out in the section on efficacy of the draft report.

I would like to discuss this further with you, at some future mutually convenient date.

Sincerely,

RICHARD P. LEHMANN, Ph. D.,
Director, Division of Nutritional Sciences,
Bureau of Veterinary Medicine.

Mr. MCLAIN. One is a letter from Dr. Bennett, who will be testifying later, to Dr. Lehman, who is the Acting Director of the Division of Nutritional Sciences at BVM. That letter is dated May 10, 1971.

Dr. Bennett was explaining to Dr. Lehman that he had reviewed many studies as to the efficacy of one penicillin ASP 250. On the basis of these studies that he reviewed—he made a determination that they did not support the efficacy for subtherapeutic uses.

In this letter, in the first paragraph you will note that it states these studies were conducted in 1963. Dr. Lehman of FDA, writes back on May 25, 1971, and says: "We obviously agree with your conclusions; in fact, we have several reviews of this material by our staff that contain conclusions equivalent to yours. We have notified the firm of the lack of data to support the growth claims, and have given them in writing, 30 days to delete these claims from their labeling."

Have they deleted those claims from their labeling?

Dr. GUEST. The answer is no. Beyond that, I cannot comment because I am not sure of the history of those letters. But the answer is no.

On the labeling now—and that is one of the combinations that I spoke to you about—there is a claim for growth promotion, as I recall. We are preparing notice of opportunity for hearing on that particular combination which would attack all the claims. But I do not know the history of the 1971 letter.

Mr. MCLAIN. Mr. Commissioner, would you care to comment? It looked like you were prepared to act as of July 25, 1971, to change this labeling. It is now 1977, and we have just heard testimony that you might act in the future.

Dr. KENNEDY. Mr. McLain, I simply am not prepared to answer that question for obvious reasons. Your knowledge of the 1971 files in my agency appears to be better than mine. I am going to have to look back at the matter. I will be happy to supply answers for the record when I have done so.

Mr. MOSS. We will hold the record at this point to receive the material.

[See tab B to letter dated Nov. 6, 1977, from Dr. Kennedy to Chairman Moss, p. 112, this hearing.]

Mr. MCLAIN. I would like to move on in the progression of events within the administration dealing with this question. In 1975 the National Advisory Food and Drug Committee decided to establish its

Subcommitte on Antibiotics in Animal Feeds. What was the stated purpose for the creation of that subcommittee, Dr. Kennedy?

Dr. KENNEDY. The Subcommittee on Antibiotics in Feeds was to examine exactly the questions that we are discussing here.

Mr. MCLAIN. Was that an outgrowth of the data that was supplied in response to your 1973 regulations?

Dr. KENNEDY. Well, yes; that and the whole issue of how the agency should proceed to deal with the public health problem, both to evaluate it and to decide on an agency action.

Mr. MCLAIN. In April of 1976, as you know, representatives from the Bureau of Veterinary Medicine presented to the subcommittee its recommendations and conclusions regarding the safety and efficacy of penicillin. Again, in June of 1976, it presented its recommendations and conclusions as to the safety and efficacy of tetracyclines.

Both Dr. Falkow, who testified Monday, and the General Accounting Office said that, at that time, the Food and Drug Administration independently had sufficient data to act on their own to take regulatory action.

Would you say that that is a correct statement?

Dr. KENNEDY. Mid-1976 is not much easier for me to reconstruct my view of the adequacy of the data than 1972, which Mr. Waxman asked me to do a moment ago. I think that in 1976 the data were probably already in on which a conclusion could be based. I doubt seriously if new data that arrived after June of 1976 were required to make the case. However, having assigned that task to a subcommittee, I think, clearly, the agency decided that it ought to wait for that subcommittee to present its report to the main committee and for the main committee to act on it.

Mr. MCLAIN. Is it your feling then that the Administration did not have sufficient expertise itself to take such determinations?

Dr. KENNEDY. I think the expertise available to the administration of the agency at that time was adequate to make the decision. I think that the bureau's position in favor of the action that we have taken could have been reached and would have been reached without the involvement of the subcommittee.

I think that we frequently use advisory committees and external opinions for purposes other than to make up for our own inadequacies. Part of the process is to involve people with a somewhat different perspective. I think that was the effort in this case.

Mr. MCLAIN. Well, we will be getting to the question of the different perspective in a moment.

Are you stating then that, had you been Commissioner back in 1975, that is inconsistent with what you might have done, the creation of the subcommittee?

Dr. KENNEDY. No.

Mr. MCLAIN. You would not have created such a subcommittee?

Dr. KENNEDY. No, I don't know whether I would have created such a subcommittee.

I think, had I wanted advisory committee advice, I would have chosen a different route to get it. I do not know whether I would have wanted advisory committee advice on the problem.

Mr. MCLAIN. If I could——

Dr. KENNEDY. It is a very hypothetical question for me because it is tough for me to plug myself into the situation that existed then. It is just a rather difficult question.

Mr. MCLAIN. The same facts might come before you again today. What we are trying to do is get some kind of feeling about what action you might take should that happen.

Dr. KENNEDY. I think you know what I did when the facts came before me.

Mr. MCLAIN. I would like to follow up on a couple of points that were raised earlier as to alternatives, Dr. Kennedy.

You are familiar with the work that is being done by Dr. Novick in New York. A statement which he made before the Senate Agriculture Committee on Wednesday was to the effect that antibiotics are only effective as growth promotants when the animals are raised under suboptimal conditions. He explained circumstances of crowded, dirty, heavily contaminated pens and feedlots, rapid animal turnover, heavily contaminated feedstuffs.

Is that consistent with your viewpoint, Dr. Kennedy.

Dr. KENNEDY. I know a great deal about Dr. Novick's reputation. I am not a veterinary scientist nor an expert in growth promotion in livestock. I would have to take his word for it.

Mr. MCLAIN. Many opponents of the action you have taken have argued that the antibiotic feeding of animals has shown no increase in the incidence in disease.

Is that argument a smokescreen, Dr. Kennedy? Is that a question we are talking about, an increase in disease?

Dr. KENNEDY. I do not know if I would characterize it as a smokescreen, but I surely do not agree with it. It is not that it may not be true as stated, but because it is not an appropriate approach to the issue.

What we are concerned about is the risk of very serious communicable disease that cannot be treated with conventonal antibiotics. Even if there had been no single incidence of such a disease taht was known to have arisen from antibiotic use in animal feels, I think we would still be justified in taking precautions against it.

Mr. MCLAIN. I do not have any further questions at this time, Mr. Chairman.

Mr. Moss. Mr. Dodge?

Mr. DODGE. Thank you, Mr. Chairman.

Commissioner Kennedy, I would like to turn, if I may, to the question of conflict of interest. It is at least alleged to have arisen in the participation on a FDA Advisory Panel of the president of Farr Farms, William Farr. It concerns a discussion of the use of tetracyclines and other antibiotics in a key meeting of FDA's National Advisory Food and Drug Committee. This is the meeting, if you will recall, of January 24, 1977, shortly before you took office. But it was in the recent past: was it not? And you are familiar with it?

Dr. KENNEDY. Yes, it is the recent past. I am familiar with the meeting, Mr. Dodge.

Mr. DODGE. At this meeting, did the committee discuss the use of various antibiotics including tetracycline in animal feed?

Dr. KENNEDY. The committee received a report of its subcommittee and spent, I think, the better part of a day, perhaps all of the day, discussing various aspects of the merits of that report.

Mr. DODGE. Did Mr. Farr participate in that discussion?

Dr. KENNEDY. He did, although my own reading of the transcript of that meeting suggests that his participation involved very little more than the sentences quoted in the GAO report.

Mr. DODGE. Nonetheless, he did participate?

Dr. KENNEDY. He was present, and he did speak.

Mr. DODGE. Did he take part in the voting on the questions before the panel on that day?

Dr. KENNEDY. To my knowledge, yes.

Votes were not recorded by individuals, but I presume he voted.

Mr. DODGE. How did the vote come out on the particular question of the use of tetracycline in animal feed that day?

Dr. KENNEDY. The vote was to reject the subcommittee's recommendation.

Mr. DODGE. That was to the effect that tetracycline's use in animal feed should not be restricted in the way that the subcommittee had recommended.

Dr. KENNEDY. That is right.

Mr. DODGE. And it is true, is it not, that Mr. Farr seconded the motion which led to the overturn of the subcommittee's recommendation?

Dr. KENNEDY. I believe that is true.

Mr. DODGE. Who is Mr. Farr? Let me put it another way. When he is not serving as a member of this advisory panel, what is his occupation? Where is he employed?

Dr. KENNEDY. Well, "employed" may not be exactly the right word for it, Mr. Dodge. He is a citizen, as I understand, of Greeley, Colo.; and he has a controlling interest in Farr Farms, which is a cattle feedlot.

Mr. DODGE. He is the president, is he not, of Farr Farms?

Dr. KENNEDY. Yes.

Mr. DODGE. It is one of the largest feedlot operations in the State?

Dr. KENNEDY. I do not know how it ranks, but I am told it is a big spread.

Mr. DODGE. He uses tetracycline extensively in his operation; does he not?

Dr. KENNEDY. I have no idea.

It would be surprising if he did not, Mr. Dodge; but I do not know.

Mr. DODGE. Is it your understanding that his operations might be affected one way or another if he were no longer permitted to use tetracycline and other antibiotics in his animal feed?

Dr. KENNEDY. Yes.

Mr. DODGE. His animals might get sicker, or they might not grow as rapidly?

Dr. KENNEDY. Well, our feeling is that it is likely that Mr. Farr and others will have substitutes that will prevent them from having their animals get sicker. But I think it is quite possible that there may be or that Mr. Farr may have perceived that there would be a negative impact on his operation from that decision; that is correct.

Mr. DODGE. The General Accounting Office—as I am sure you are aware, after reviewing all these facts, as stated in a GAO report which is available to you and as GAO stated in testimony before this subcommittee on Monday—found Mr. Farr's participation in those mat-

ters before that panel on that day to be personal, to be substantial, found the matter under discussion to be a particular matter, and found that the result of the proceeding would bear on his financial interest. On that basis, the GAO found that this action met all of the requirements of 18 U.S.C. 208 for the identification of a conflict of interest. They raised the matter with you, suggesting that a question of conflict of interest is presented.

You apparently disagree that such a conflict is presented. I wonder why.

Dr. KENNEDY. Well, I disagreed because I am not prepared as yet to make an evaluation of whether I agree with the GAO about the particular matter part of the question.

I think I should say——

Mr. DODGE. In what respect is the matter that the panel was addressing that day not a particular matter? Was it not a regulatory decision of some import before the agency?

Dr. KENNEDY. Yes.

Mr. DODGE. Have you read the language of 18 U.S.C. 208, which does throw some light on the question of what a particular matter is?

Dr. KENNEDY. Yes; I could not quote it back to you, but I have read it.

Mr. DODGE. Let me refresh your recollection. It describes the types of involvement of employees with which it is concerned as "decisions, approval, disapproval, recommendation, rendering of advice," and so forth, "or other particular matters."

Mr. Moss. I am going to have to vote. I will be back in 10 minutes. We will suspend.

[Brief recess.]

Mr. Moss. The hearing will resume.

Mr. Dodge?

Mr. DODGE. Thank you, Mr. Chairman.

Commissioner Kennedy, we reached a point where I had, I think, just finished asking you for your views on whether or not the matter before the panel at that time was a "particular matter" under 18 U.S.C. 208.

Dr. KENNEDY. I find that as difficult to decide as our chief counsel did. I think it is a complicated subject.

I am not prepared to say that it is or that it is not. I think there is a very difficult interpretation.

Mr. DODGE. If your mind is now open on the question at this point, it puzzles me slightly because the posture of FDA in response to the GAO report and in response to this subcommittee in the past has been a fighting posture. There has been an effort to defend FDA's desicions on conflicts, which tread the edge of the line of acceptability or of an appropriate interpretation, it seems to me, of section 208.

If your mind is open, it would seem to me that you would want to take an opportunity to strike out on the side of the public interest rather than allow the continuing possibility of the possible invasion of private interests into the decisionmaking process of FDA.

Dr. KENNEDY. Mr. Dodge, I never lose an opportunity to strike out in the public interest.

I think the question here is whether the public interest is best served by taking the narrowest possible view of "particular matter" and

thereby depriving FDA and other Government agencies of the service of many scientists and others from universities and from elsewhere outside the Government on these matters.

Let me just say, however, that I do have an open mind on the subject. We have initiated inquiries about this particular question with the Civil Service Commission. We have had extended discussions about it since I joined the agency. We have recently written a letter of inquiry to the Department of Justice asking them to help us clarify it.

I am determined not to put our advisors or our agency in the position where we are taking the advice of people on matters in which there is even an appearance of conflict of interest. But I have to balance that, as I said in this committee's previous hearings, against our need to get the best scientists.

Mr. Moss. Where is that stated in the law that that is to be a balancing assignment on your part?

Dr. KENNEDY. Well, it is not, Mr. Chairman.

Mr. Moss. The law states in 18 U.S.C. 208 that, "except as permitted by" and then it goes on and deals with your particular matters here—through decision, approval, disapproval, recommendation, the rendering of advice, investigation or otherwise.

Dr. KENNEDY. Mr. Chairman, it was the belief of our chief counsel—and it is my less-educated belief—that the law is indistinct on this point. That is why we have asked the Department of Justice for a clarification.

Mr. Moss. Well, I would like to ask your chief counsel—maybe we will have to arrange a meeting with him then—to show us a draft that would do what we thought we were doing back so long ago. I do not know how it could be more precise than it is.

When you take the case of Mr. Farr, it seems to me that it screams out that this is a clear conflict—not marginal. It gives me sort of a sense of outrage that, when the law is as clear as it is, it is administered in such a lackadaisical manner.

Dr. KENNEDY. Well, Mr. Chairman, I have to agree that Mr. Farr's participation in that vote is wrong. But I think our interpretation of this particular matter is not wrong because of other types of committees——

Mr. Moss. I don't know. I just know this one instance. You may recall that earlier I had another series of GAO reviews of FDA personnel, and we found some other patterns that were disturbing.

Dr. KENNEDY. I know that, Mr. Chairman.

Mr. Farr's presence on that committee I believe to have been appropriate. I think the referral of that matter to the committee was inappropriate. I think that put Mr. Farr in a position that was not of his own making and, for reasons of timing, made it impossible for him to avoid the appearance of conflict of interest.

Mr. Moss. He cast a vote knowing full well of his own interest.

Dr. KENNEDY. Well, Mr. Chairman, in Mr. Farr's defense—but not in the agency's—I just want to state that that was his very first meeting. We had not adequately informed him about the requirements of the law; nor, I think, did the people in the agency quite realize the extent to which that discussion would raise those problems. I think we made a mistake. I guarantee you that it will not be repeated. I would

just hope that the record would reflect my view that Mr. Farr was not personally at fault in any way in that matter.

Mr. Moss. Clearly this is on the record. Therefore, it does reflect the view you have just stated.

I think then the Department, in making the appointments—we have so many advisory groups and subgroups around Government—better have a policy of perhaps an orientation course for them to inform them of what seems to be so clear to most of us who have been around Government very long.

Dr. KENNEDY. Mr. Chairman, one of the things we have done is to ask that executive secretaries of advisory committees and panels read the individual member's disqualifications at the beginning of every meeting in public to make sure that everybody understands them. We are really very disturbed that this incident took place. I think I can assure you that we will not have another one as glaring as this.

Mr. Moss. I think that is a commendable precaution to be taken to prevent a reoccurrence of this.

Dr. KENNEDY. Thank you, Mr. Chairman.

Mr. DODGE. I have no further questions, Mr. Chairman.

Mr. Moss. Mr. Wunder?

Mr. WUNDER. Thank you, Mr. Chairman.

The questions I have were sent to me by Mr. Stockman. He wanted to be here but could not. He asked that I ask these questions on his behalf.

Commissioner Kennedy, have there been any deleterious effects on American consumers reported or detected in 27 years of continuous use of tetracycline in animal feed?

Dr. KENNEDY. Mr. Wunder, I think my earlier testimony dealt with that question. It is not possible to state, for any single case of antibiotic resistance in bacteria, that it owed its origin to the use of antibiotics in feeds. All we know is that possible routes of transmission exist, that they are demonstrated by convincing scientific data, and that there is, therefore, a substantial risk that this use will impact negatively on the public health.

Mr. WUNDER. Is that a potential risk, a theoretical risk, if you will?

Dr. KENNEDY. It is more than theoretical. The situation is as follows. The routes of transmission are so well proven and the linked ecology of microbes and their plasmids is so organized that that kind of transmission is virtually inevitable. All it requires is time and continued selection.

Mr. WUNDER. Have there been any documented cases in which animals have developed a clinical disease where successful treatment could not be achieved by using normal therapeutic levels? In other words, has the subtherapeutic use of antibiotics brought about——

Dr. KENNEDY. I do not know of a good instance, but I would like to ask Dr. Van Houweling for some help with this one, if I may.

Dr. VAN HOUWELING. There is one incidence that has been reported and referred to several times in our deliberations. A well-conducted study, carried out in California, showed there was a problem in diseases in animals that had been on a low level antibiotic. Other than that, I am not aware of any documented cases, but there have been allegations to this effect.

Mr. WUNDER. Is there any scientific documentation which shows that there has been an increase in drug-resistant pathogenic diseases due to the addition of subtherapeutic animal drugs?

Dr. KENNEDY. I tried to deal with that question, I guess, in my answer to an earlier one, Mr. Wunder. The fact is that, for a single instance of antibiotic-resistant pathogenesis in many, it is not possible to trace whether it was due to a historic case of overuse of antibiotics in hospital therapy or whether it was due to antibiotics in feeds.

The fact is that both routes of transmission are patent. Although we cannot label either one as the villain in a particular case, their existence, I think, makes it necessary to reduce them.

Mr. WUNDER. Which raises the question: If you cannot identify the villain, do you have any plans to look into the question of antibiotics in hospital therapy?

Dr. KENNEDY. The medical community is well aware of those difficulties. I think labeling changes for antibiotics that have been carried out partly under FDA's regulatory mandate have had a considerable effect in the reduction of overprescribing.

But the fact of the matter is that our law does not allow us to reach the process of prescribing. The old saying is that FDA regulates drugs but not doctors. Prescription is not a matter which FDA is allowed to interfere with.

So, we can use the power of recommendation, and we have done so extensively. We think the problem is getting better; but we cannot, at a single stroke, eliminate it.

Mr. WUNDER. Thank you, Mr. Chairman.

Mr. MOSS. Are there further questions?

Gentlemen, I want to thank you for your appearance this morning.

We will be sending material to you for response. Mr. Wunder will be sending some questions for the minority. We ask that they be responded to promptly in order that they may be included in the record. A reservation for the purpose of receiving them is made in the record at this point.

[Testimony resumes on p. 185.]

[The following material was received for the record:]

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JAMES NELLIGAN
OPERATIONS DIRECTOR

J. THOMAS GREENE
COUNSEL TO THE CHAIRMAN

October 6, 1977

Honorable Donald Kennedy
Commissioner
Food and Drug Administration
Rockville, Maryland 20854

Dear Commissioner Kennedy:

The Subcommittee on Oversight and Investigations appreciates receiving the testimony which you presented to the Subcommittee on September 23, 1977, at hearings concerning the use of antibiotics in animal feeds. At that time, it was requested that the Administration provide supplemental information to the Committee in order that we might complete the hearing record. The transcript of the hearing reflects that the record is being held to receive the following information:

1. Transcript at page 21 - a legal memorandum prepared by the Office of the General Counsel of the Food and Drug Administration (FDA) detailing the legal basis upon which you base your statement that you cannot comment before a Congressional Committee on substantive matters subsequent to and concerning the issuance of a Notice Of Opportunity For Hearing.

2. Transcript at page 44 - a detailed description of the action taken by the Administration regarding ASP 250 in response to the exchange of letters between Dr. Richard P. Lehman and Dr. John V. Bennett dated May 10 and May 25, 1971 (copies enclosed), as well as the basis upon which FDA acted or failed to act.

In addition, reservation was made in the record for further questions from the Minority Members of the Subcommittee. The following questions have been submitted by Congressmen James Collins and Dave Stockman:

1. Is there any scientific evidence which shows that there has been an increase in the shedding of Salmonella or other bacteria from animals which have been maintained for long periods of time on feeds containing subtherapeutic levels of antibacterial drugs?

2. Are drug-resistant bacterial strains more or less physically fit than non-resistant strains for survival under naturally occurring environmental conditions?

3. The Antibiotics in Animal Feeds Subcommittee (AAFS) concluded on Page 6 of their report to the National Advisory Food and Drug Committee (NAFDC) that "both therapeutic and subtherapeutic use of antibiotics will result in the selection of antibiotic-resistant strains of microflora in animals."

   (a) Has this situation been shown to present a health risk to either man or other animals?

   (b) Is it true that farm animals which have antibiotic-resistant strains of microflora in their gut in general grow faster, gain weight faster, require fewer vitamin supplements, and have fewer illnesses than normal untreated animals?

4. Great Britain now requires veterinary prescriptions for several antibacterial compounds listed as alternatives to tetracycline by FDA. It appears they use the same rationale for this restriction as you are using for restricting penicillin and tetracycline. What is your timetable for following suit? If you do not plan to do so, why not?

5. We understand that the use of tetracycline under prescription in Great Britain is approximately the same as their use in feeds prior to the prescription requirement. We also understand that Britain has about 2,500 veterinarians in an area the size of Oregon, whereas in the United States we have a total of 6,200 veterinarians in food animal practice to cover an area of more than 3.5 million square miles. In the U. S. we apparently have one veterinarian for each 645,000 food animals, compared to one physician for each 740 humans. If the American experience should parallel the British, that is, increased animal disease requires veterinarians prescribing the same quantities of tetracyclines as were used in feed to prevent disease, can

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one veterinarian prescribe adequately, on a professional basis, for 645,000 animals? If not, how many additional veterinarians will be needed, and what plans are being made for providing them? Given a realistic projection for the effective date of your proposed restrictions, how many veterinarians will be available at that time?

6. At the hearings on September 23, you testified that the FDA may place the antibiotic products on prescription status before the hearing procedures are over by using informal rulemaking procedures. Would you please specify the exact procedures that you will be following, including the statutory authority for them? Additionally, will these procedures involve any of the same issues in the Notices Of Opportunities For Hearings that you have and will be publishing?

7. At those same hearings, Dr. Van Houweling testified that he knew of one instance in California in which animals had developed antibiotic resistance and a clinical disease that could not be successfully treated because of that. Would you please identify the references and supply any documents supporting that statement?

8. Your Notice Of Opportunity For Hearing on Penicillin cites a number of documents which we understand are not available to the public. We are aware of the following examples:

   (a) Reference #5, Linton, A. H., et al. "The Colonization of the Human Gut by Antibiotic Resistant E. coli from Chickens." This is found on page 43779. Rollins, L. D. FDA Project 108 found on page 43783.

   (b) Reference #17, Linton, A. H., et al. "Antibiotic Resistant and Sensitive E. coli. O-serotypes in the Gut and on the Carcass by Commercially Slaughtered Broiler Chickens and the Potential Public Health Implications." Found on page 43777.

   Will you make these documents available for use by the public in the hearing procedure and in requesting a hearing?

9. We understand that at least one research report has been submitted to FDA showing that feed additives listed by FDA as alternatives for tetracycline antibiotics actually increase the spreading of Salmonella organisms from infected to non-infected chickens. What are your plans to deal with this information, and what is your timetable for dealing with it?

We ask that you respond promptly to these requests in order that the hearing record may be completed. Thank you for your continued cooperation.

Sincerely,

JOHN E. MOSS
Chairman
Subcommittee on
Oversight and Investigations

JEM:pmw

Enclosures [NOT PRINTED]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

NOV 0 8 1977

Honorable John E. Moss
Chairman, Subcommittee on Oversight
and Investigations
Committee on Interstate and
Foreign Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This responds to your letter of October 6, 1977 pertaining to the Subcommittee's hearing on September 23, 1977.

Our responses are contained in the enclosures. Responses to the information requested on the first page of your letter pertaining to the separation of functions and ASP-250 issues are designated as Tabs A and B respectively. Responses to the questions beginning on page 2 of your letter are numbered correspondingly (Tab C).

We hope the enclosures are responsive to your questions.

Sincerely yours,

Donald Kennedy
Commissioner of Food and Drugs

3 Enclosures
Tab A - Separation of Function *** withdraw
approval of ANADA's
Tab B - ASP-250 issues (Chronology)
Tab C - Responses to questions 1-9

TAB A

Separation of Functions in Formal
Evidentiary Hearings of Proposals to Withdraw
Approval of New Animal Drug Applications

I.

New animal drug applications (NADA's) are private licenses granted by the Food and Drug Administration (FDA) under section 512 of the Federal Food, Drug, and Cosmetic Act to market new animal drugs after the Agency has concluded that the drugs are safe and effective for their intended uses (21 U.S.C. 360b(c)). By statute, when FDA proposes to refuse to approve a NADA (21 U.S.C. 360b(c)(2)) or proposes to withdraw approval of a previously granted application (21 U.S.C. 360b(e)(1)), the applicant or holder of the approved NADA has the right to due notice and the opportunity for a formal evidentiary hearing in accord with section 5 of the Administrative Procedure Act (APA) (5 U.S.C. 554) on the grounds for the Agency's decision. Hess & Clark, Division of Rhodia v. Food and Drug Administration, 495 F.2d 995 (D.C. Cir. 1974). But even before enactment of the APA, the Supreme Court had interpreted statutory provisions for formal administrative hearings to impose constitutional restraints on an agency's conduct. Because the agency is performing an adjudicatory function in these situations, it is subject to the fundamental requirements for fairness which are the essence of due process. However, the hearing need not be congruent with a judicial trial. Morgan v. United States, 209 U.S. 1 (1938) (Morgan II).

Thus, since the inception of expansive administrative regulation, the Supreme Court has demanded that agencies provide the parties to these hearings with basic procedural rights. Among the first recognized, and perhaps the most fundamental, are the right to know the claims advanced by the proponent of the action, the basis for those claims, and a full and fair opportunity to rebut them. Morgan II, supra. Accordingly, ex parte discussions of the issues between the government's prosecutors and an ultimate fact-finder, without a reasonable opportunity for rebuttal, are a vital defect in the adjudicatory process. Morgan II at 22.

Through the years, the courts have expanded the right to a hearing and the rights to be provided during administrative hearings, and in a recent article Judge Henry A. Friendly of the United States Court of Appeals for the Second Circuit summarized and discussed the rights and requirements applicable to such hearings. Friendly, Some Kind of Hearing, 123 U. Pa. L. Rev. 1267 (1975). In sum, they include the following:

A. An unbiased tribunal;

B. Notice of the proposed action and the grounds asserted for it;

C. An opportunity to present reasons why the action should not be taken;

D. The right to call witnesses;

E. The right to know the evidence against one;

F. The right to have the decision based only on the evidence presented;

G. Counsel;

H. Making of a record; and

I. A statement of reasons for the decision.

These rights are essentially catalogued in the APA (5 U.S.C. 551 et seq.), and FDA has codified them in its procedural regulations, 21 CFR Parts 10, 12, 13, 14, 15, and 16. Therefore, the Agency must function within this framework.

II.

Foremost among the rights is the right to an impartial tribunal. Morgan II at 22; Pillsbury Company v. FTC, 354 F.2d 952, 964 (5th Cir. 1966); Friendly, supra at 1279. For this reason the APA requires agencies to separate prosecutorial and judicial functions among their staffs for at least all formal adjudications (5 U.S.C. 554(d)). In this manner all affected parties have the right to an impartial hearing on the facts and to a decision based on the facts and policies placed on the public record, with an opportunity for scrutiny and rebuttal.

The public benefits from this separation in several ways. First, it mandates a decision on facts and policies that have been the subject of full public debate. It also limits the fact finder to the record as the basis for his decision and provides the opportunity for comprehensive judicial review. Formally separating the prosecutorial and judicial functions thus assures that the policies and factual predicate supporting the agency action are exposed to the full rigor of the adversary process. In fact, the United States Court of Appeals for the District of Columbia Circuit in a recent case perceived the benefit from such formalized procedures to be so great that it extended the proscription on ex parte contacts to an informal rulemaking procedure conducted by the Federal Communications Commission. Home Box Office, Inc. v. FCC, No. 75-1280 et al. (D.C. Cir. March 25, 1977).

III.

In licensing withdrawal procedures under FDA's procedural regulations, the separation of functions vests after the notice of opportunity for hearing is published. The Commissioner and his staff participate in the formulation of the principal issues that must be addressed in that notice and their bases. After the publication, the Office of the Commissioner

assumes the role of the ultimate fact-finder, and the FDA bureau charged with regulatory responsibility for the article in question becomes the advocate for the withdrawal. For NADA's, this is the Bureau of Veterinary Medicine. The NADA holder then has the burden of coming forward with evidence to demonstrate that material factual issues exist that require a hearing for resolution, and the Bureau of Veterinary Medicine initially evaluates this request for a hearing. (When the basis for the action is a question about the safety of food derived from food-producing animals, the Bureau of Foods has the primary responsibility for reviewing the request for a hearing.) If a hearing is justified, the Bureau drafts a notice of hearing which lists the specific issues that require resolution, and this is then sent to the Office of the Commissioner for an independent review to assure that the hearing will address all appropriate policy and fact issues.

If, after reviewing the material submitted with the request for hearing, the Bureau concludes that the NADA holder has failed to satisfy the threshold requirement of showing disputed material fact issues in dispute, the Bureau recommends to the Office of the Commissioner that the NADA's approval be withdrawn by administrative summary adjudication. In this case the Commissioner's staff again independently reviews the recommendation. If appropriate, the Commissioner will issue an order summarily adjudicating the case, see, e.g., 21 CFR 314.200(g). The Supreme Court upheld this procedure in Weinberger v. Hynson, Westcott, & Dunning, Inc., 412 U.S. 609 (1973).

Using this procedure, the Commissioner has the maximum flexibility to fulfill his mandatory dual roles as proponent and impartial fact-finder. It was particularly adept for the multitude of summary adjudication actions that FDA conducted under the Drug Efficacy Study Implementation program because it minimized judicial concern about bias and ex parte communications. However, as the DESI program is being concluded and new issues arise, the Agency has initiated administrative adjudication in other areas, areas where courts have been curtailing the availability of administrative summary judgment, e.g., Pactra Industries, Inc. v. Consumer Product Safety Com'n, Nos. 74-2902, 74-3168 (9th Cir., May 2, 1977); Hess & Clark, Division of Rhodia, Inc. v. Food and Drug Administration, supra. This has caused a reevaluation of the present system, and FDA will propose to amend its procedural regulations. The envisioned amendments will provide the Commissioner with more latitude for active participation in the process of determining the policy and factual issues that should be debated when a hearing is necessary. Any changes, of course, will be consistent with the constraints imposed by the Constitution and the courts.

TAB B

ASP-250 ISSUES (CHRONOLOGY)

The original Food Additive Petition submission for Aureo SP-250 was dated March 29, 1962. The product was approved and a regulation published in the Federal Register on July 6, 1963.

The original efficacy data for Aureo SP-250 consisted of field trials demonstrating the efficacy of the total product but they did not demonstrate the contribution of each ingredient to the effectiveness of the product. The latter was not a requirement at the time. In 1971, FDA began implementing the National Academy of Sciences/National Research Council (NAS/NRC) recommendation that each drug in a combination be shown to contribute to the effectiveness of a product. Firms were given the opportunity to provide data for their products. Thus, in a letter dated March 2, 1971, we gave American Cyanamid the opportunity to develop data to show the contribution of each ingredient to the effectiveness of ASP-250.

Concurrently with the additional requirements to implement the NAS/NRC recommendations, the Antibiotic Task Force appointed by FDA Commissioner Edwards was meeting to consider the use of nontherapeutic antibiotics in animal feed in the United States. Both Drs. Richard P. Lehmann and John V. Bennett were members of the Task Force and the correspondence dated May 10 and May 25, 1971 between them took place during that time.

The firm responded to our March 2, 1971 letter with submissions dated August 17 and November 11, 1971 and January 10, 1972, which we found inadequate. We informed them of the inadequacies by letter on June 9, 1972. The same letter also informed them of the new requirements proposed in the February 1, 1972 proposal arising from the Antibiotic Task Force recommendation. The proposal was subsequently finalized as a regulation in the Federal Register on April 20, 1973 (currently 21 CFR 558.15). This regulation established criteria, provided guidelines and established dates for data submission to determine the effectiveness of combination antibacterial drugs based upon the recommendations of the Antibiotics Task Force, in addition to the requirements for safety data.

All of the firms, including American Cyanamid, holding new animal drug applications covering the combinations of chlortetracycline, sulfonamides and penicillin were advised of the regulation on the use of these drugs in animal feed by letters issued on July 3, 1973. The firms were advised of the new requirements and the recommended types of efficacy studies that should be described and submitted in experimental protocols. Thus, all firms marketing existing approved products, including American Cyanamid, were given time in which to provide additional data because uniform action was initiated against all subtherapeutic antibacterials.

The results of the studies were evaluated and are now the subject of the actions being taken by FDA against nontherapeutic uses of penicillin and the

tetracyclines. Concurrently we are also finalizing actions against firms which have not provided us with adequate effectiveness data, including ASP-250. Additional data were recently submitted by a competitive firm which are now being evaluated before a final decision is reached on action to be taken against ASP-250 and competitive products.

October 13, 1977

Background Chronology

1. Our letter of March 2, 1971 stated "this application should be amended to establish the effectiveness of each drug ingredient for the diseases cited above or limit the claims to increased rate of gain and increased feed efficiency of swine up to 75 pounds of body weight."

2. Two memorandum of conference, both dated May 18, 1971, with representatives of American Cyanamid pointed out two specific points:

   a. With regard to disease claims, that contribution of each component to the efficacy of the drug combination, must be supported by appropriate data.

   b. This product appeared to be designed to suppress or control clinical diseases as apposed to the suppression of subclinical infection as is the case when antibiotics are administered at the so-called growth promotion levels.

3. The firm letter of June 10, 1971 stated that they proposed to revise the labeling in a manner that would more accurately describe the actions of their drug.

4. On June 18, 1971 our letter informed the firm that "The purpose of this letter is to notify you that such revised labels should be submitted to the Agency within thirty days. In the absence of the above requested information, we would consider recommending action as provided for under Section 512(e)(1) of the Act in regard to your new drug application, and the uses presently provided for."

5. July 13, 1971 we met with representatives of the firm and we responded to their proposed label revision by stating that ASP-250 does not qualify as a growth promotant.

6. A memorandum from in-house meetings show that it was concluded that no legal action based on the June 18, 1971 letter is planned until the efficacy data for disease control submitted by the firm under cover letter dated August 17, 1971, November 11, 1971 and January 10, 1972 has been reviewed.

7. Our letter of June 9, 1972 to the firm comments on the 33 exhibits submitted on dates under item 6, designed to show the effectiveness of ASP-250.

   "We have reviewed the data and have concluded that the application is incomplete. Our previous correspondence and conferences with you have consistantly pointed out the need for controlled studies to demonstrate that ASP 250 is more effective than when each ingredient is administered at its therapeutic level. A review of the data submitted does not provide this information.

The antibiotic task force in their report under "Antibiotic Effectiveness" has recommended guidelines for drug combinations. Generally, when two or more drugs are combined, each must be shown to contribute to the total effect of the product by appropriate statistical design and scientific methodology.

Additional information or data concerning the effectiveness and safety to animals for this product should be submitted in accordance with the criteria for combination drugs once the criteria have been established to implement the Task Force Report."

8. Rachelle Laboratories had a regulatory action against them because Chlorachel-250 was seized which is comparable product to ASP-250 and they did not hold an approved NADA. Rachelle responded by submitting an abbreviated NADA, which was refused for filing; however, we were instructed to review the application. On December 20, 1972 we were instructed to review all of the data contained in NADAs 35-688 and Rachelle 91-688 as requested by General Council's memo of December 12, 1972.

9. In an in House meeting on February 8, 1973 it was determined that a regulation should be drafted to limit ASP-250 to swine up to 75 pounds body weight. This was based on a discussion of all the pertinent data in NADA 35-688 file plus General Councils comments in their February 8, 1973 memo on interpratation of 21 CFR section 135.4a (Now 514.1)(b)(8)(v) regarding combination drugs. Following is a draft of the claims proposed:

   a. Increased rate of daily weight gains and improved feed efficiency. (these claims being supported by data to show that each drug contributes)

   b. Reduction of the incidence of porcine streptococcus (Group E) lymphadehtis (Jowl abscesses), has been shown to occur in swine fed 50 grams per ton of chlortetracycline hydrochloride.

   c. Maintenance of weight gains in the presence of atrophic rhinitis has been shown to occur in swine given 100 grams per ton of sulfamethazine.

10. The proposed regulation was returned with a memo from General Council office dated May 29, 1973 commenting on the February 12, 1973 effectiveness of drug combination. The Federal Regulation did not publish.

11. All firms marketing the combination drug received a letter as to the requirements on the use of antibiotics in the feed of animals. These letters were dated July 3, 1973.

12. From July 3, 1973 to the present time, efficacy data was reviewed, Federal Regulations were proposed to withdraw the products based on efficacy. This has not been done.

13. Running parallel to the efficacy review was the human and animal health safety requirements to comply with 21 CFR section 558.15. The Antibiotic Task Force has recommended the removal of penicillin from feed premixes. This recommendation has been published in the Federal Register on the proposal to have the subtherapeutic use of penicillin in animal feeds removed.

Paul F. Reichert, D.V.M.
Veterinary Medical Officer

TAB C

RESPONSE TO QUESTIONS IN OCTOBER 6 LETTER

Question #1

Is there any scientific evidence which shows that there has been an increase in the shedding of Salmonella or other bacteria from animals which have been maintained for long periods of time on feeds containing subtherapeutic levels of antibacterial drugs?

Answer

There is indeed scientific evidence to show that there is an increase in the shedding of Salmonella from animals which have been maintained for long periods of time on feeds containing subtherapeutic levels of antibacterial drugs. The evidence comes from both epidemiological studies and controlled experimental investigations.

Epidemiological surveys have documented a steady and continued increase in the proportion of Salmonella which are resistant to antibiotics (Neu et al., 1975, Ryder et al., 1977, Manten et al., 1971). A recent survey (Gustafson et al., 1976), sponsored by the Animal Health Institute, suggests an interesting correlation between a high incidence of salmonellosis in swine and a high level of antibiotic resistance in the Salmonella isolated from the swine. In this survey, 54 of 151 hogs sampled in Pennsylvania were infected with Salmonella (35) and 26 of 251 hogs sampled in Iowa were infected (10). However, in Georgia, 215 of 256 hogs sampled were infected with Salmonella (84) and the percentage of drug resistance in the Salmonella was 36 percent compared to only 5 percent in Iowa and none in Pennsylvania.

An increase in the number of Salmonella shed by animals and in the duration of the shedding encourages the spread of disease. A number of studies have demonstrated that feeding of antibiotics, at subtherapeutic levels for prolonged periods, increases the duration and amount of shedding. From what is currently understood of the mechanism by which this occurs, it is to be expected that, when the infecting bacterial strain is antibiotic resistant, shedding is likely to be prolonged and, when the infecting strain is sensitive to the antibiotic fed, shedding is less likely to be prolonged. The emergence of resistant strains, however, is encouraged by the selective pressure of low-level antibiotic use and can develop in previously

antibiotic sensitive populations by transfer of R-plasmids between bacteria. (R-plasmids or R-factors are transferable extrachromosomal genetic elements which determine drug resistance.) The probability of transfer occurring depends upon the level of R-plasmids in the normal enteric flora, the ease with which the particular strains donate and receive R-plasmids, and a number of other variables.

For example, in one FDA-sponsored study (Williams et al., 1976), chlortetracycline at 100 g/ton was fed to swine. When a tetracycline-sensitive Salmonella typhimurium strain was used to infect the swine, there was little or no difference between medicated and nonmedicated swine in the shedding of Salmonella with respect to quantity, duration, or prevalence of bacteria shed. This particular S. typhimurium (DVR 80, 289-1) strain is generally a poor acceptor of swine E. coli R-plasmids. However, when a tetracycline-resistant Salmonella strain was used to infect the swine, Salmonella shedding persisted longer, was more prevalent, and occurred in higher quantities in swine medicated with tetracyclines compared to nonmedicated swine.

In another FDA-sponsored contract at the University of Missouri, studies were conducted to test the influence of the continuous feeding of chlortetracycline on the fecal shedding of S. typhimurium in experimentally infected calves. Feeding chlortetracycline, at 50 and 100 g/ton of feed, resulted in a significantly higher quantity and duration of shedding than occurred in controls not receiving antibiotic. At the higher antibiotic level one calf died of salmonellosis and one excreted Salmonella for six months.

A publication by Smith and Tucker (1975a) reported that chickens fed on diets containing 100 mg/ton of a nitrofuran (nitrovin) excreted larger amounts of S. typhimurium than did controls fed antibiotic-free diets. Smith and Tucker (1975b) also studied the amount of S. typhimurium excreted when chickens were fed any of several different major antibiotics.

"500 mg/kg of ampicillin, furazolidone, neomycin, polymyxin, spectinomycin or streptomycin or 100 mg/kg of trimethoprim and 500 mg/kg of sulphadiazine for 46 days reduced to a varying degree the amount of S. typhimurium and E. coli excreted, the greatest reduction in S. typhimurium being brought about by the last treatment. The effect was less obvious when the concentration of the antibiotics in the food was decreased fivefold. An important reason for the very limited effect of some of the antibiotics was the emergence of antibiotic-resistant populations of S. typhimurium and E. coli. High concentrations of antibiotic-resistant organisms also arose in the faeces of the chickens fed diets containing tetracyclines and chloramphenicol, treatments which had no apparent effect on the amount of S. typhimurium and E. coli excreted. Much of the antibiotic resistance encountered was determined by R-factors, a particular R-factor usually being found in the E. coli populations of individual chickens before it was found in their S. typhimurium populations."

Smith, an eminent British veterinarian, further states:

"The available evidence indicates that the administration of antibiotics to human naturally infected with salmonellae of the food poisoning types usually prolongs the carrier rate (Dixon, 1965; Rosenstein, 1967; Aserkoff & Bennett, 1969; Clementi, 1973). In experimentally infected chickens too, antibiotic administration either prolongs the carrier rate (Garside, Gordon & Tucker, 1969), or does not significantly abbreviate it (Olesink, Snoeyenbos & Smyser, 1973). In all these reports faecal specimens were classed as positive irrespective of the numbers of salmonella organisms they contained, Because the culture media employed permit salmonella to be isolated from faecal specimens containing only a few of these organisms per gram (Smith, 1952), many of the individuals classed as faecal excreters might have been only lightly infected. What risk such individuals pose to the community in which they live is debatable."

Other studies, (Sato and Kodamo, 1974; Bulling and Stephen, 1972; Finlayson and Barnum, 1973, Hobbs et al, 1960) some of which are discussed in detail in the FDA Task Force Report (1972) also demonstrate that the long-term feeding of subtherapeutic levels of antibiotics can lead to increased shedding of Salmonella.

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Question #2

Are drug-resistant bacterial strains more or less physically fit than non-resistant strains for survival under naturally occurring environmental conditions?

Answer

It is no longer believed that resistant strains of salmonellae are less adaptive than sensitive or wild strains as shown by Jarolmen (1971). Certainly some Salmonella strains are better R-plasmid recipients than others. Recent studies have shown that both virulent and nonvirulent strains of salmonellae can acquire resistance (Wilcock et al., 1976). Whether a Salmonella strain colonizes depends upon its ability to adhere to the animal or human gut. There are data to indicate that, when antibiotic pressure is removed, nonresistant (sensitive) organisms can regain dominance in the environment (Datta, 1969; Levy et al., 1976; and Langlois and Hays, 1976), if sufficient numbers are present. However, this cannot occur when only resistant bacteria are present in the environment.

In human medicine, evolution has indeed been overturned by the manipulation of bacteria by human beings. One example cited by Naomi Datta[1] is that more than 80 percent of hospital staphlococci are now penicillin resistant. Walton (1971) believes that the use of antibiotics in animal feeds may have contributed to this change.

[1]Naomi Datta "Evolution and Plasmid Diversity": Paper presented at the 75th Official Opening Session of the Annual Meeting of the American Society for Microbiology, New York, New York, 1975.

Only one large disease epidemic which spread to man and produced human deaths (Anderson, 1969) has been documented during the 25 years of low-level antibiotic use in animals; actually this was from high level, indiscriminate therapeutic antibiotic use in animals as well as low-level use in crowded feedlots.

However, transferable ampicillin resistance was not present in human cases of Neisseria gonorrheae or Haemophilus influenzae for 25 years despite use of antibiotics, and yet outbreaks with ampicillin-resistant organisms are occurring now with increasing frequency in these dangerous diseases. Veterinary and human medicine should indeed complement each other. In neither should there be capricious use of important therapeutic agents, such as antibiotics used for therapy in man.

Sabo and Krčméry (1974) studied Salmonella choleraesuis in swine fed tetracyclines. Earlier, they had found tetracycline-resistant salmonellae which did not transfer the tetracycline determinant; however, in 1973 2 of 23 monoresistant strains were found to be transferable. These strains transferred with a good frequency to an E. coli K_{12} recipient. The authors now feel that E. coli tetracycline plasmids can be transferred to all S. choleraesuis strains, including variants which are fully virulent and can cause epizootics of fatal enteric disease in man; this is in contrast to the earlier concept developed by Jarolmen (1971). That wild-type smooth variants are poor recipients and donors, in contrast to rough, avirulent strains.

This question was thoroughly discussed in the appendix of the FDA Task Report Force on the use of Antibiotics in Animal Feeds (1972). The following points are made (1) R-factors do infect encapsulated virulent bacteria *in vitro* and *in vivo*; (2) R-plasmids do not detectably affect the *in vitro* growth rate and/or the virulence for experimental animals (Watanabe, 1971); (3) R-plasmid-bearing bacteria have often been isolated from sites of human disease. Many examples of disease caused by encapsulated R-plasmid-bearing *Shigella* are given. Examples of R-factor-bearing *Klebsiella* causing hospital infections are common. Data indicates that R-plasmid-bearing bacterial strains are equally able to survive as sensitive bacteria under naturally occurring environmental conditions, including in the presence of sea water (Feary *et al.*, 1972).

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Question #3

The Antibiotics in Animal Feeds Subcommittee (AAFS) concluded on Page 6 of their report to the National Advisory Food and Drug Committee (NAFDC), that "both therapeutic and subtherapeutic use of antibiotics will result in the selection of antibiotic-resistant strains of microflora in animals."

a. Has this situation been shown to present a health risk to either man or other animals?

Answer

Examples have been presented above of health risks which have occurred in both man and other animals due to the subtherapeutic use of antibiotics in animal feed. In addition, one reason for the development of the 1972 FDA Task Force report was the occurrence of two incidents which pointed out how Salmonella shedding might be enhanced by resistant Salmonella.

Aserkoff and Bennett (1969) for example, presented data on the effect of antibiotic therapy on the excretion of Salmonella in feces of humans infected with acute salmonellosis. Following a large S. typhimurium epidemic, caused by eating contaminated chicken, feces of untreated patients and patients treated with tetracycline, ampicillin, and chloramphenicol were examined for Salmonella, and the antibiotic susceptibility of the S. typhimurium strains was determined. Patients generally received the recommended regimen of antibiotic therapy (one gram per day). Fecal samples from 87 patients not receiving medication and 185 patients treated with antibiotics were examined. Of the patients treated with antibiotics, 65 percent were shedding Salmonella 12 days after infection, and 27 percent were positive 31 days after infection. In the untreated patients, however, Salmonella shedding was observed in 42.5 percent at day 12 and 11.5 percent at day 31.

Therapy also favored the acquisition of antibiotic resistance by the infecting (poultry) strain, which was initially susceptible to antibiotics. Of the patients receiving antibiotics 18 excreted resistant Salmonella, while none of the 87 untreated patients excreted resistant Salmonella (P .05). The antibiotic resistance acquired in the Salmonella strain was shown to be transferable.

Anderson (1965) carefully documented the building of a reservoir of multiple antibiotic-resistant Salmonellae in an outbreak of Salmonella typhimurium phage type 29 in calves, which lasted in Britain from 1963 to 1969. Antibiotics were used both therapeutically and prophylactically in crowded feed lots. As each new antibiotic therapy was tried, a new antibiotic resistance emerged in the pathogen, so that eventually the S. typhimurium strain carried resistance to a wide range of antibiotics. In addition to disease and death in cattle, the shedding (excretion) of the multiple resistant S. typhimurium caused infections and even some deaths in humans in contact with the animals.

Weinstein (1975) states that tetracyclines have lost most of their original use in treating human disease. Effectiveness against many Gram-negative infections is not uniform, since high levels of resistant organisms have developed; similarly, staphylococcal organisms have acquired a high frequency of tetracycline resistance. Tetracycline-resistant Group A streptococci and pneumococci have also appeared (Finland, 1974).

A recent model system in humans, illustrating what might occur in animals, has been provided with the emergence of penicillin-resistant Neisseria gonorrheae after more than 20 years of sensitivity to the drug. This outbreak has been largely attributed to the long-term, low-level use of penicillin by Manilan prostitutes. In humans, also, drug-resistant organisms and disease have occurred following the long-term use of low-level tetracycline for the treatment of acne.

Tetracyclines in subtherapeutic dosages have long been used in treatment of acne in humans. Some report good results; others, however, question the value of this therapy and have shown that drug-resistant pathogens develop during treatment. Schmidt et al., (1973) investigated the effects of long-term, low-level oxytetracyline administration for acne on human bowel flora. Before initiation of the study, E. coli had been only 20 percent resistant to tetracycline. After 10 weeks on 250 mg/day, coliforms in patients became 97 percent resistant. There was a simultaneous change in streptomycin and sulfonamide resistance as well as an increase in ampicillin resistance. Tetracycline-resistant Streptococcus faecalis, Staphylococcus and other micrococci, and resistant Proteus were found with increasing frequency. Bartlett et al. (1975) also found increased tetracycline resistance in E. coli in patients medicated with tetracyclines. Möller et al. (1977) treated patients with low, oral doses of tetracyclines for 4 weeks; multiple antibiotic-resistant E. coli were isolated from more than 50 percent of patients. Some of these bacteria contained as many as 6 antibiotic-resistances (Tet-Su-Sm-Cm-Km-Amp). Had these individuals become infected with a sensitive pathogen able to act as a recipient for the E. coli R-plasmids, there might have been a great risk to the humans involved.

b. Is it true that farm animals which have antibiotic-resistant strains of microflora in their gut in general grow faster, gain weight faster, require fewer vitamin supplements, and have fewer illnesses than normal untreated animals?

Answer

This statement cannot be substantiated from any data presented by the Bureau of Veterinary Medicine by firms or in the scientific literature.

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Question #4

Great Britian now requires veterinary prescriptions for several antibacterial compounds listed as alternatives to tetracycline by FDA. It appears they use the same rationale for this restriction as you are using for restricting penicillin and tetracycline. What is your timetable for following suit? If you do not plan to do so, why not?

Answer

It is true that a few of the drugs that appear on Great Britain's prescription list also appear on our list of alternatives to the tetracylines. These drugs have been subjected to the same set of human and animal safety criteria by the Agency as the tetracyclines and penicillin. In our evaluation of these drugs, it is clear that risks involved in these are less as compared to the tetracyclines and penicillin use. In addition, from the very beginning, in the recommendations of the Antibiotics Task Force of 1972, several drugs were designated as priority drugs. It was with this basis and with the data available from the published literature, from drug industry research, and from FDA's own research, that the Agency designated the tetracyclines and penicillin for early restriction. Phase II of the program is continuing. The drugs remaining available to the animal producer will remain under continuing surveillance. If new information arises that show that the questions involving the safety of these drugs are sufficient to propose restrictions, the Agency will immediately take steps to do so.

We do not find it unusual that individual scientists and individual nations interpret benefits and risks and regulatory needs differently. For example, the Canadian Government has announced a policy which will allow for an indepth look at the efficacy of drugs used in feeds, but have elected not to severely restrict any feed-use drug at this time. At the same time, the Japanese Government is restricting the use of certain antibiotics (e.g., the tetracyclines) by allowing their use in only the very young animal. The philosophy there is that the greatest need is early in the animal's life and secondly that such use will allow for an extended drug withdrawal period to slaughter.

It should also be pointed out that a number of drugs on our alternatives list are under active review in the European Economic Community. Final decisions on these have not been made. When these decisions are made, British regulations may change depending on the final outcome. Again the FDA will continue to monitor the actions of other nations, but certainly decisions on continued drug usage will be largely guided by situations in this country and our interpretation of benefit/risks involved.

Question #5

We understand that the use of tetracycline under prescription in Great Britain is approximately the same as their use in feeds prior to the prescription requirement. We also understand that Britain has about 2,500 veterinarians in an area the size of Oregon, whereas in the United States we have a total of 6,200 veterinarians in food animal practice to cover an area of more than 3.5 million square miles. In the U. S. we apparently have one veterinarian for each 645,000 food animals, compared to one physician for each 740 humans. If the American experience should parallel the British, that is, increased animal disease requires veterinarians prescribing the same quantities of tetracyclines as were used in feed to prevent disease, can one veterinarian prescribe adequately, on a professional basis, for 645,000 animals? If not, how many additional veterinarians will be needed, and what plans are being made for providing them? Given a realistic projection for the effective date of your proposed restrictions, how many veterinarians will be available at that time?

Answer

We have made a number of attempts to obtain information from England on the amount of tetracycline drug being used now and prior to the Swann restrictions. These attempts have been largely unsuccessful. Therefore, we cannot confirm your understanding expressed in question #5, that approximately the same amounts of tetracyclines are being used in Great Britain, now as compared to the use prior to prescription. If you have information regarding this question, we would like very much to receive it.

We assume that your data which shows one veterinarian for each 645,000 food animal in the United States includes swine, cattle, sheep, and poultry. Particularly with broiler chickens, turkevs, and laying chickens in which very large numbers of animals are ordinarily grown in very limited areas, it would not be unreasonable to expect that one veterinarian could service several million birds.

In addition, the greatest need for antibiotics used in feeds is in concentrated feedlot situations for cattle, lambs, and swine. At the present time, certain areas of the country contain the large majority of the feedlots for the various species. (e.g., Iowa raises 1/4 of the Nation's swine for slaughter. Texas, Colorado, and California account for the greatest measure of feedlot cattle.) Because of these concentrated production areas one veterinarian can service considerably more than 645,000 animals.

We anticipate that in a few isolated areas such as in the cow-calf operation of the far west and the southeastern United States that on occasion, the services of a veterinarian might entail establishment of a new kind of relationship with the animal producer and the veterinarian. The same will be true in some integrated poultry operations.

We anticipate our proposed restrictions becoming effective in late 1978. At this time with the recent increases in veterinary medicine colleges, the total number of graduates per year will be 1,690 as compared to 1,064 in 1968.

The FDA has made no plans to initiate provisions for additional veterinarians, although our impression is that no particular change will be needed to increase the present numbers beyond those expected through establishment of new schools and planned increases in class size.

Under the Federal Food, Drug, and Cosmetic Act, we do not believe that our responsibility is to provide veterinarians for particular programs. We believe that the need for placing a drug under a veterinarian's order depends on safety considerations and the inability to write adequate directions for use on the labeling. If action concerning veterinarian's order results in voids in the availability of veterinarians in certain areas, we believe that those voids will be filled by the traditional laws of supply and demand.

Question #6

At the hearings on September 23, you testified that the FDA may place the antibiotic products on prescription status before the hearing procedures are over by using informal rulemaking procedures. Would you please specify the exact procedures that you will be following, including the statutory authority for them? Additionally, will these procedures involve any of the same issues in the Notices of Opportunity for Hearings that you have and will be publishing?

Answer

The notices of opportunity for hearing (NOH's) proposing to withdraw approval of the new animal drug applications (NADA's) for the subtherapeutic uses of penicillin and the tetracyclines and the proposal to restrict the use to the order of a licensed veterinarian are legally severable actions based on separate statutory provisions and standards of review. The Director of the Bureau of Veterinary Medicine issued on NOH's pursuant to 21 U.S.C. 360b(e). Essentially, these notices propose to withdraw the licenses to market the antibiotics, and under the Administrative Procedure Act, the Federal Food, Drug, and Cosmetic Act, and the amplifying case law, the affected parties have the opportunity for a formal evidentiary hearing if they demonstrate existence of a genuine and substantial issue of a material fact that requires a hearing for resolution. The Commissioner of Food and Drugs is the ultimate fact-finder, and judicial review of his decision is based on the substantial evidence on the record standard of review (5 U.S.C. 706(2)(E)).

On the other hand, 21 U.S.C. 371(a) grants the Commissioner authority to promulgate substantive regulations for the efficient enforcement of the Act, and these regulations are subject to judicial review under the arbitrary and capricious standard (5 U.S.C. 706(2)(A)). This rulemaking authority, in conjunction with the substantive authority in sections 502(f)(1); 512(a), (b), (d), (i), and (m) of the Act, permits the Commissioner to impose controls on the distribution of new animal drugs. In the aggregate, they permit the Commissioner to restrict the distribution of new animal drugs and require affected parties to keep certain required records and reports on drugs and medicated animal feeds which will permit him to determine whether the continued use of the drugs under those circumstances is safe, effective, or otherwise appropriate.

Thus, this informal rulemaking procedure is essentially to allow public input on a policy question--controlling the disposition of subtherapeutic antibiotics by a veterinarian's order and the FD Form 1800 mechanism. It does not involve any specific fact-finding on the issues; therefore, his status as the impartial ultimate fact-finder remains in the adjudication untainted. The notice of proposed rulemaking will provide all affected parties with the opportunity

for full public participation in the policy decision through opportunity to submit written comments, objections, alternative solutions, and other issues for the Commissioner's consideration before he reaches a decision on the provisions of any regulations that he will subsequently promulgate to implement the policy. The underlying issues are the same but the procedures are legally severable. One action proposes to withdraw licenses to market; the second action proposes to establish marketing procedures.

Question #7

At those same hearings, Dr. Van Houweling testified that he knew of one instance in California in which animals had developed antibiotic resistance and a clinical disease that could not be successfully treated because of that. Would you please identify the references and supply any documents supporting that statement?

Answer

a. Dr. C. A. Hjerpe, Associate Professor of Veterinary Medicine, University of California, Davis, School of Veterinary Medicine, Department of Medicine, Davis, California 95616 - paper attached.

b. Dr. Clyde K. Smith, Professor, Microbiology, Ohio Agricultural Research and Development Center, letter of September 22, 1977, and his two reports attached.

UNIVERSITY OF CALIFORNIA, DAVIS

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SCHOOL OF VETERINARY MEDICINE
DEPARTMENT OF MEDICINE

DAVIS, CALIFORNIA 95616

November 18, 1975

Dr. Stanley Falkow
Department of Microbiology
School of Medicine
University of Washington
Seattle, Washington

Dear Dr. Falkow:

Enclosed is the data you requested concerning a serious problem with antimicrobic-resistant pasteurella pneumonia in a cattle feedlot, which was associated with medication of feed with chlortetracycline (CTC). The problem occurred in the Steve Marks Cattle Co. feedlot in Zamora, California. The feedlot is located 23 miles north of Davis. It consists of a 10,000-head capacity slatted-floor confinement facility and an additional 3,000-head of conventional, corral-type capacity for dry-weather feeding. I visit this feedlot 4 times per week in an advisory and problem-solving capacity, accompanied by 3rd and 4th year veterinary medical students. We attempt to necropsy all animals that die, but 15 to 25% must be skipped for various reasons which include advanced autolysis, time limitations, vacations and holidays. Cases in which pneumonia has contributed to death are identified, and pneumonic tissues are submitted for bacteriologic examination. Any pasteurellas which are isolated are tested for antimicrobic sensitivity by the method of Kirby and Bauer. Results are then considered together with the history of antimicrobic therapy, in order to identify (and hopefully minimize) the causes of treatment failure.

Construction was completed and the feedlot occupied on 1/22/72. Veterinary medical service to the feedlot was initiated on 2/1/72. Initially, the most serious health problem was primary bacterial pneumonia, which accounted for 42.5% of all deaths during the 1st 19 months of operation (Table 1). Many additional animals were necropsied in which secondary bacterial pneumonia was a significant complication. A total of 500 pneumonic lungs were submitted for microbiologic examination during this 19-month period. Pasteurella hemolytica and P. multocida were the predominant bacterial organisms isolated (Table 2). Mycoplasmas were also isolated from a large proportion of these cases (Table 2). The significance of these mycoplasmas is unknown, although I do not presently consider them to be pathogenic. My strongest arguments for this position are that: (1) most cases of pneumonia in this feedlot respond well to treatment with sulfamethazine or procaine penicillin G, which are not inhibitory for mycoplasmas; (2) I was unable

to produce a clinical disease in 10 calves which were experimentally inoculated with large numbers of M. agalactiae var. bovis by the intrabronchial route. M. agalactiae var. bovis was the most frequently identified mycoplasma in a series of 25 pneumonia cases from the feedlot, in which mycoplasma isolates were typed using a fluorescent antibody technique (Table 3).

During the 1st 11 months of operation, no antibiotics were included in feedlot rations. Beginning on 12/27/72, CTC was added to the starting ration so as to provide a daily intake of approximately 1.25 mg./lb. of body weight during the 1st 21 days after arrival in the feedlot. This was accomplished by mixing 500 mg. of CTC*/10 lb. (100 Gm./ton) of starting ration. This program was initiated in hopes of reducing excessive morbidity, mortality and treatment expense, which resulted mainly from a high incidence of bacterial pneumonia. Several authors have reported reductions in morbidity from respiratory disease in feeder cattle of approximately 50% with similar programs.[1-5] Additional benefits reported included improvements in rate of gain and feed efficiency of up to 20% during the period of feed medication.[1-3] Initial results of CTC feed medication in this feedlot appeared favorable, based on apparent reductions in sick pen populations. Within a month, however, we had begun to observe increased numbers of pneumonic cattle which did not respond satisfactorily to treatment with standard antimicrobics (oxytetracycline, sulfamethazine and procaine penicillin G). This refractoriness was consistent with the results of antimicrobic sensitivity testing of pasteurellas isolated from pneumonic lesions (Tables 4, 5 and 6). Feeding of CTC was terminated on 3/7/73, after 5,258 cattle had been medicated. Pasteurellas isolate during the period of feed medication from pneumonic lungs were resistant to significantly more antimicrobics than were those isolated prior to initiation of CTC feed medication (Table 7). Increased antimicrobic resistance was also observed during the period of feed medication in non-medicated cattle which had been received prior to 12/27/72 (Table 7). The problem of antimicrobic-resistant pasteurella pneumonia persisted in the feedlot in groups of cattle received through 1/31/ (Table 8). Thereafter, inshipments of new cattle were drastically curtailed for 3 months. When buying was resumed in May of 1974, the feedlot population had dwindled to 5,294 head on feed. Curtailment of inshipments was fortuitously successful in breaking the infection cycle of salmonellosis (Table 9) as well as that of antimicrobic-resistant pasteurellosis (Table 8). The problem of multiple antimicrobic resistance, as experienced from 12/27/72 to 1/31/74, has not recurred to date, although tetracycline resistance continues to be a nagging problem (Table 10

During the 13-month period when antimicrobic-resistant pneumonia was a serious problem, mortality associated with primary and secondary bacterial pneumonias was increased, both in yearling cattle (Table 11) and in calves (Table 12). Half-way through the period of antimicrobic resistance, a new treatment system was designed and implemented, in an effort to reduce mortality from antimicrobic-resistant bacterial infections. This system was described in the Proceedings of the 11th Annual Oklahoma Cattle Feeders Seminar, Stillwater, February 1975 (Attachment 1). In brief, a daily rectal temperature record is maintained on each sick animal, and used by feedlot personnel in attempting to determine if an animal is responding to a particular antimicrobic. When a response is lacking, another antimicrobi is substituted and the response again evaluated. This process continues until the

animal recovers or dies.

The economic loss to the feedlot from antimicrobic-resistant pasteurella pneumonia was estimated to be $206,000 (Table 13). This value was calculated from the increased mortality rates, culling rates and medicine costs which were associated with the period of antimicrobic resistance (Tables 14 - 16). It does not include allowances for reduced feed efficiency, increased yardage and interest charges, increased labor costs and other increased costs that were undoubtedly associated with the problem. Periods when different treatment systems were utiliz were analyzed separately. Increases in overall mortality during the period of antimicrobic resistance could be largely attributed to increases in mortality from primary and secondary bacterial pneumonias (Table 17).

A slight increase in antimicrobic resistance was detected in the pasteurella population isolated from 12/1/72 to 12/26/72, just prior to initiation of feed medication. This trend appeared to be greatly magnified by the CTC feed medication program (Tables 18 - 20). Increased resistance to penicillin G, erythromycin, neomycin, tetracycline, sulfathiazole, gentamicin, cephalothin and ampicillin was observed in the P. hemolytica population. Sensitivity to chloramphenicol and polymyxin B was not affected (Table 21). Similar findings were noted in the P. multoci population, except that resistance to neomycin was not significantly increased, and a small but significant increase in polymyxin B resistance was observed (Table 22).

Additional background information is provided in figure 1 and Tables 23 and 24. Concentrations of oxytetracycline in serum resulting from administration in several dosages and by intramuscular, subcutaneous and intravenous injection are shown together with minimum inhibitory concentrations of oxytetracycline for P. hemolytica and P. multocida (Fig. 1). Oxytetracycline is usually administered by intramuscular or subcutaneous injection in a dose of 5 mg./lb. of body weight for treatment of pneumonia in cattle. Concentrations of chlortetracycline and oxytetracycline in serum resulting from continuous oral administration in feed are presented for comparison (Tables 23 and 24).

If you have need of any further information concerning this matter, please feel free to contact me.

Sincerely,

C. A. Hjerpe, D.V.M.
Associate Professor of
Veterinary Medicine

CAH:mw

Enclosures

References:

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TABLE 1 - Death Loss (1/22/72 - 8/31/73)

Diagnosis	No. of cases	% of total*
Primary bacterial pneumonias	378	42.5
Interstitial pneumonia	76	8.5
BVD	68	7.6
Salmonellosis	68	7.6
Bloat	56	6.3
IBR	29	3.3
Hemophilus TEM	22	2.5
Cellulitis	14	1.6
Paresis	13	1.5
Anaplasmosis	13	1.5
Urolithiasis	12	1.3
Polyarthritis	11	1.2
Post-castration hemorrhage	9	1.0
Empyema	9	1.0
Suppurative meningio-encephalitis	9	1.0
TRP	8	
Trauma	6	
Peritonitis	6	
Infectious myositis	5	
Myelomalacia (HPR)	5	
Septicemia	5	
Esophagitis (HPR)	4	
Suffocation	4	
Traumatic Pharyngitis	4	
Abomasal ulcer	3	
Cast	3	
Necrotic laryngitis	3	
Castration infection	2	
Drug reaction	2	
Fatal hemorrhage	2	
Mycotic ruminitis	2	
O-P toxicity	2	
Portal vein occlusion	2	
Pulmonary abscesses	2	
Pyelonephritis	2	
Fracture	2	
Bladder rupture	1	
Dystocia	1	
Encephalopathy	1	
Intestinal Obstruction	1	
Intussusception	1	
Liver Abscesses	1	
Non-suppurative encephalitis	1	
Pericarditis	1	
Pharyngeal abscess	1	
Strangulation	1	
Uterine prolapse	1	
Vaginal perforation	1	
Vegetative endocarditis	1	
Verminous bronchopneumonia	1	
Undetermined	15	
Unknown (not autopsied)	170	
TOTAL	1,060	

TABLE 2- Results of Microbiological Examination of Lungs from 500 Cases of Bovine Bacterial Pneumonia

ganisms isolated	No. of isolations	Frequency of isolation (%)
coplasma	331	86.2*
steurella hemolytica	260	52.0
multocida	130	26.0
cherichia coli (non-hemolytic)	70	14.0
rynebacterium pyogenes	61	12.2
oteus spp.	22	4.4
steurella spp.	21	4.2
coli (hemolytic	15	3.0
gative (no growth)	13	2.6
lmonella newport	10	2.0
mophilus oakley	7	1.4
tinobacillus-like organisms	5	1.0
reptococcus viridans	5	1.0
pha streptococci	4	0.8
rynebacterium spp.	2	0.4
teric spp.	2	0.4
caligenes fecalis	1	0.2
avobacterium spp.	1	0.2
eudomonas aeruginosa	1	0.2
dublin	1	0.2
typhimurium	1	0.2
aphylococcus aureus	1	0.2
reptococcus fecalis	1	0.2
reptococcus fecium	1	0.2
l Pasteurellas	414	82.8

total of 331 lungs were examined for Mycoplasmas.

TABLE 3 - Results Of FA Typing Of Mycoplasmas Isolated From Lungs Of 25 Fatal Bovine Pneumonia Cases

Mycoplasmas isolated	No. Cases	Frequency (%)
M. agalactiae v. *bovis* in association with unknown Mycoplasma(s)	10	40
M. agalactiae v. *bovis* only	9	36
Unknown mycoplasma(s) only	6	24
All *M. agalactiae* v. *bovis* isolates	19	76

TABLE 4 - Antimicrobic Resistance Patterns in 29 Isolates of *P. hemolytica* Recove During the Period of Prophylactic CTC Feed Medication

No. of Isolates	Antimicrobics												
	Penicillin G	Dihydrostreptomycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
7	X*	X		X	X	X	X		X	X	X		X
5	X	X		X	X	X	X		X	X			X
4	X	X		X	X	X	X		X	X	X	X	X
3	X	X		X	X	X	X		X	X		X	X
2	X	X		X	X	X			X	X			X
2	X	X				X			X	X			X
1		X		X	X				X	X			
1	X	X		X		X			X	X			X
1		X		X		X	X		X	X	X		
1	X	X		X		X			X	X		X	X
1		X		X	X	X	X		X	X	X	X	
1		X		X	X		X		X	X			

*Indicates resistance.

TABLE 5 - Antimicrobic Resistance Patterns in 13 Isolates of *P. multocida* Recovered During the Period of Prophylactic CTC Feed Medication

No. of isolates	Antimicrobics												
	Penicillin G	Dihydrostreptomycin	Chloramphanicol	Erthromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
3	X*	X		X	X	X	X		X	X	X	X	X
1	X	X		X	X	X			X	X	X		
1	X	X				X	X		X	X			
1	X	X		X	X	X	X	X	X	X	X	X	
1	X	X		X	X	X	X		X	X			X
1	X	X				X	X		X				
1	X	X		X	X		X	X	X	X	X		X
1	X	X			X	X	X		X		X		X
1	X			X		X			X	X			
1	X	X		X	X	X	X		X	X			
1		X		X	X	X	X		X	X			

*Indicates resistance.

TABLE 6 - FREQUENCY OF ISOLATION OF ANTIMICROBIC-RESISTANT PASTEURELLA BACTERIA FROM CASES OF UNCOMPLICATED* BOVINE BACTERIAL PNEUMONIA UNSUCCESSFULLY TREATED WITH VARIOUS ANTIMICROBICS

Antimicrobic used in treatment	No. of isolates	Frequency of resistance	
		No.	%
Oxytetracycline	55	52**	94.5
Sulfamethazine	50	44†	88.0
Penicillin	43	34	79.1
Erythromycin	30	24	80.0

*No other complicating pathology present and no bacteria other than E. coli or streptococci isolated from the pneumonic lung.
**Isolates tested against tetracycline.
†Isolates tested against sulfathiazole.

TABLE 7 - Antimicrobic Resistance of Pasteurella hemolytica and P. multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program

CTC medication Status	Time of Death	Antimicrobic resistance* P. hemolytica	P. multocida
Not medicated	Feb. 1 - Dec. 26, 1972	3.2**,a (82)+	3.4b (52)
Medicated[11]	Dec. 27, 1972 - Mar. 6, 1973	6.2a (29)	6.0b (13)
Not medicated[c]	Dec. 27, 1972 - Mar. 6, 1973	5.3 (4)	6.0 (5)

How many isolates resisted

*Antimicrobics tested were penicillin G, dihydrostreptomycin, chloramphenicol, neomycin, tetracycline, polymyxin B, sulfathiazole, gentamicin, cephalothin, and ampicillin. **The mean no. of antimicrobics to which the isolates were resistant. +No. of isolates tested. [11]From Dec. 27, 1972 to Mar. 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb) for the first 21 days after arrival. a,bValues having the same superscript are significantly different ($P < 0.001$). [c]These cattle were received prior to initiating prophylactic CTC medication.

TABLE 6 - Mortality from Antimicrobic Resistant Pasteurella Pneumonia in Feedlot Cattle: Influence of a Prophylactic Chlortetracycline Feed Medication** Program.

Time period	Relationship to CTC feeding program	No. of cattle received	Mortality	
			Resistant P. hemolytica isolated	Resistant P. multocida isolated
2-15-72 to 12-26-72	Before	15,468	7† (0.045)[11]	11 (0.071)
12-26-72 to 3-6-73	During	5,258	38 (0.723)[a]	11 (0.209)[b]
3-7-73 to 3-31-73	After	1,360	1 (0.074)	2 (0.147)
April 1973	"	1,399	17 (1.215)[a]	1 (0.071)
May 1973	"	2,345	6 (0.256)[a]	0 (0.000)
June 1973	"	4,426	25 (0.565)[a]	7 (0.158)
July 1973	"	1,122	7 (0.624)[a]	1 (0.089)
August 1973	"	680	2 (0.294)[b]	2 (0.294)[c]
September 1973	"	733	0 (0.000)	0 (0.000)
October 1973	"	1,174	8 (0.681)[a]	1 (0.085)
November 1973	"	1,172	1 (0.085)	3 (0.256)[c]
December 1973	"	1,578	5 (0.317)[a]	5 (0.317)[b]
January 1974	"	1,617	6 (0.371)[a]	4 (0.247)[c]
February 1974	"	467	0 (0.000)	0 (0.000)
March 1974	"	28	0 (0.000)	0 (0.000)
April 1974	"	25	0 (0.000)	0 (0.000)
May 1974	"	5,817	0 (0.000)	0 (0.000)
June 1974	"	1,484	0 (0.000)	0 (0.000)
July 1974	"	3,569	3 (0.084)	0 (0.000)
August 1974	"	525	0 (0.000)	0 (0.000)

* Resistant to tetracycline, sulfathiazole and penicillin G. ** From Dec.27, 1972 to March 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.) for the first 21 days after arrival.

† Number of deaths[11] Mortality (%)[a,b,c] significantly greater than ...

TABLE 9 - Deaths by Month from Salmonellosis in Feedlot Cattle.

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1972	---	2	1	0	0	0	1	4	4	1	3	12
1973	7	5	6	1	1	1	3	16	3	3	6	7
1974	4	8	1	0	0	0	0	0	0	0	0	0

TABLE 10 - Antimicrobic Sensitivity Of Pasteurellae Isolated From Nasal Secretions Of Cattle With Feedlot Pneumonia*

	Date of Isolation			
	1972**		1974+	
Antimicrobic	No. tested	Sensitive (%)	No. Tested	Sensitive (%)
Tetracycline	73	97.3	97	62.9
Sulfathiazole	73	78.1	53	90.6
Penicillin G	73	63.0	94	77.7
Erythromycin	23	34.8	97	21.6

*Isolated on the first day of clinical illness, prior to initial treatment.
**Isolated between July 12, 1972 and December 5, 1972.+Isolated during July of 1974.

TABLE 11 - Mortality Associated with Bacterial Pneumonia in Yearling Feedlot Cattle: Influence of Antimicrobic Resistance in Causative Pasteurellae.

me iod	Relationship to antimicrobic resistance problem	No. yearling cattle received	Mortality associated with pneumonia: Primary pneumonias	Secondary pneumonias	All pneumonias
5-72 o 26-72	Before	8,076	28*(0.35)**	35(0.43)	63(0.78)
27-72 o 1-74	During	12,576	86(0.68)	37(0.29)	123(0.98)
-74 o 1-74	After	10,931	12(0.11)[+]	8(0.07)	20(0.18)[11]

* No. of deaths. ** Mortality (%). [+] Reduction of 69% compared with "Before".
[11] Reduction of 77% compared with "Before".

TABLE 12 - Mortality Associated with Bacterial Pneumonia in Feedlot Calves: Influence of Antimicrobic Resistance in Causative Pasteurellae

Time eriod	Relationship to antimicrobic resistance problem	No. calves received	Mortality associated with pneumonia: Primary pneumonias	Secondary pneumonias	All pneumonias
-15-72 to -26-72	Before	7,392	65*(0.88)**	29(0.39)	94(1.27)
-27-72 to 31-74	During	10,296	217(2.11)	69(0.67)	285(2.78)
1-74 to 31-74	After	711	3(0.42)[+]	2(0.28)	5(0.70)[11]

* No. of deaths. **Mortality (%). [+] Reduction of 51% compared with "Before".
[11] Reduction of 45% compared with "Before".

TABLE 13- An Estimate of the Economic Loss Resulting from Antimicrobic-Resistant Bacterial Infections in Feedlot Cattle

	Time period and treatment system utilized	No. cattle	Net loss per steer*	Total losses
Calves	No records (1-1-73 - 8-6-73)	6,009	$18.68	$112,248.12
	Individual treatment records utilized (8-7-73 - 1-31-74)	3,086	$11.54	$ 35,612.44
Yearlings	No records (1-1-73 - 8-6-73)	7,567	$ 2.17	$ 16,420.39
	Individual treatment records utilized (8-7-73 - 1-31-74)	3,542	$11.96	$ 42,362.32
Totals		20,204		$206,643.27

*From Table 15

TABLE 14- Animal Health Data Used in Calculating The Economic Loss from Antimicrobic Resistant Bacterial Infections in Yearling Cattle

Antimicrobic resistance problems	Treatment system used	Mortality	Culling rate	Medicine cost
Occasional problems (2/17 -12/31/72)*	No individual records (2/17/72 - 8/6/73)*	198/10,282 (1.93)**	372/10,265 (3.62)**	$5.03 (9,161)+
Serious problems (1/1/73 - 1/31-74)*		134/7,567 (1.77)	487/7,567 (6.44)	$4.05 (7,397)
	Individual treatment record system utilized (8/7/73-4/30/75)*	79/3,542 (2.23)	255/3,542 (7.20)	$7.03 (3,476)
Occasional problems (2/1/74 - 4/30/75)*		186/17,174 (1.08)	251/11,770 (2.13)	$5.40 (11,680)

*The time period during which cattle were received. **Percent. + No of cattle included in the analysis.

TABLE 15 - Animal Health Data Used In Calculating the Economic Loss from Antimicrobic Resistant Bacterial Infections in Calves

Antimicrobic resistance problems	Treatment system used	Mortality	Culling rate	Medicine cost
Occasional problems (2/17 - 12/31/72) *	No individual records (2/17/72 - 8/6/73)*	335/8,801 (3.81)**	249/8,801 (2.83)**	$ 6.51 (8,500)+
Severe problems (1/1/73 - 1/31-74)*		354/6,009 (5.89)	799/6,009 (13.30)	$ 7.95 (6,009)
	Individual treatment record system utilized (8/7/73 - 4/30/75)*	125/3,086 (4.05)	222/3,086 (7.19)	$11.83 (3,086)
Occasional problems (2/1/74 - 4/30/75)*		13/708 (1.84)	38/708 (5.37)	$ 5.81 (706)

*The time period during which cattle were received. **Percent. +No. of cattle included in the analysis.

TABLE 16- An Analysis of the Influence of Antimicrobic - Resistant Bacterial Infections on Mortality, Culling Rate, and Medicine Cost in Feedlot Cattle

	Time period and treatment system utilized	Change in mortality	Net loss per steer (mortality)	Change in culling rate	Net loss per steer (culling)	Net loss per steer (medicine)	Total net loss per steer
ɜs	No records (1/1/73 - 8/6/73)	+2.08%*	+$5.72**	+10.47%*	+$11.52**,+	+$1.44*	+$18.68
	Individual treatment records utilized (8/7/73 - 1/31/74)	+2.21%[a]	+$6.08**	+ 1.82%[a]	+$ 2.00**,+	+$3.46[a]	+11.54
lngs	No records (1/1/73 - 8/6/73)	-0.16%*	-$0.52[b]	+ 2.82%*	+$ 3.67[b,+]	-$0.98*	+$ 2.17
	Individual treatment records utilized (8/7/73 - 1/31/74)	+1.15%[a]	+$3.74[b]	+ 5.07%[a]	+$ 6.59[b,+]	+$1.63[a]	+$11.96

*Based on comparison with the baseline period of 2/17/72 - 12/31/72 (Tables 13 and 14). ** Based on a $275 feeder steer + Based on an estimated 40% loss in value when a cull steer is sold at auction or consigned. [a] Based on comparison the baseline period of 2/1/74 - 4/30/75 (Tables 13 and 14. [b] Based on a $325 yearling feeder steer.

TABLE 17 - Comparison Of Changes In Overall Mortality With Changes In Mortality From Primary And Secondary Bacterial Pneumonias, As Influenced By Antimicrobic Resistance In Pasteurella Bacteria

	Yearlings		Calves	
Relationship to Antimicrobic Resistance Problem	Overall Mortality (%)	Mortality From Bacterial Pneumonia (%)	Overall Mortality (%)	Mortality From Bacteria Pneumonia (%)
During	1.92	0.98	5.27	2.78
Before	1.93	0.78	3.81	1.27
Changes	-0.01	+0.20	+1.46	+1.51
During	1.92	0.98	5.27	2.78
After	1.08	0.18	1.84	0.70
Changes	+0.84	+0.80	+3.43	+2.08

TABLE 18 - Antimicrobic Resistance of Pasteurella hemolytica and P. multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program

Time of death	Antimicrobic resistance*	
	P. hemolytica	P. multocida
Feb 1972	...(0)	...(0)
Mar.	6.0**(1)+	...(0)
Apr.	3.8 (4)	...(0)
May	4.0 (1)	1.3 (3)
June	3.3 (3)	1.0 (1)
July	2.7 (25)	...(0)
Aug.	3.3 (7)	4.2 (6)
Sep.	4.3 (4)	...(0)
Oct.	2.6 (17)	2.8 (10)
Nov.	3.3 (8)	3.2 (17)
Dec. 1-26	4.3[b](12)	4.1 (15)
Dec. 27-Jan. 31, 1973"	5.8 (10)	6.4 (10)
Feb. 1-Mar. 6"	6.2 (23)	5.5 (8)
Mar. 7-31	5.9[a](13)	5.5 (6)c
Apr.	6.0 (1)	2.5 (2)
May	4.7[a](18)	2.5 (4)
June	5.2[a](24)	1.7 (7)
July	4.1[b](36)	5.4[d](5)
Aug	4.3[a](26)	3.6 (19)

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Time of death	P. hemolytica	P. multocida
Sep.	5.0 (2)	3.7 (7)
Oct.	4.7 (3)	2.8 (4)
Nov.	5.1[a] (14)	3.5 (4)
Dec.	5.0[b] (7)	3.6 (10)
Jan. 1974	...(0)	4.0 (10)
Feb.	4.6[a] (17)	3.5 (25)
Mar.	...(0)	3.0 (3)
Apr.	...(0)	...(0)
May	...(0)	...(0)
Jun.	...(0)	...(0)
Jul	0.0 (1)	2.7 (3)
Aug.	3.0 (1)	2.8 (4)

*Antimicrobics tested were penicillin G, dihydrostreptomycin, chloramphenicol, neomycin, tetracycline, polymyxin B, sulfathiazole, gentamicin, cephalothin and ampicillin. **The mean no. of antimicrobics to which the isolates were resistant. +No. of isolates tested. "From Dec. 27, 1972, to Mar. 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.) for the first 21 days after arrival. Superscripts indicate that the bacterial population isolated during that time period was significantly more resistant than the population isolated from Mar. 1, 1972 to Dec. 26, 1972. (a, $P=<0.001$; b, $P=<0.01$; c, $P=<0.02$; d, $P=<0.05$).

TABLE 19 - Antimicrobic Sensitivity Of Pasteurella hemolytica Isolated From Fatal Bovine Pneumonia Cases: Influence Of A Prophylactic CTC Medication Program

Time of death	Penicillin G	Dihydrostreptomycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
Mar. 1972	0.0* (1)**	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	0.0[b] (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0.0 (1)
Apr.	0.0 (5)	0.0 (5)	100.0 (5)	... (0)	0.0 (5)	100.0 (5)	... (0)	80.0 (5)	0.0 (5)	60.0 (5)	80.0 (5)	100.0 (4)	0.0 (5)
May	0.0 (1)	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	100.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0.0 (1)
Jun.	0.0 (3)	0.0 (3)	100.0 (3)	... (0)	0.0 (3)	33.3 (3)	... (0)	100.0 (3)	0.0 (3)	33.3 (3)	66.7[a] (3)	100.0 (3)	33.3 (3)
Jul.	7.7[c] (26)	3.8 (26)	100.0 (25)	... (0)	26.9 (26)	92.3 (26)	... (0)	100.0 (26)	0.0 (26)	80.8 (26)	100.0 (26)	100.0 (26)	50.0 (26)
Aug.	28.6 (7)	0.0 (7)	100.0 (7)	... (0)	0.0 (7)	85.7 (7)	... (0)	100.0 (7)	0.0 (7)	85.7 (7)	100.0 (7)	100.0 (7)	28.6 (7)
Sep.	0.0 (4)	0.0 (4)	100.0 (4)	... (0)	25.0 (4)	75.0 (4)	... (0)	75.0 (4)	0.0 (4)	75.0 (4)	75.0 (4)	100.0 (4)	0.0 (4)
Oct.	63.2 (19)	15.8 (19)	100.0 (19)	47.1 (17)	42.1 (19)	63.2 (19)	... (0)	89.5 (19)	0.0 (19)	68.4 (19)	75.0 (19)	100.0 (17)	68.4 (19)
Nov.	25.0 (8)	12.5 (8)	100.0 (8)	37.5 (8)	50.0 (8)	62.5 (8)	... (0)	100.0 (8)	0.0 (8)	37.5 (8)	100.0 (8)	100.0 (8)	50.0 (8)
Dec. 1-26	25.0 (12)	0.0 (12)	100.0 (12)	50.0 (12)	8.3 (12)	16.7[b] (12)	... (0)	91.7 (12)	0.0 (12)	58.3 (12)	83.3 (12)	91.7[c] (12)	8.3[c] (12)
Dec. 27 to Jan. 31, 1973[+]	20.0 (10)	0.0 (10)	100.0 (10)	0.0[b] (10)	0.0[d] (10)	20.0[b] (10)	40.0 (10)	90.0 (10)	0.0 (10)	20.0[b] (10)	60.0[b] (10)	70.0[b] (10)	20.0 (10)
Feb. 1 to Mar. 6[+]	4.3[b] (23)	0.0 (23)	100.0 (23)	0.0[b] (23)	8.7[d] (23)	0.0[b] (23)	15.0 (23)	100.0 (23)	0.0 (23)	0.0[b] (23)	52.2[b] (23)	47.8[b] (23)	13.0 (23)
Mar. 7-31	0.0[a] (13)	0.0 (13)	100.0 (13)	15.4 (13)	0.0[a] (13)	7.7[b] (13)	23.1 (13)	92.3 (13)	0.0 (13)	7.7[b] (13)	100.0 (13)	92.3 (13)	0.0[c] (13)
Apr.	0.0 (1)	0.0 (1)	100.0 (1)	0.0 (1)	0.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0.0 (1)
May	5.6 (18)	16.7 (18)	94.4[a] (18)	11.1[c] (18)	16.7 (18)	11.1[b] (18)	61.1 (18)	100.0 (18)	0.0 (18)	38.9[a] (18)	83.3 (18)	77.8[b] (18)	11.1 (18)
Jun.	8.0 (25)	4.0 (25)	84.0[b] (25)	24.0 (25)	28.0 (25)	12.0[b] (25)	40.0 (25)	100.0 (25)	0.0 (25)	24.0[b] (25)	92.0 (25)	87.5[c] (24)	16.0 (25)
Jul.	13.2 (38)	2.6 (38)	100.0 (37)	45.9 (37)	44.7 (38)	18.4[b] (33)	73.0 (37)	97.3 (37)	0.0 (8)	50.0 (38)	94.7 (38)	84.2[d] (38)	26.3 (38)
Aug.	7.4 (27)	3.7 (27)	100.0 (27)	40.7 (27)	33.3 (27)	0.0[b] (27)	74.1 (27)	100.0 (26)	... (0)	44.4[a] (27)	100.0 (26)	100.0 (26)	18.5 (27)

Table 1[illegible] - Page 2

Time of death	Penicillin G	Dihydrostrepto-mycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
p.	0.0 (2)	0.0 (2)	100.0 (2)	0.0 (2)	0.0 (2)	0.0[a] (2)	100.0 (2)	100.0 (2)	... (0)	50.0 (2)	100.0 (2)	100.0 (2)	0.0 (2)
t.	0.0 (3)	0.0 (3)	100.0 (3)	66.7 (3)	66.7 (3)	0.0[c] (3)	66.7 (3)	66.7 (3)	... (0)	33.3 (3)	100.0 (3)	100.0 (3)	0.0 (3)
v.	0.0[a] (14)	0.0 (14)	100.0 (14)	35.7 (14)	7.1 (14)	0.0[b] (14)	35.7 (14)	100.0 (14)	... (0)	35.7[a] (14)	100.0 (14)	92.9 (14)	14. (14
c.	0.0 (7)	0.0 (7)	100.0 (7)	14.3 (7)	14.3 (7)	28.6[a] (7)	57.1 (7)	100.0 (7)	... (0)	28.6[a] (7)	85.7 (7)	100.0 (7)	14. (7)
n. 1974	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0
b.	11.8 (17)	0.0 (17)	100.0 (17)	62.5 (16)	58.8 (17)	5.9[b] (17)	76.5 (17)	100.0 (17)	... (0)	11.8[b] (17)	94.1 (17)	76.5[b] (17)	17 (1
r.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0
r.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0
y	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0
n.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0
l.	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	... (0)	100.0 (1)	100.0 (1)	100.0 (1)	10 (1
g.	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	100.0 (1)	10 (

*Percent sensitive. ** No. of isolates tested. +From Dec. 27, 1972 to Mar. 6, 1973, all attle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb. or the first 21 days after arrival. These isolates were all obtained from medicated cattle. uperscripts indicate that the bacterial population isolated during that time period was significantly more resistant from the population isolated from Mar 1, 1972 to Dec. 26, 1972 (a, P= < 0 , P= < 0.001; c, P= < 0.02; d, P= < 0.01).

TABLE 20 - Antimicrobic Sensitivity of Pasteurella multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program

Time of death	Penicillin G	Dihydrostreptomycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamycin	Cephalothin	Ampicillin
Mar. 1972	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Apr.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
May	66.7* (3)**	33.3 (3)	100.0 (3)	... (0)	100.0 (3)	100.0 (3)	... (0)	100.0 (3)	0.0 (3)	66.7 (3)	100.0 (3)	66.7 (3)	100 (3
Jun.	100.0 (1)	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100 (1
Jul.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Aug.	83.3 (6)	0.0 (6)	100.0 (6)	... (0)	0.0 (6)	0.0[a] (6)	... (0)	100.0 (6)	0.0 (6)	0.0 (6)	83.3 (6)	100.0 (6)	100 (6
Sep.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Oct.	80.0 (10)	10.0 (10)	100.0 (10)	40.0 (10)	40.0 (10)	40.0 (10)	... (0)	80.0[b] (10)	0.0 (10)	30.0 (10)	100.0 (10)	100.0 (10)	90.0 (10
Nov.	47.1 (17)	5.9 (17)	100.0 (17)	29.4 (17)	47.1 (17)	41.2 (17)	... (0)	100.0 (17)	0.0 (17)	23.5 (17)	94.1 (17)	88.2 (17)	70.6 (17
Dec. 1-26	37.5 (16)	6.3 (16)	93.8 (16)	43.8 (16)	12.5[a] (16)	31.3 (16)	... (0)	100.0 (16)	0.0 (16)	26.7 (15)	87.5 (16)	81.3 (16)	68.8 (16
Dec. 27-Jan. 31, 1973+	10.0 (10)	0.0 (10)	100.0 (10)	10.0 (10)	20.0 (10)	0.0 (10)	14.3 (7)	70.0 (10)	0.0 (10)	0.0 (10)	30.0 (10)	40.0 (10)	70.0 (10)
Feb. 1-Mar.6+	0.0 (8)	12.5 (8)	100.0 (8)	12.5 (8)	12.5 (8)	0.0 (8)	12.5 (8)	87.5 (8)	0.0 (8)	12.5 (8)	50.0 (8)	62.5 (8)	37.5 (8)
[illegible]	16.7 (6)	0.0 (6)	100.0 (6)	0.0 (6)	33.3 (6)	16.7 (6)	20.0 (5)	100.0 (6)	0.0 (6)	16.7 (6)	83.3 (6)	66.7[d] (6)	16.7 (6)
	0.0 (2)	50.0 (2)	100.0 (2)	50.0 (2)	100.0 (2)	50.0 (2)	100.0 (2)	100.0 (2)	0.0 (1)	50.0 (2)	100.0 (2)	100.0 (2)	100. (2)
	75.0 (4)	0.0 (4)	100.0 (4)	66.7 (3)	75.0 (4)	25.0 (4)	75.0 (4)	100.0 (4)	0.0 (4)	50.0 (4)	75.0 (4)	100.0 (4)	100. (4)
	75.0 (8)	12.5 (8)	100.0 (8)	75.0 (8)	62.5 (8)	75.0 (8)	75.0 (8)	100.0 (8)	0.0 (8)	75.0 (8)	87.5 (8)	100.0 (7)	75.0 (8)
	20.0 (5)	0.0 (5)	100.0 (5)	50.0 (4)	40.0 (5)	0.0 (5)	40.0 (5)	100.0 (5)	... (0)	0.0 (5)	60.0[a] (5)	100.0 (5)	40.0 (5)
	68.4 (19)	0.0 (19)	100.0 (19)	57.9 (19)	36.8 (19)	5.3[b] (19)	57.9 (19)	94.7 (19)	... (0)	15.8 (19)	89.4 (19)	94.7 (19)	78.9 (19)
	50.0 (8)	0.0 (8)	100.0 (8)	50.0 (8)	50.0 (8)	0.0[a] (8)	62.5 (8)	100.0 (8)	... (0)	25.0 (8)	87.5 (8)	85.7 (7)	62.5 (8)
	75.0 (4)	0.0 (4)	100.0 (4)	75.0 (4)	50.0 (4)	25.0 (4)	100.0 (4)	75.0 (4)	... (0)	25.0 (4)	100.0 (4)	100.0 (4)	100.0 (4)
	50.0 (4)	0.0 (4)	100.0 (4)	0.0 (4)	50.0 (4)	25.0 (4)	100.0 (4)	75.0 (4)	... (0)	50.0 (4)	100.0 (4)	100.0 (4)	75.0 (4)

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Time of death	Penicillin G	Dihydrostreptomycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
Dec.	70.0 (10)	0.0 (10)	100.0 (10)	50.0 (10)	70.0 (10)	10.0 (10)	70.0 (10)	100.0 (10)	... (0)	10.0 (10)	90.0 (10)	90.0 (10)	70. (10
Jan. 1974	60.0 (10)	0.0 (10)	100.0 (10)	10.0 (10)	10.0 (10)	0.0[c] (10)	60.0 (10)	100.0 (10)	... (0)	0.0 (10)	70.0[a] (10)	100.0 (10)	60. (10
Feb.	52.0 (25)	0.0 (25)	100.0 (25)	39.1 (23)	44.0 (25)	4.0[b] (25)	60.0 (25)	100.0 (25)	... (0)	8.0 (25)	92.0 (25)	68.0[a] (25)	88. (25
Mar.	66.7 (3)	0.0 (3)	100.0 (3)	33.3 (3)	66.7 (3)	33.3 (3)	66.7 (3)	100.0 (3)	... (0)	33.3 (3)	100.0 (3)	100.0 (3)	66. (3)
Apr.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
May	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Jun.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Jul.	100.0 (3)	0.0 (3)	100.0 (3)	100.0 (3)	66.7 (3)	0.0 (3)	66.7 (3)	100.0 (3)	... (0)	100.0 (3)	100.0 (3)	100.0 (3)	100. (3)
Aug.	100.0 (4)	0.0 (4)	100.0 (4)	25.0 (4)	50.0 (4)	0.0 (4)	75.0 (4)	100.0 (4)	... (0)	0.0 (4)	100.0 (4)	100.0 (4)	100. (4)

*Percent sensitive. **No. of isolates tested. +From Dec. 27, 1972, to March 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.)for the first 21 days after arrival. These isolates were all obtained from medicated cattle. Superscripts indicate that the bacterial population isolated during that time period was significantly more resistant than the population isolated from March 1, 1972, to December 26, 1972. (a, P=< 0.05; b, P=< 0.01; c, P=< 0.02; d, P=< 0.001).

TABLE 22 - Antimicrobic Sensitivity of Pasteurella multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program.

	Time of Death			
	Prior to CTC Medication (3-1-72 to 12-26-72)	During Medication* (12-27-72 to 3-6-73)		
Antimicrobic		Medicated	Not Medicated**	Combined
Penicillin G	56.6+ (53)[a,a,b]	0.0 (13)[a]	20.0 (5)	5.6 (18)[b]
Dihydrostreptomycin	7.5 (53)	7.7 (13)	0.0 (5)	5.6 (18)
Chloramphenicol	98.1 (53)	100.0 (13)	100.0 (5)	100.0 (18)
Erythromycin	37.2 (43)[c]	15.4 (13)	0.0 (5)	11.1 (18)[c]
Neomycin	32.1 (53)	15.4 (13)	20.0 (5)	16.7 (18)
Tetracycline	37.7 (53)[d,e]	0.0 (13)[d]	0.0 (5)	0.0 (18)[e]
Kanamycin	... (0)	8.3 (12)	33.3 (3)	13.3 (15)
Polymyxin B	96.2 (53)[f,g]	84.6 (13)	60.0 (5)[f]	77.8 (18)[g]
Tylosin	0.0 (53)	0.0 (13)	0.0 (5)	0.0 (18)
Sulfathiazole	26.9 (52)	7.7 (13)	0.0 (5)	5.6 (18)
Gentamicin	92.5 (53)[h,i,j]	38.5 (13)[h]	40.0 (5)[i]	38.9 (18)[j]
Cephalothin	88.7 (53)[k,l,m]	53.8 (13)[k]	40.0 (5)[l]	50.0 (18)[m]
Ampicillin	79.2 (53)[n,o]	46.2 (13)[n]	80.0 (5)	55.6 (18)[o]

*From December 27, 1972, to March 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.) for the first 21 days after arrival. **These cattle were received prior to initiating prophylactic CTC medication. +Percent sensitive. "Number of isolates tested. Values having the same superscript are significantly different (c,o, P = < 0.05; n,g, P = < 0.02; d-f,k,l, P = < 0.01; a,b,h-j,m, P = < 0.001).

TABLE 23--Serum Concentrations of Oxytetracycline in Cattle Resulting From Continuous Ad Libitum Administration in Medicated* Feeds

Dosage (mg./lb.b.w.)	Basal Diet	
	Alfalfa Pellets**	Oat hay (ground)**
	Serum Oxytetracycline Concentration (µg./ml.)+	
1	NM"	NM
5	NM	0.15
15	0.21	0.40
25	0.37	0.45
40[a]	1.20	...

*Oxytetracycline provided as Terramycin Crumbles (2 Gm.oxytetracycline/lb.) Agricultural Division, Pfizer Inc., New York, N.Y. 10017.

**Alfalfa Pellets and Oat Hay contained 1.38% and 0.43% calcium, respectively.+Mean values from 2 steers sampled at 48, 60, 72 and 84 hours after initiation of feed medication. "NM=concentration not measurable. [a]Terramycin Crumbles fed ad libitum as total ration (calcium content was 1.27%).

TABLE 24--Serum Concentrations Of Chlortetracycline in Cattle Resulting From Continuous Ad Libitum Administration In Medicated Feeds*

Dosage (mg./lb. b.w.)	Basal Diet	
	Alfalfa Pellets	Oat Hay (ground)**
	Serum Chlortetracycline concentration (µg./ml.)+	
1	NM"	0.02
5	0.21	0.25
15	0.45	0.26
25	0.50	0.63
40[a]	1.70	...

*Chlortetracycline provided as CTC-2 (2Gm.Chlortetracycline/lb.) Diamond Shamrock Chemical Co., Newark, N.J. 07102 **Alfalfa Pellets and Oat Hay contained 1.38% and 0.43% calcium, respectively. +The mean values from 2 steers sampled at 48, 60, 72 and 84 hours after initiation of feed medication. "NM= concentration not measurable. [a]CTC-2 fed ad libitum as total ration (calcium content was 1.32%).

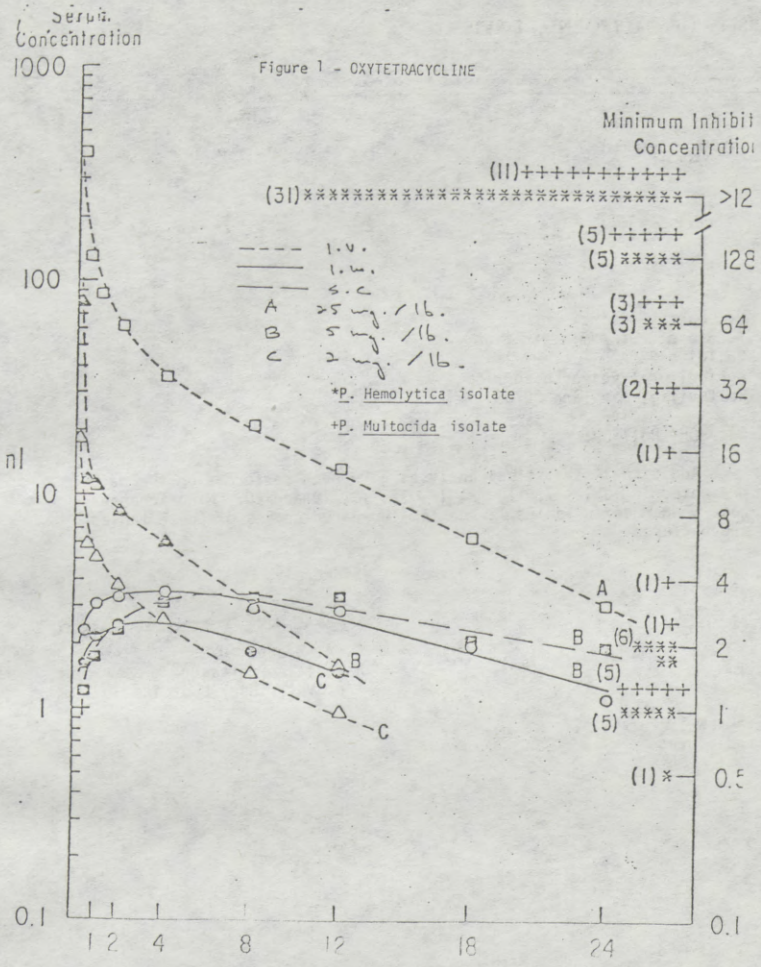


Figure 1 - OXYTETRACYCLINE

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SCHOOL OF VETERINARY MEDICINE
DEPARTMENT OF MEDICINE

DAVIS, CALIFORNIA 95616

January 5, 1976

Dr. Larry Rollins
Food and Drug Administration
Building 328A
Agricultural Research Service
Beltsville, Maryland 20705

Dear Dr. Rollins:

Additional statistical analyses have been performed on the data presented in Tables 7, 11, 12, 14, 15, 18, 19 and 20. Minor changes have been made in Tables 13 and 16. Up-dated copies of these tables are enclosed.

Sincerely,

C. A. Hjerpe, DVM
Associate Professor
of Veterinary Medicine

CAH:mw
Enclosures

TABLE 7 - Antimicrobic Resistance of Pasteurella hemolytica and P. multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program

CTC medication status	Time of death	Antimicrobic resistance* P. hemolytica	P. multocida
Not medicated	Feb. 15-Dec. 26, 1972	$3.2^{**,a,b}(82)^{+}$	$3.4^{c,d}(52)$
Medicated[11]	Dec. 27, 1972 - Mar. 6, 1973	$6.2^{a}(29)$	$6.0^{c}(13)$
Not medicated[e]	Dec. 27, 1972 - Mar. 6, 1973	$5.3^{b}(4)$	$6.0^{d}(5)$

*Antimicrobics tested were penicillin G, dihydrostreptomycin, chloramphenicol, neomycin, tetracycline, polymyxin B, sulfathiazole, gentamicin, cephalothin, and ampicillin. **The mean no. of antimicrobics to which the isolates were resistant. +No. of isolates tested. "From Dec. 27, 1972 to Mar. 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.) for the first 21 days after arrival. Values having the same superscript are significantly different: a,c, P = <0.001; b,d, P = <0.01. [e]These cattle were received prior to initiating prophylactic CTC medication.

TABLE 11 - Mortality Associated with Bacterial Pneumonia in Yearling Feedlot Cattl

Influence of Antimicrobic Resistance in Causative Pasteurellae.

...e ...iod	Relationship to antimicrobic resistance problem	No. yearling cattle received	Mortality associated with pneumonia: Primary pneumonias	Secondary pneumonias	All pneumonias
...-72					
...-72	Before	8,075	$28^{*}(0.35)^{**,a,d}$	$35(0.43)^{b}$	$63(0.78)^{c}$
...-72					
...-74	During	12,576	$85(0.68)^{d,e}$	$37(0.23)^{f}$	$123(0.98)^{g}$
...74					
...-74	After	10,931	$12(0.11)^{+,a,e}$	$8(0.07)^{b,f}$	$20(0.18)^{11,c}$

...No. of deaths. ** Mortality (%). [†] Reduction of 69% compared with "Before". ...Reduction of 77% compared with "Before". Values having the same superscript are ...ntly different (a,b,c,e,f,g, P = <0.001; d, P = <0.01)

TABLE 12 - Mortality Associated with Bacterial Pneumonia in Feedlot Calves: Infl. of Antimicrobic Resistance in Causative Pasteurellae

Time period	Relationship to antimicrobic resistance problem	No. calves received	Mortality associated with pneumonia: Primary pneumonias	Secondary pneumonias	All pneumonias
-15-72 to -25-72	Before	7,392	65*(0.88)**,a	29(0.39) b	94(1.27) c
-27-72 to 1-74	During	10,296	217(2.11) a,d	69(0.67) b	286(2.78) c,e
-74 to -74	After	711	3(0.42)†,d	2(0.28)	5(0.70)††,

*No. of deaths. **Mortality (%). † Reduction of 51% compared with "Before". ††Reduction of 45% compared with "Before". Values having the same superscript are significantly different (a,c,e,P = <0.001; b,P = <0.02; d,P = <0.01)

TABLE 13- An Estimate of the Economic Loss Resulting from Antimicrobic-Resistant Bacterial Infections in Feedlot Cattle

	Time period and treatment system utilized	No. cattle	Net loss per steer*	Total losses
Calves	No records (1-1-73 - 8-6-73)	6,009	$18.68	$112,248.12
	Individual treatment records utilized (8-7-73 - 1-31-74)	3,086	$11.54	$ 35,612.44
Yearlings	No records (1-1-73 - 8-6-73)	7,567	$ 2.17	$ 16,420.39
	Individual treatment records utilized (8-7-73 - 1-31-74)	3,542	$11.96	$ 42,362.32
Totals		20,204		$206,643.27

TABLE 14- Animal Health Data Used In Calculating The Economic Loss from Antimicrobic Resistant Bacterial Infections In Yearling Cattle

Antimicrobic resistance problems	Treatment system used	Mortality [1]	Culling rate	Medicine cost
Occasional problems (2/17 -12/31/72)*	No individual records (2/17/72 - 8/6/73)*	198/10,282 (1.93)**,d	372/10,265 (3.62)**,a,e	$5.03 (9,161)+
Serious problems (1/1/73 - 1/31-74)*		134/7,567 (1.77)	487/7,567 (6.44)a	$4.05 (7,397)
	Individual treatment record system utilized (8/7/73-4/30/75)*	79/3,542 (2.23)b	255/3,542 (7.20)c	$7.03 (3,476)
Occasional problems (2/1/74 - 4/30/75)*		186/17,174 (1.08)b,d	251/11,770 (2.13)c,e	$5.40 (11,680)

*The time period during which cattle were received. **Percent. + No of cattle included in the analysis.
Values having the same superscript (a,b,c,d,e) are significantly different (P=<0.001).

TABLE 15 - Animal Health Data Used In Calculating the Economic Loss from Antimicrobic Resistant Bacterial Infections In Calves

Antimicrobic resistance problems	Treatment system used	Mortality	Culling rate	Medicine cost
Occasional problems (2/17 - 12/31/72) *	No individual records (2/17/72 - 8/6/73)*	335/8,801 (3.81)**,a,d	249/8,801 (2.83)*,b,e	$ 6.51 (8,500)+
Severe problems (1/1/73 - 1/31-74)*		354/6,009 (5.89) a	799/6,009 (13.30) b	$ 7.95 (6,009)
	Individual treatment record system utilized (8/7/73 - 4/30/75)*	125/3,086 (4.05) c	222/3,086 (7.19)	$11.83 (3,086)
Occasional problems (2/1/74 - 4/30/75)*		13/708 (1.84) c,d	38/708 (5.37) e	$ 5.81 (706)

*The time period during which cattle were received. **Percent. +No. of cattle included in the analysis.
Values having the same superscript are significantly different (a,b,e,P = <0.001; c,d,P = <0.01).

TABLE 16- An Analysis of the Influence of Antimicrobic - Resistant Bacterial Infections on Mortality, Culling Rate, and Medicine Cost in Feedlot Cattle

	Time period and treatment system utilized	Change in mortality	Net loss per steer (mortality)	Change in culling rate	Net loss per steer (culling)	Net loss per steer (medicine)	Total los per stee
Calves	No records (1/1/73 - 8/6/73)	+2.08%*	+$5.72**	+10.47%*	+$11.52**,+	+$1.44*	+$18.
	Individual treatment records utilized (8/7/73 - 1/31/74)	+2.21%[a]	+$6.08**	+ 1.82%[a]	+$ 2.00**,+	+$3.46[a]	+11.5
Yearlings	No records (1/1/73 - 8/6/73)	-0.16%*	-$0.52[b]	+ 2.82%*	+$ 3.67[b],+	-$0.98*	+$ 2.1
	Individual treatment records utilized (8/7/73 - 1/31/74)	+1.15%[a]	+$3.74[b]	+ 5.07%[a]	+$ 6.59[b],+	+$1.63[a]	+$11.9

*Based on comparison with the baseline period of 2/17/72 - 12/31/72 (Tables 14 and 15). ** Based on a $275 feeder steer calf. + Based on an estimated 40% loss in value when a cull steer is sold at auction or consigned. [a] Based on comparison with the baseline period of 2/1/74 - 4/30/75 (Tables 14 and 15). [b] Based on a $325 yearling feeder steer.

TABLE 18 - Antimicrobic Resistance of Pasteurella hemolytica and P. multocida Isolated from Fatal Bovine Pneumonia Cases: Influence of a Prophylactic CTC Medication Program

Time of death	Antimicrobic resistance*	
	P. hemolytica	P. multocida
Feb 1972	...(0)	...(0)
Mar.	6.0**(1)+	...(0)
Apr.	3.8 (4)	...(0)
May	4.0 (1)	1.3 (3)
June	3.3 (3)	1.0 (1)
July	2.7 (25)	...(0)
Aug.	3.3 (7)	4.2 (6)
Sep.	4.3 (4)	...(0)
Oct.	2.6 (17)	2.8 (10)
Nov.	3.3 (8)	3.2 (17)
Dec. 1-26	4.3[b](12)	4.1 (15)
Dec. 27-Jan. 31, 1973"	5.8[a](10)	6.4[a](10)
Feb. 1-Mar. 6"	6.2[a](23)	5.5[b](8)
Mar. 7-31	5.9[a](13)	5.5[c](6)
Apr.	6.0 (1)	2.5 (2)
May	4.7[a](18)	2.5 (4)
June	5.2[a](24)	1.7 (7)
July	4.1[b](36)	5.4[d](5)
Aug	4.3[a](26)	3.6 (19)

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Time of death	P. hemolytica	P. multocida
Sep.	5.0 (2)	3.7 (7)
Oct.	4.7 (3)	2.8 (4)
Nov.	5.1[a] (14)	3.5 (4)
Dec.	5.0[b] (7)	3.6 (10)
Jan. 1974	...(0)	4.0 (10)
Feb.	4.6[a] (17)	3.5 (25)
Mar.	...(0)	3.0 (3)
Apr.	...(0)	...(0)
May	...(0)	...(0)
Jun.	...(0)	...(0)
Jul	0.0 (1)	2.7 (3)
Aug.	3.0 (1)	2.8 (4)

*Antimicrobics tested were penicillin G, dihydrostreptomycin, chloramphenicol, neomycin, tetracycline, polymyxin B, sulfathiazole, gentamicin, cephalothin and ampicillin. **The mean no. of antimicrobics to which the isolates were resistant. +No. of isolates tested. "From Dec. 27, 1972, to Mar. 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb.) for the first 21 days after arrival. Superscripts indicate that the bacterial population isolated during that time period was significantly more resistant than the population isolated from Mar. 1, 1972 to Dec. 26, 1972. (a, P=< 0.001; b, P=< 0.01; c, P=< 0.02; d, P=< 0.05).

TABLE 19- Antimicrobic Sensitivity Of Pasteurella hemolytica Isolated From Fatal Bovine Pneumonia Cases: Influence Of A Prophylactic CTC Medication Program

Time of death	Penicillin G	Dihydrostrepto-mycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
Mar. 1972	0.0* (1)**	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	0.0[b] (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0 (
Apr.	0.0 (5)	0.0 (5)	100.0 (5)	... (0)	0.0 (5)	100.0 (5)	... (0)	80.0 (5)	0.0 (5)	60.0 (5)	80.0 (5)	100.0 (4)	0 (
May	0.0 (1)	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	100.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0 (
Jun.	0.0 (3)	0.0 (3)	100.0 (3)	... (0)	0.0 (3)	33.3 (3)	... (0)	100.0 (3)	0.0 (3)	33.3 (3)	66.7[a] (3)	100.0 (3)	33 (
Jul.	7.7[c] (26)	3.8 (26)	100.0 (25)	... (0)	26.9 (26)	92.3 (26)	... (0)	100.0 (26)	0.0 (26)	80.8 (26)	100.0 (26)	100.0 (26)	50 (
Aug.	28.6 (7)	0.0 (7)	100.0 (7)	... (0)	0.0 (7)	85.7 (7)	... (0)	100.0 (7)	0.0 (7)	85.7 (7)	100.0 (7)	100.0 (7)	28 (
Sep.	0.0 (4)	0.0 (4)	100.0 (4)	... (0)	25.0 (4)	75.0 (4)	... (0)	75.0 (4)	0.0 (4)	75.0 (4)	75.0 (4)	100.0 (4)	0 (
Oct.	63.2 (19)	15.8 (19)	100.0 (19)	47.1 (17)	42.1 (19)	63.2 (19)	... (0)	89.5 (19)	0.0 (19)	68.4 (19)	75.0 (19)	100.0 (17)	68 (1
Nov.	25.0 (8)	12.5 (8)	100.0 (8)	37.5 (8)	50.0 (8)	62.5 (8)	... (0)	100.0 (8)	0.0 (8)	37.5 (8)	100.0 (8)	100.0 (8)	50 (
Dec. 1-26	25.0 (12)	0.0 (12)	100.0 (12)	50.0 (12)	8.3 (12)	16.7[b] (12)	... (0)	91.7 (12)	0.0 (12)	58.3 (12)	83.3 (12)	91.7[c] (12)	8. (1
Dec. 27 to Jan. 31, 1973[+]	20.0 (10)	0.0 (10)	100.0 (10)	0.0[b] (10)	0.0[d] (10)	20.0[b] (10)	40.0 (10)	90.0 (10)	0.0 (10)	20.0[b] (10)	60.0[b] (10)	70.0[b] (10)	20 (1
Feb. 1 to Mar. 6[+]	4.3[b] (23)	0.0 (23)	100.0 (23)	0.0[b] (23)	8.7[d] (23)	0.0[b] (23)	15.0 (23)	100.0 (23)	0.0 (23)	0.0[b] (23)	52.2[b] (23)	47.8[b] (23)	13 (2
Mar. 7-31	0.0[a] (13)	0.0 (13)	100.0 (13)	15.4 (13)	0.0[a] (13)	7.7[b] (13)	23.1 (13)	92.3 (13)	0.0 (13)	7.7[b] (13)	100.0 (13)	92.3 (13)	0 (1
Apr.	0.0 (1)	0.0 (1)	100.0 (1)	0.0 (1)	0.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	0.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	0 (1
May	5.6 (18)	16.7 (18)	94.4[a] (18)	11.1[c] (18)	16.7 (18)	11.1[b] (18)	61.1 (18)	100.0 (18)	0.0 (18)	38.9[a] (18)	83.3 (18)	77.8[b] (18)	11 (1
Jun.	8.0 (25)	4.0 (25)	84.0[b] (25)	24.0 (25)	28.0 (25)	12.0[b] (25)	40.0 (25)	100.0 (25)	0.0 (25)	24.0[b] (25)	92.0 (25)	87.5[c] (24)	15 (2
Jul.	13.2 (38)	2.6 (38)	100.0 (37)	45.9 (37)	44.7 (38)	18.4[b] (38)	73.0 (37)	97.3 (37)	0.0 (8)	50.0 (38)	94.7 (38)	84.2[d] (38)	26 (3
Aug.	7.4 (27)	3.7 (27)	100.0 (27)	40.7 (27)	33.3 (27)	0.0[b] (27)	74.1 (27)	100.0 (26)	... (0)	44.4[a] (27)	100.0 (26)	100.0 (26)	19 (2

Table 19 - Page 2

me of death	Penicillin G	Dihydrostrepto-mycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
p.	0.0 (2)	0.0 (2)	100.0 (2)	0.0 (2)	0.0 (2)	0.0[a] (2)	100.0 (2)	100.0 (2)	... (0)	50.0 (2)	100.0 (2)	100.0 (2)	0. (2
t.	0.0 (3)	0.0 (3)	100.0 (3)	66.7 (3)	66.7 (3)	0.0[c] (3)	66.7 (3)	66.7 (3)	... (0)	33.3 (3)	100.0 (3)	100.0 (3)	0. (3
v.	0.0[a] (14)	0.0 (14)	100.0 (14)	35.7 (14)	7.1 (14)	0.0[b] (14)	35.7 (14)	100.0 (14)	... (0)	35.7[a] (14)	100.0 (14)	92.9 (14)	14 (1
ec.	0.0 (7)	0.0 (7)	100.0 (7)	14.3 (7)	14.3 (7)	28.6[a] (7)	57.1 (7)	100.0 (7)	... (0)	28.6[a] (7)	85.7 (7)	100.0 (7)	14 (1
an. 1974	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
eb.	11.8 (17)	0.0 (17)	100.0 (17)	62.5 (16)	58.8 (17)	5.9[b] (17)	76.5 (17)	100.0 (17)	... (0)	11.8[b] (17)	94.1 (17)	76.5[b] (17)	
ar.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
pr.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
ay	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
un.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
ul.	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	... (0)	100.0 (1)	100.0 (1)	100.0 (1)	
ug.	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	100.0 (1)	

*Percent sensitive. ** No. of isolates tested. +From Dec. 27, 1972 to Mar. 6, 1973, all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 kg. (10 lb for the first 21 days after arrival. These isolates were all obtained from medicated cattle. Superscripts indicate that the bacterial population isolated during that time period was significantly more resistant from the population isolated from Mar 1, 1972 to Dec. 26, 1972 (a, P= < b, P= < 0.001; c, P= < 0.02; d, P= < 0.01).

TABLE 47 - ANTIMICROBIC SENSITIVITY OF
Pneumonia Cases: Influence of a Prophylactic CIC Medication Program

Time of Death	Penicillin G	Dihydrostreptomycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	Ampicillin
Mar. 1972	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
Apr.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)
May	66.7* (3)**	33.3 (3)	100.0 (3)	... (0)	100.0 (3)	100.0 (3)	... (0)	100.0 (3)	0.0 (3)	66.7 (3)	100.0 (3)	66.7 (3)	10 (
Jun.	100.0 (1)	0.0 (1)	100.0 (1)	... (0)	0.0 (1)	100.0 (1)	... (0)	100.0 (1)	0.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	10 (
Jul.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (
Aug.	83.3 (6)	0.0 (6)	100.0 (6)	... (0)	0.0 (6)	0.0[a] (6)	... (0)	100.0 (6)	0.0 (6)	0.0 (6)	83.3 (6)	100.0 (6)	10 (
Sep.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (
Oct.	80.0 (10)	10.0 (10)	100.0 (10)	40.0 (10)	40.0 (10)	40.0 (10)	... (0)	80.0[b] (10)	0.0 (10)	30.0 (10)	100.0 (10)	100.0 (10)	90 (1
Nov.	47.1 (17)	5.9 (17)	100.0 (17)	29.4 (17)	47.1 (17)	41.2 (17)	... (0)	100.0 (17)	0.0 (17)	23.5 (17)	94.1 (17)	88.2 (17)	70 (1
Dec. 1 -26	37.5 (16)	6.3 (16)	93.8 (16)	43.8 (16)	12.5[a] (16)	31.3 (16)	... (0)	100.0 (16)	0.0 (16)	26.7 (15)	87.5 (16)	81.3 (16)	68 (1
Dec. 27- Jan. 31, 1973[+]	10.0[d] (10)	0.0 (10)	100.0 (10)	10.0[b] (10)	20.0 (10)	0.0[d] (10)	14.3 (7)	70.0[d] (10)	0.0 (10)	0.0[d] (10)	30.0[d] (10)	40.0[d] (10)	7((1
Feb. 1 to Mar.6[+]	0.0[d] (8)	12.5 (8)	100.0 (8)	12.5 (8)	12.5 (8)	0.0[d] (8)	12.5 (8)	87.5 (8)	0.0 (8)	12.5 (8)	50.0[d] (8)	62.5[d] (8)	3 (
Mar. 7-31	16.7 (6)	0.0 (6)	100.0 (6)	0.0 (6)	33.3 (6)	16.7 (6)	20.0 (5)	100.0 (6)	0.0 (6)	16.7 (6)	83.3 (6)	66.7[d] (6)	1
Apr.	0.0 (2)	50.0 (2)	100.0 (2)	50.0 (2)	100.0 (2)	50.0 (2)	100.0 (2)	100.0 (2)	0.0 (1)	50.0 (2)	100.0 (2)	100.0 (2)	1
May	75.0 (4)	0.0 (4)	100.0 (4)	66.7 (3)	75.0 (4)	25.0 (4)	75.0 (4)	100.0 (4)	0.0 (4)	50.0 (4)	75.0 (4)	100.0 (4)	1
Jun.	75.0 (8)	12.5 (8)	100.0 (8)	75.0 (8)	62.5 (8)	75.0 (8)	75.0 (8)	100.0 (8)	0.0 (8)	75.0 (8)	87.5 (8)	100.0 (7)	7
Jul.	20.0 (5)	0.0 (5)	100.0 (5)	50.0 (4)	40.0 (5)	0.0 (5)	40.0 (5)	100.0 (5)	... (0)	0.0 (5)	60.0[a] (5)	100.0 (5)	4
Aug.	68.4 (19)	0.0 (19)	100.0 (19)	57.9 (19)	36.8 (19)	5.3[b] (19)	57.9 (19)	94.7 (19)	... (0)	15.8 (19)	89.4 (19)	94.7 (19)	7 (
Sep.	50.0 (8)	0.0 (8)	100.0 (8)	50.0 (8)	50.0 (8)	0.0[a] (8)	62.5 (8)	100.0 (8)	... (0)	25.0 (8)	87.5 (8)	85.7 (7)	6
Oct.	75.0 (4)	0.0 (4)	100.0 (4)	75.0 (4)	50.0 (4)	25.0 (4)	100.0 (4)	75.0 (4)	... (0)	25.0 (4)	100.0 (4)	100.0 (4)	1
Nov.	50.0 (4)	0.0 (4)	100.0 (4)	0.0 (4)	50.0 (4)	25.0 (4)	100.0 (4)	75.0 (4)	... (0)	50.0 (4)	100.0 (4)	100.0 (4)	

Table 20, Page 2

Time of death	Penicillin G	Dihydrostrepto-mycin	Chloramphenicol	Erythromycin	Neomycin	Tetracycline	Kanamycin	Polymyxin B	Tylosin	Sulfathiazole	Gentamicin	Cephalothin	
Dec.	70.0 (10)	0.0 (10)	100.0 (10)	50.0 (10)	70.0 (10)	10.0 (10)	70.0 (10)	100.0 (10)	... (0)	10.0 (10)	90.0 (10)	90.0 (10)	7 (
Jan. 1974	60.0 (10)	0.0 (10)	100.0 (10)	10.0 (10)	10.0 (10)	0.0[c] (10)	60.0 (10)	100.0 (10)	... (0)	0.0 (10)	70.0[a] (10)	100.0 (10)	6 (
Feb.	52.0 (25)	0.0 (25)	100.0 (25)	39.1 (23)	44.0 (25)	4.0[b] (25)	60.0 (25)	100.0 (25)	... (0)	8.0 (25)	92.0 (25)	68.0[a] (25)	8 (
Mar.	66.7 (3)	0.0 (3)	100.0 (3)	33.3 (3)	66.7 (3)	33.3 (3)	66.7 (3)	100.0 (3)	... (0)	33.3 (3)	100.0 (3)	100.0 (3)	6
Apr.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
May	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
Jun.	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	... (0)	
Jul.	100.0 (3)	0.0 (3)	100.0 (3)	100.0 (3)	66.7 (3)	0.0 (3)	66.7 (3)	100.0 (3)	... (0)	100.0 (3)	100.0 (3)	100.0 (3)	
Aug.	100.0 (4)	0.0 (4)	100.0 (4)	25.0 (4)	50.0 (4)	0.0 (4)	75.0 (4)	100.0 (4)	... (0)	0.0 (4)	100.0 (4)	100.0 (4)	

*Percent sensitive. **No. of isolates tested. [+]From Dec. 27, 1972, to March 6, 1973 all cattle entering the feedlot were fed a starting ration containing 500 mg. of CTC/4.5 k (10 lb.)for the first 21 days after arrival. These isolates were all obtained from medica cattle. Superscripts indicate that the bacterial population isolated during that time per was significantly more resistant than the population isolated from March 1, 1972, to Decem 26, 1972. (a, P=< 0.05; b, P=< 0.01; c, P=< 0.02; d, P=< 0.001).

OARDC
Ohio Agricultural Research and Development Center
WOOSTER, OHIO 44691
TELEPHONE (216) 264-1021
DEPARTMENT OF
VETERINARY SCIENCE

September 22, 1977

Dr. C. D. Van Houweling
Director, Bureau of Veterinary Medicine
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Van Houweling:

Enclosed please find two research reports concerning outbreaks of shipping fever associated with antibiotic resistant strains of Pasteurella hemolytica. I have observed an increasing frequency of isolation of antibiotic resistant strains since 1973 when we recovered the first isolates of this type from veal calves and feeder calves. During 1975 and 1976 the incidence of antibiotic resistant P. hemolytica among feeder calves conditioned at the OARDC beef research unit approached 50% or greater.

I do not have epidemiologic data at this time to determine the exact source and reservoir of these antibiotic resistant strains of P. hemolytica, however the high incidence and the difficulty of treating these cases of shipping fever is of great concern.

I will not be able to attend the meeting October 5, 1977 covering the use of antibiotics in feed and controlled drugs but I do urge careful investigation and strict control of antibiotic substances used in the feeding and treatment of food producing animals. Whereas antibiotic resistant strains of P. hemolytica are not a great threat to the human population, the cases of pneumonia and shipping fever involving these organisms are impossible to treat effectively.

If I can be of any help to you in the future, I would be pleased to do so.

Sincerely,

Clyde K. Smith DVM.

Clyde K. Smith, DVM, PhD
Professor, Microbiology

CKS/mr

Enc.

cc: Dr. E. M. Kohler

99-031 30A

September 22, 1

AN OUTBREAK OF SHIPPING FEVER ASSOCIATED WITH ANTIBIOTIC-RESISTANT STRAINS OF PASTEURELLA HEMOLYTICA

C. K. Smith, J. E. Jones, and F. M. Byers
Departments of Veterinary Science and Animal Science

An outbreak of shipping fever occurred among 156 steers which had been obtained from six Ohio graded feeder calf sales. Eighty-eight percent of the calves were affected and the death loss was 10 percent. The major etiologic agents associated with this outbreak were antibiotic-resistant strains of Pasteurella hemolytica. Vaccination of the steers with an experimental vaccine 2 weeks prior to the outbreak lowered the incidence of disease and the rate of repeat treatments.

Pasteurella hemolytica, one of the causative agents of shipping fever complex (SFC), is commonly recovered from the nasal passage and lungs of recently shipped cattle. Strains of *P. hemolytica*, which are resistant to many commonly used antibiotics, have been isolated from cattle with increasing frequency. A major outbreak of SPC associated with antibiotic-resistant Pasteurella has been reported in California and isolated outbreaks have been identified in Ohio. Antibiotic-resistant strains of *P. hemolytica* were responsible for the three outbreaks of SFC that occurred among the feeder calves received at OARDC, Wooster, at the North Appalachian Experimental Watershed, Coshocton, and at the Mahoning County Farm; Canfield, during the fall of 1975. This report will present a study of the outbreak of shipping fever which occurred at OARDC, Wooster.

One hundred, fifty-six calves were obtained from six graded feeder calf sales in Ohio during a 2-week period. These calves were randomly allocated to experimental treatments within the 12-pen unit. The calves received one of three protein supplements: (a) soybean meal, (b) urea, or (c) soybean meal and urea. Aureo S-700 was added to the ration of one-half (two pens) of each of the above three supplement groups.

These calves were further subdivided to receive: (a) intradermal vaccination with a live culture of *P. hemolytica*, (b) intradermal vaccination with a live culture of *P. hemolytica* and a subcutaneous injection of 1.5 mg./kg. of levamisole, (c) subcutaneous injection of 1.5 mg./kg. of levamisole, and (d) untreated control group. The animals receiving the vaccinations and injections were co-mingled with untreated calves in each of the 12 pens.

Ninety-one of the steers (Group 1) received the vaccination treatment at an interval of 2 weeks in advance of the remaining 65 steers (Group 2) because of their earlier arrival at the feedlot. Nasal specimens were taken at weekly intervals and cultured on blood agar plates. Isolates of *P. hemolytica* were tested for their sensitivity to penicillin, tetracycline, erythromycin, streptomycin, and ampicillin.

The overall incidence of SFC among the 156 steers was 88.4% and the total mortality rate was 10.25% (Table 1). The outbreak of shipping fever commenced 5 days after the arrival of Group 2 calves and continued for the next 4 weeks. The steers in Group 1, which had arrived 2 weeks previously, had a lower incidence of shipping fever and a lower mortality than the steers in Group 2. The steers in Group 1 had an overall incidence of shipping fever of 81.3%. The vaccinated steers had a disease incidence of 73% while the unvaccinated control steers had an 87% incidence. This difference approaches significance.

The incidence of disease among steers in Group 2 was virtually the same in the vaccinated and control groups. The reduction in the incidence of disease between the vaccinated steers in Group 1 and the vaccinated and unvaccinated steers in Group 2 was significant in favor of the Group 1 steers. There were no deaths among the Group 1 vaccinated steers, but 16 deaths occurred among the other lots of calves. The reduction in the rate of repeat treatment among the Group 1 vaccinated steers was significant when compared to the Group 2 steers.

The major etiologic agents in this outbreak of shipping fever were antibiotic-resistant strains of *P. hemolytica*. This data is presented in Table 2. Fifty-three percent of the isolates of *P. hemolytica* were sensitive only to erythromycin. Only 37.6% of the isolates were sensitive to the antibiotics usually used to treat cases of shipping fever. The strains sensitive to tetracycline and/or erythromycin were only marginally sensitive to these antibiotics. Antibiotic-resistant strains of *P. hemolytica* were isolated from the lungs of all of the steers that died during this outbreak of shipping fever.

TABLE 1.--The Incidence of Shipping Fever Complex Mortality and Frequency of Treatment in Vaccinated and Nonvaccinated Steers.

Group	No.	Cases SFC	% SFC	No. of Treatments	Treatment Rate	Mortality
1 Vaccinated	48	35	73	87	1.8	0
Not Vaccinated	43	39	87	126	2.9	2
Sub Total	91	74	81.3	213	2.3	
2 Vaccinated	36	35	97	183	5.0	9
Not Vaccinated	29	29	100	126	5.6	5
Sub Total	65	64	98	346	5.3	
Total	156	138	88.4	559	3.6	16(10.25%)

TABLE 2.--The Number of Antibiotic-Resistant Strains of Pasteurella sp. Isolated from the Nasal Passage of Steers.*

Isolates	No.	Sensitive to Pen-Ery-Te-A**	Ery-Te	Ery
P. hemolytica	64	24(37.6%)	6(9.4%)	34(53%)
P. multocida	11	11(100%)	0	0

*35 of 156 steers sampled weekly for 4 weeks after receiving.
**Pen - Penicillin
Ery - Erythromycin
Te - Tetracycline
A - Ampicillin

The incidence of disease was not influenced by the injection of levamisole. The vaccination of the steers at an interval of 2 weeks prior to the outbreak of shipping fever reduced the incidence of disease and mortality among the feeder steers. This group had sufficient time to develop an immune response to protect them against shipping fever associated with *P. hemolytica*. The relatively high incidence of antibiotic-resistant strains of *P. hemolytica* complicated the treatment of clinical cases of shipping fever. The average rate of repeat treatment among the Group 2 calves was 5 per animal compared to 1.8 and 2.9 per animal for the vaccinated and control lots of Group 1, respectively. Treatment with penicillin was ineffective and treatment with high levels of tetracycline and erythromycin only tended to control the course of the disease. The increased incidence of isolation of antibiotic-resistant strains of *P. hemolytica* indicates the need for an increased effort in the biologic control of shipping fever by using vaccines.

September 22, 1977

The Pattern and Incidence of Antibiotic Resistant Strains of *Pasteurella hemolytica* Isolated from Newly Shipped Beef Calves

C. K. Smith
Department of Veterinary Science

Summary

The nasal microflora was cultured from 154 of 413 steers during a 28-day period after arrival at the OARDC beef research unit. It was found that from 64 to 77% of these steers carried antibiotic resistant strains of *Pasteurella hemolytica* prior to treatment with antibiotics. An additional 3 to 20% of the groups converted from sensitive to resistant following treatment or without treatment during the sampling period.

Introduction

Pasteurella hemolytica is one of the leading causes of respiratory disease in the bovine. It is one of the organisms associated with the shipping fever complex. This organism is usually recovered from the nasal passage and the lungs of affected steers. Several strains of *P. hemolytica* have been cultured from beef calves during the past four years that are resistant to the antibiotics that are commonly used to treat clinical cases of shipping fever. It has been reported that these antibiotic resistant strains of *P. hemolytica* are readily transmitted to non-infected calves (Beef Day Report, OARDC 1975). A rational program of therapy is nearly impossible when a majority of the calves in a feedlot are carrying the antibiotic resistant strains of *P. hemolytica*.

This paper presents the patterns of resistance and the incidence of isolation of strains of *P. hemolytica* among newly shipped beef calves.

Procedure

The nasal microflora was cultured from 154 of 413 steers during a four-week period after arrival at the feedlot. Eighty-two of these steers were sampled on a weekly basis during the four-week period and 72 additional animals were sampled when they were being treated for respiratory disease. The nasal swabs were cross-streaked directly on blood agar plates and biplates containing EMB and blood agar. The blood agar plate was used to test the sensitivity of Pasteurella hemolytica and Pasteurella multocida to penicillin, tetracycline, erythromycin, streptomycin, ampicillin and chloromycetin after the Kirby Bauer technique. Sulfonamides were tested on Mueller-Hinton agar.

Results

There were 190 isolations of P. hemolytica from the Hereford steers and 121 isolations from the Angus and cross-bred group (Table 1). Sixty-five percent of the isolates of P. hemolytica recovered from the Hereford calves and 89% of the isolates from the Angus - cross-bred group were resistant to penicillin, tetracycline, erythromycin and ampicillin or tetracycline only. Thirty-five and 11% of the isolates of P. hemolytica from these respective groups were sensitive to penicillin, tetracycline, erythromycin and ampicillin. All of the isolates of P. hemolytica cultured were resistant to sulfonamides and they were all sensitive to chloromycetin.

TABLE 1.—The Pattern of Antibiotic Resistance of Strains of Pasteurella hemolytica Isolated from Steers During a Four-week Period Following Arrival.

	Hereford		Angus and cross-bred	
	No.	%	No.	%
Total isolations	190		121	
Resist – Pen, Te, Ery, Amp	115	60	53	44
Resist – Te only	9	5	54	45
Sensitive – Pen, Te, Ery, Amp	66	35	14	11
Sensitive – Chloromycetin	190	100	121	100
Resist – Sulfonamides	190	100	121	100

Pen – penicillin
Te – tetracycline
Ery – erythromycin
Amp – ampicillin

One hundred fifty-four of a total of 413 steers were sampled on a routine basis or when they were observed to be affected with respiratory disease. Among the group of Hereford steers, 64% were found to be carrying antibiotic resistant strains of P. hemolytica prior to the time that they were treated with antibiotics. Seventy-seven percent of the Angus – cross-bred group carried antibiotic resistant strains of P. hemolytica prior to treatment procedures (Table 2). Among these groups, 20 and 3% of the respective groups of animals converted from sensitive to resistant following treatment or without treatment during the 28-day period. Sixteen percent of the Hereford group and 10% of the Angus – cross-bred group maintained a flora of P. hemolytica that was sensitive to commonly used antibiotics during the 28-day period.

Table 2.—Incidence of Antibiotic Resistant Strains of Pasteurella hemolytica in Nasal Flora of Steers During a Four-week Period Following Arrival.

	Hereford	Angus and cross-bred
Total number	156	257
Sample number	81	73
Resistant prior to treatment	64%	77%
Sensitive to resistant (converted)	20%	3%
Sensitive throughout period	16%	10%

Hereford – 37 routine sample for 4 weeks
Angus and cross-bred – 45 routine sample for 4 weeks

Discussion and Conclusions

The high percentage of newly purchased animals that carry antibiotic resistant strains of P. hemolytica is a cause of concern for the feedlot operator and the veterinarian. When two-thirds to three-fourths of these animals have antibiotic resistant strains of P. hemolytica, an effective therapy program is nearly impossible. Disease incidence and death losses under these conditions usually exceed 60 and 15% respectively, The probable source of these organisms are direct or indirect contacts with cattle that have been treated or associated with these antibiotics for extended periods of time. The ineffectiveness of a treatment program accents the need for an effective vaccination program to control respiratory disease in newly weaned and shipped beef calves.

Question #8

Your Notice of Opportunity for Hearing on Penicillin cites a number of documents which we understand are not available to the public. We are aware of the following examples:

(a) Reference #5, Linton, A. H. et al. "The Colonization of the Human Gut by Antibiotic Resistant E. coli from Chickens." This is found on page 43779. Rollins, L. D. FDA Project 108 found on page 43783.

(b) Reference #17, Linton., et al. "Antibiotic Resistant and Sensitive E. coli. O-serotypes in the Gut and on the Carcass by Commercially Slaughtered Broiler Chickens and the Potential Public Health Implications." Found on page 43777.

Will you make these documents available for use by the public in the hearing procedure and in requesting a hearing?

Answer

These documents are on file with the Hearing Clerk along with the other references cited in the Federal Register notice. The two Linton, et al. articles have not yet been published, but drafts are on file for public viewing. Rollins Project 108 is on file under the authorship of Dorothy Pocurull

Question #9

We understand that at least one research report has been submitted to FDA showing that feed additves listed by FDA as alternatives for tetracycline antibiotics actually increase the spreading of Salmonella organisms from infected to non-infected chickens. What are your plans to deal with this information, and what is your timetable for dealing with it?

Answer

The study that has been submitted to the FDA concerning Salmonella infections in chickens shows the following:

Growth promotion levels of chlortetracycline 100 or 200 g/ton virginiamycin 100 g/ton, tylosin 40 g/ton, monensin 100 g/ton and bambermycins 3 or 4 g/ton, were tested for their effects on the spread of a tetracycline sensitive and a tetracycline resistant strain of salmonella typhimurium from seeder to contact chicks. In the two studies carried to day 13, the 4 gram+ acting antibacterials--virginiamycin, tylosin, monensin, and bambermycins--resulted in a significantly (0.05 or less) higher prevalence of infection in contact chicks compared with spread in nontreated controls. The prevalence of Salmonella was 1.5 to 2.6 times higher in medicated than controls. With chlortetracycline treatment, prevalence of sensitive organisms in medicated was 1/3 to 1/14of controls, prevalence less than 0.01; with the resistant organisms, treated had 1.45 times higher prevalence than controls, but this prevalence was not statistically significant (prevalence=0.10).

Smith and Tucker in studies to 117 days showed that bambermycins and tylosin increased Salmonella shedding but virginiamycin and bacitracin did not do so. The Smith and Tucker experiments were somewhat different from the study you asked about. Smith and Tucker experiments followed the excretion of salmonellae after experimental inoculation of the chicks, the antibacterials being given at the time of inoculation or a few days beforehand. In a study referred to in your letter, seeder chicks were inoculated with Salmonella, and the effect of the antibacterial on the spread of the Salmonella from seeder chicks to contact chicks was determined.

The coliforms in 4 or 5 groups of chicks receiving chlortetracycline in the study were on day 9 from 50 to 100 percent resistant to tetracycline; 0.33 percent were resistant in the fifth group. In none of these were any salmonellae resistant. It appears that the strain of Salmonella used in this study did not readily become resistant in vivo to the tetracyclines.

This work represents only one study with one Salmonella strain under a special set of circumstances. Other studies using the same drugs and other Salmonella

strains have shown varying results. However, we consider the study you ask about to be very important. This work and previous work submitted by the sponsors of these drugs will be considered in our continuing review of the alternative drugs. If this and other information indicates a need to restrict the use of these drugs, the Agency will propose to do so.

The new information taken together with scientific knowledge from other sources concerning these drugs does not constitute a need to move quickly for curtailment, but instead suggests that new questions have been raised and that the drug be kept under careful surveillance.

Mr. Moss. Thank you very much.
Dr. KENEDY. Thank you, Mr. Chairman.
Mr. Moss. Our next witness is Dr. John Bennett.

STATEMENT OF JOHN V. BENNETT, M.D., DIRECTOR, BACTERIAL DISEASES DIVISION, BUREAU OF EPIDEMIOLOGY, CENTER FOR DISEASE CONTROL, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Dr. BENNETT. Thank you, Mr. Chairman.

It is my understanding that I was asked to appear before the committee to serve as a resource individual in the deliberations that you are undertaking.

The only statement I would like to make is to identify myself in terms of my position and functions at the Center for Disease Control. I am the Director of the Bacterial Diseases Division in the Bureau of Epidemiology and a commissioned officer in the Public Health Service. I have been at the Center since 1965. My responsibilities then and now involve surveillance of diseases caused by bacteria and the investigation and control of outbreaks caused by bacterial agents.

I was a member of the task force in 1970–1971 and have remained interested and involved in this area since that time.

Mr. Moss. Mr. McLain?

Mr. MCLAIN. Thank you, Mr. Chairman.

First, Dr. Bennett, let me commend you. Of the many experts in this area that we have talked to in preparing for these hearings, every one of them commended you for our interview. We appreciate your being here.

I would like to begin by dealing with the Task Force on Antibiotics in Animal Feeds which was created in 1970. You were a member of that task force; were you not?

Dr. BENNETT. Correct.

Mr. MCLAIN. There was also a subunit within that task force dealing with the human health hazards.

Dr. BENNETT. Correct.

Mr. MCLAIN. What was the charge of that particular group, Dr. Bennett?

Dr. BENNETT. It was to define, as well as we could, based on the available information, in publications as well as through our own experiences, the potential hazards that existed to humans as a result of the practices of using antibiotics in animals for the purposes of growth promotion especially. We were not asked to address the therapeutic uses, but rather the growth promotant uses of antibiotics at that time.

Mr. MCLAIN. What were your findings after your review?

Dr. BENNETT. I think the conclusion was a fairly strong conclusion from two standpoints. One was the hazards that Commissioner Kennedy has alluded to this morning and which Dr. Novick and others who have appeared before this subcommittee have alluded to. That is the problem of the resistance transfer factor, the genetic pool of resistance determinants that is expanded by the practice.

The second—and the one that I am most especially concerned about—is the one relating to salmonellosis, which is a disease transmitted

from animals to man—from food-producing animals to man. The impact of this subtherapeutic use of antibiotics on the reservoir of salmonellosis and the risk of salmonella infections in humans that derive from that practice was included.

So, on both those two counts, I think the subcommittee of the task force clearly perceived that there was a hazard. The recommendations were made and subsequently, in fact, adopted by and supported by the entire task force in the report that was issued; that there should be restrictions on the use of certain drugs for these purposes: namely the penicillins, tetracyclines, sulfonamides, and stroptomycin.

I would like to say in passing that, although a lot of controversy has existed and has been alluded to about the task force and its deliberations, controversy surrounded the appendices to the task force report and in no way dealt with the task force report itself.

There was unanimous agreement on the need to restrict the use of penicillins, tetracyclines, streptomycin, and sulfonamides by the entire task force in 1970–71.

As I say, the recommendations, as they related to the human disease, derived from our subcommittee. It was, in fact, ultimately accepted by the entire task force. These restrictions were necessary from the standpoint of human health.

Mr. McLain. As you refer to the appendix and the work of the particular subcommittee, I assume what you are alluding to is the finding by the subcommittee that not only was there a hazard, but that there was an imminent hazard within the meaning of the Food, Drug, and Cosmetic Act.

Dr. Bennett. I would have to separate those, Mr. McLain. I think that there were a group of persons on the task force that felt that this term "imminent hazard" was, in fact, applicable. That was not, however, the same group that was involved in the Subcommittee on Human Health. The Subcommittee on Human Health, as I recall, consisted of three or four of us from the task force and not a larger group.

I myself have found it difficult to accept the concept of imminent hazard because that seems to imply to me a greater crisis or greater urgency than I myself have perceived. I think it is a cumulative problem, as Commissioner Kennedy has alluded to. It is a serious problem and demanding of action, but not the kind of immediate problem that we so commonly experience in the work that I do at the Center.

Mr. McLain. Talking about the immediacy of the problem, have we not in recent years seen greater outbreaks of antibiotic resistant pathogens, particularly in the last 3 years with haemophilus influenza and gonococcus strains and recently in South Africa with the multiple-resistant pneumonia?

Dr. Bennett. Yes; I think these are all very frightening events. The multiple resistant strains of pneumococcus now being isolated in South Africa are especially noteworthy in that regard.

Any practice that tends to increase the pool of genetic material capable of conferring those resistances is something that I think we all have to be concerned about from a public health standpoint. Certainly, the R factor pool is greatly expanded in the animal kingdom by the use of antibiotics. It is certainly a very, very common practice. Somewhere in the vicinity of about 50 percent of all antibiotics that are used in the United States are used for animal purposes.

Study after study consistently demonstrates that the use of these drugs, especially the tetracyclines, but also penicillins and others, stimulates the development of multiple resistance. Multiple resistance then can, in fact, be transmitted through the chains that have been alluded to by other persons who have testified before your committee. Transmission comes through the foodstuffs, through direct contact with animals, through direct contact with the meat, and through inadequately cooked meat.

Transmission of "nonpathogens" like E. coli containing resistance packages, but also pathogens like salmonella, brucella, leptospirosis, and others that have been alluded to here this morning, take place by such mechanisms.

Mr. McLain. You mentioned your extensive work with salmonellosis. What is salmonella?

Dr. Bennett. Salmonella is an organism that is called a gram negative bacterium because of its staining characteristics under a microscope. It is a common cause of gastroenteritis in humans. It is a common pathogen throughout the animal kingdom. It affects reptiles. It affects warm-blooded mammals of a variety of different sorts. There are many different serotypes—1,600 or so, as of the last count that I am aware. Various salmonella strains can be subdifferentiated into different serotypes. We use these very commonly for tracking purposes epidemiologically to try to determine where the sources of various infections might have come from.

Some serotypes are host-adapted, that is, they tend to exist in large numbers within a particular animal species without causing much in the way of disease in that animal species, although they may be quite virulent for other animal species.

Some serotypes tend to be generally virulent for food-producing animals and humans. Salmonella typhimurium is one of those. But it is a very widespread cause of disability in humans. I would estimate that about 1 in 100 humans in the United States on an annual basis experience salmonellosis. That may not be a tremendously large risk for the individual person per year; that depends on one's frame and reference and value judgments, I suppose. But that does amount to 2.5 million cases per year.

In doing some of the studies that we have done in trying to cost out the expenses of salmonellosis, it appears that about 30 percent of these cases are seen by physicians and that hospitalization is recommended for a reasonable number of these.

Septicemic consequences of the gastroenteritis occurs in about 1 percent of these cases. In these instances the blood stream is invaded. Gastroenteritis is usually not clinically serious, but septicemia is a serious complication.

If we look at the total economic cost just for human salmonellosis—let alone that for animals—we are talking in the vicinity of something that would affect our economy to the tune of about $2.5 billion a year. The average cost per hospitalization for a case of salmonellosis is well over $1,000 for each.

Though it may be trivial in the individual circumstance and most commonly results only in gastroenteritis and diarrhea that keeps somebody temporarily out of work for a day or so, it can in fact be serious. There is a recognized case fatality ratio, which is about 0.003.

So, there is mortality. When you apply this to the large number of human cases, there is a large number of deaths from salmonellosis. Perhaps as many as 9,000 deaths from salmonella per year in the United States.

So, any practice that tends to expand the reservoir of salmonella in animals—and therefore have it transmitted through the animal chain to humans—increases the risk of human disease from salmonellosis. The arguments proposed by the task force back in 1970–71 for antibiotic expansion of the salmonella reservoir are as valid today as they were at the time that they were proposed, and there are several factors that tend to operate to expand the reservoir of salmonella as a result of the subtherapeutic antibiotic uses.

Study after study consistently shows that if you use a drug—be it tetracycline or penicillins—which seem to be the main target of conversation here today—for a period of time, perhaps 30–45 days, even though one starts out with sensitive salmonella strains, inevitably by the end of that time the salmonella will become resistant. It will be not just resistant to the drug that is being used, but very frequently to multiple drugs—the resistance determinants are picked up as a package—including some drugs that may not have even been used therapeutically on that farm.

In any event, once resistant strains develop among the animal kingdom, the continued use in a farm circumstance of a drug to which the organism is resistant, will lead to almost universal colonization of those animals. It requires much less salmonella—which are now resistant to that drug—to colonize another animal. The number of organisms that are excreted by each colonized animal are larger because you are suppressing the competing normal flora, the sensitive flora.

Time after time in studies that have been done since the task force report, resistant salmonella develop even though initially sensitive. Once resistant strains develop, the effects that I have just mentioned will come into play. The net result of all this is an expansion of the number of organisms that are being excreted by the animals.

Animals are sent to abbatoirs. There is an amplification and cross-contamination with the salmonella that are now multiply resistant. Sooner or later, human infections occur.

I suspect this committee has probably heard testimony in regard to the frequency with which our retail meat products are contaminated with salmonella. It is indeed a staggering realization. As much as 30 to 50 percent of poultry that is available on market shelves have salmonella that can be cultured from them. This is a very common problem. Any lapse in cooking practice or cross-contamination in a home or in a restaurant has a potential for producing an outbreak of disease in people.

I have heard the question asked this morning—and I think it is a very good question—"So what if the strains are resistant?" Well, one "so-what" is that it expands the reservoir in the animal kingdom. The second is that it does compromise human therapy.

We have analyzed data available to us about the 1975 strains of salmonella, about 759 strains, that were submitted to the Center for Disease Control. We followed up with questionnaire studies and some other studies of those particular strains. But, in looking at the results from those particular studies, it is pretty clear to us that there have

been substantial changes that have taken place in the resistances of salmonella since an earlier study in about 1970.

Furthermore, it is also clear to us that a number of persons—about 30 percent of those, for example, with bloodstream poisoning with salmonella—initially receive antibiotics to which their infecting organism is resistant. Of course, the clinician, when he starts that drug, does not know it is salmonella. He knows his patient has a serious infection. There are signs of bloodstream invasion, so he uses drugs that he feels will be effective in that circumstance.

Appropriate therapy is critically important in the survival from septicemia; septicemia kills about one-third of the people who develop it. I think this situation speaks very clearly to the potential problems that exist from resistant strains derived from animals, getting to humans.

Now, not all salmonella that occurs in man can be directly traced to animals. But, at least from the standpoint of outbreaks, 50 percent of all cases involved in outbreaks of salmonella are attributable, by epidemiologic means, to meat and meat products from animal sources. It is very likely that endemic, sporadic cases have at least that frequency also.

It is a rough kind of figure for us to discuss. Perhaps as much as one-half of all salmonellosis is directly attributable to animal origins of salmonella.

This is important because the problem of resistances in these organisms may make it more difficult to tract humans. As you look at the composite group experience that 1 percent of cases develop septicemia, and consider that there are 2.5 million cases of salmonellosis each year and that 30 percent of cases with septicemia initially get treated with the wrong drug, then that does add up to morbidity without much question.

I would like to make some further points in regard to the study I alluded to. There has been an increase from 1968 to 1975 in the frequency of resistant strains. There has been more than a doubling of multiply resistant strains in that time.

Furthermore, the serotypes that now show the greatest frequency of multiple resistance are salmonella typhimurim—50 percent and slightly above. Heidelberg and Newport are serotypes that commonly infect both animals and humans. They are the strains found from human infections that are the most frequently positive for multiple resistance.

On the other hand, salmonella enteritidis, which is another different serotype, is common in humans but uncommon in animals, and it shows very low resistance in our 1975 studies.

We have seen a tremendous increase in the number of strains that have resistance to six or more antibiotics. A very small fraction of the strains that we saw pre-1970 were so resistant. Now, it has certainly become a much more common phenomenon.

As disquieting as all of that may be, we have also seen the emergence of chloramphenicol resistance in salmonella. This is a drug that most infectious disease experts would consider to be a drug of choice in the treatment of systemic complications from salmonella. Most infectious disease experts would not recommend antibiotic therapy of uncomplicated salmonellosis. It is septicemia and other complications of sal-

monella that deserve such treatment, and chloramphenocol has been the mainstay in the past of treatment in these areas.

Salmonella Newport—2.5 percent of those isolates are now resistant to chloramphenicol. We have not seen that before. In our 1968 survey, we had no strains that were resistant to chloramphenicol. Quite clearly, things have happened in that time period. Strains are more resistant than they have been before.

There may be other aspects of that particular study that need to be mentioned, especially the separation of those strains into community-acquired or hospital infections. We also attempted to determine whether or not the individual from whom the strain was isolated had been exposed to antibiotics before the culture was obtained and to examine the influence of those factors.

When we looked at community-acquired infections—those infections occurring in people who were in no way associated with a hospital—and in persons who had not been exposed to antibiotics before the culture was obtained, the frequency of multiple resistance in that group of persons was 18 percent. That compares to the overall frequency of multiple resistance of 16 percent in the pre-1970 studies—the overall resistance. And in the 1970 studies we had hospital isolates and community-acquired isolates, isolates that came from treated and untreated patients.

Mr. McLain. What does that tell us?

Dr. Bennett. That tells us that there has been, without much doubt whatsover, an increase in the frequency of resistance of animal strains of salmonella; because it is these strains specifically that could be most credibly attributed to animal sources. Community-acquired infections and the resistance seen there cannot be blamed on therapy of the humans because this group I am talking about had not been exposed to antibiotics prior to the isolation.

Mr. McLain. Let me just follow up a little. The next step, you talk about the increase in resistant strains that we have seen.

Has there been a corollary increase in the morbidity as a result of certain diseases?

Dr. Bennett. I think, from what I said earlier, there probably has been in terms of the difficulty in selecting the right drug for treatment of serious complications of salmonella; though, as Commissioner Kennedy said, it may be difficult in any one individual circumstance to say, "This person suffered as a result of that," and trace that back to the animal.

Mr. McLain. Without tracing it back?

Dr. Bennett. I think so; definitely, from what I was saying. If we have 30 percent of people with systemic complications of salmonella that get the wrong drug in the beginning because of resistances that have developed in these strains, yes; that is compromising the effectiveness of therapy of human salmonellosis—in those circumstances where it is necessary.

I would stress again that uncomplicated gastroenteritis is not an indication, either in animals or in humans, for the use of antibiotics for salmonella. It will simply prolong the carriage of those strains once the antibiotics are stopped and will stimulate the development of multiple resistance. As much as 10 percent of humans with salmonella

who are treated develop multiple resistance as a result of the treatment of uncomplicated gastroenteritis.

We want to save our antibiotics for those circumstances where blood stream invasion occurs or some serious systemic problem occurs. That is when they are really necessary.

Mr. McLain. Let me go to the point of trying to gauge the seriousness of this problem. Dr. Falkow testified that, in fact, resistant salmonella have killed people in some cases because of treatment failure.

Would you be supportive of that statement?

Dr. Bennett. Definitely; there is no question about that. One could look internationally as well as nationally for that sort of information.

The development in recent years of a pandemic of salmonella and shigella infections in Central America is perhaps what Dr. Falkow had as a frame of reference there. Those salmonella strains developed multiple resistance that included chloramphenicol and ampicillin and almost every drug that previously had been known to be effective in the treatment of this disease.

Yes, many people died because there were no adequate antibiotics. Physicians quite naturally tended to use chloramphenicol, which was considered the drug of choice, and did not realize for some time that the strains had, in fact, become truly resistant to chloramphenicol.

There have been other isolated instances. Of course, where one selects a drug, the drug is then instituted in therapy. It is only after the culture result is returned and the susceptibility patterns of the organisms are known that one realizes they have made an error. You start with a particular drug which oridinarily is successful in therapy of a particular disease. But, when the result comes back, you find that the organisms is, in fact, resistant. At that point, of course, one has to modify therapy.

In the United States at least, chloramphenicol has been one of those drugs. If you suspected or knew that you were dealing with a salmonella infection—be it typhoid fever or be it salmonella other than salmonella typhi—chloramphenicol would be the drug one would use for serious complications of that infection.

As I say, we are now running into the circumstance in the United States where chloramphenicol-resistant salmonella are there. They are derived from the animal sources as well, I am sure, as being stimulated in part from human drug exposures.

Certainly, the isolates that I mentioned—those that come from community-acquired infections, where there is no exposure of that human to antibiotics prior to the culture—it is in those circumstances, I think, where we must accept that, in all probability, those organisms are deriving from animal sources through the food production chain.

Mr. McLain. Dr. Bennett, another statement made by Dr. Falkow was that he sees more of a threat today from R plasmid development from the emergence of antibiotics, a greater threat than that threat posed by recombinant DNA research.

Do you have a feeling in that regard?

Dr. Bennett. I think with the sorts of precautions that have been publicized with recombinant DNA work that the statement is probably true, if those precautions are adhered to.

The safety of recombinant DNA research depends very much on the motives of the people that are involved. If someone has a Machi-

avellian scheme that they wish to implement to develop an Andromeda strain, that could certainly be done. I do not believe we have very many scientists that have such objectives; but, if they did, then recombinant DNA research would clearly be the greater hazard, in my opinion.

Mr. McLain. A great deal has been made of the distinction of the various subtherapeutic uses of antibiotics in animal feeds between growth promotion, disease prophylaxis, and feed efficiency.

How do you view the significance of those distinctions?

Dr. Bennett. Very fuzzily. I say that after a lot of study in this area. I am really not sure they can be clearly, Mr. McLain.

The initial charge of the task force involved the assessment of growth promotant use. The distinction between growth promotion and disease prevention has become less and less clear to me as time has passed since 1970.

Earlier this morning reference was made to correspondence between myself and Mr. Lehman of the Food and Drug Administration [see p. 94]. That particular episode derived from a review of the FDA files on ASP 250. I was a task force member at the time. I asked for those files that best exemplified the growth promotant effect that was alleged. I reviewed those files at great length and come to the conclusion that was expressed in that letter.

I could not find evidence of growth promotion independent of disease prevention because growth promotion was observed while infectious disease occurred in the controls.

I really do not know whether growth promotion occurs independent of disease prevention. In many of the trials showing growth promotion, the effect has probably occurred because healthy animals grow better than sick animals. The hooker in this, however, is that, if one tends to use antibiotics continuously for disease prevention, one has to be very careful what diseases they are dealing with. There are some diseases that have organisms that are rather remarkably and stably sensitive to antibiotics: for example, Group A streptococcus and penicillin. We can prevent rheumatic fever by prophylaxis with penicillin. That organism has remained stable in its sensitivity to penicillin through the course of time. We used to think that pneumococcus was stably sensitive to penicillin until this most recent episode in South Africa, where it is now resistant. So, there may be some dangers in making assumption of what is a stable sensitivity.

The point I am getting around to is this. There are some microorganisms one can identify that will produce fairly stably predictable sensitivities. They are not, however, the gram negative organisms: the salmonella and the E. coli. There is rapid transfer of resistances between different genera of these gram negative organisms.

If one intends to prevent disease with these strains on a continuous basis with antibiotics, the result is already known. You will end up with strains resistant to the drug you are using and many other drugs as well. Once that happens, the usefulness of those drugs in treating systemic disease in animals or humans is gone.

If what we are doing is using these antibiotics to prevent disease in animals to achieve growth promotion, then I think any knowledgeable infectious disease expert in government and outside of government will tell you that that is doomed to failure in the long run with

the gram negative organisms, especially in an animal circumstance where there is repeated fecal-oral transmission of strains. It is a perfect circumstance for the development of multiple resistance.

It will not work in the long term, though it might work in the short run. In the short run, you may see some growth promotant effect as a result of the prevention of disease. But it will not be so in the long run, and not on a continuous practice basis.

I might also say in regard to this whole issue of growth promotion that there are several aspects of it that have never really been emphasized in a way that I believe they should have been.

If one looks at the growth promotant data that has been published, you would have to be impressed that the mean values for the medicated animals differ very slightly from those of control animals. We are talking about small differences. Now, from a statistical standpoint, when you are dealing with such small differences in means, you must appreciate that at times therefore the controls must exceed the medicated animals in terms of their performance in growth. And that, in fact, is true. But how frequently? That information is not available to the farmer who may wish to use these compounds.

My own best guess, looking at the data, would be: Maybe 60 percent of the time he has a benefit, and 40 percent of the time he does not for his efforts. But we are talking now about a circumstance where no one can predict in advance, with any consistency, whether the compound is going to have a growth promotant effect or not. Even with the earlier studies that have been done, there was never total consistency in this effect.

Testimony from Dr. Falkow or Dr. Novick alluded to this morning indicated that it is only when you have a "dirty" operation, in essence, that these antibiotics seem to make a difference in growth.

Well, if that is true, it would suggest that perhaps it is making a difference because of short-term effectiveness in preventing disease that may occur, and not through some mysterious mystical "growth promotant" effect that has some other obscure basis.

The lack of development of data since the task force that elucidates effectiveness of antibiotics for growth promotant purposes in the absence of disease prevention further supports this concern. There have been no new data that I have seen that would convince me that this practice is, in fact, effective for "growth promotion," per se.

I would also indicate that there is an interesting exercise that one can perform on some of the extrapolations that have been done on the economics of this practice. If you change just one assumption about growth promotion, you can change a whole host of conclusions.

Suppose you decide, as a farmer, that you will not be altruistic to society as a whole to produce more protein but you will go your own selfish way and simply market your animals at day X, regardless of what they weigh, and that day is the same day as Farmer Jones, your next door neighbor, who uses growth promotants. In this circumstance—even assuming growth promotion occurs and through Farmer Jones has, in fact, produced more protein in his animals—the farmer who decides not to use the growth promotants is at an economic advantage. The feed he is using is cheaper.

It would perhaps be profitable to review the actual analysis of the appendix to the task force report dealing with economics. It is also

supported in the publication, the Journal of Animal Science, which I think it would be interesting to review.

One of the options that was explored was just this. The farmer says, "OK, I've had it. All I am going to do is market my animals at day X." The consequences of that decision are examined in the paper and the same conclusion was reached about the economic advantage shifting to the farmer who doesn't use medicated feed—such actions are not economically advantageous to society as a whole, but they are for the individual farmers.

I guess what I am saying here is that, throughout these deliberations since 1970, there has been so much emphasis upon the acceptance of the growth promotant effect that it is almost unpatriotic to question this. But, yet, when one looks for the hard data to support the true effectiveness of this practice, it is not there. It is very evanescent.

The farmer has never been told, if you use it, maybe 60 percent of the time you will get growth promotion; maybe 40 percent of the time you will not—if those are the right figures. I am not sure what they are, but that probably is about right. In addition, the farmer himself, if he chooses to explore his economic options, might be better off economically if he did not use the product.

There are serious questions, I think, that have not been addressed adequately even by our task force. Such issues contributed to the disputes that I mentioned before over the appendices.

But I wish to reemphasize that the appendices were the focus of the dispute, not the task force report. There was unanimity in that report about the need to restrict penicillins, sulfonamides, streptomycins, and tetracyclines from animal feed.

Mr. McLain. Talking about the advantages to farmers, you are suggesting that there are economic advantages not to use these.

To whose advantage is it, Dr. Bennett?

Dr. Bennett. If one believes the arguments, it is the population at large, the consumer and the community as a whole because more protein—the argument is—of a higher quality is produced by the practice. Since the supply of protein would go down, the price would go up; and the consumer would pay a higher price for the meat. If growth promotant compounds were not used, the price of meat would go up. That is the argument.

Mr. McLain. Is it in the interest of feedlot owners to use antibiotics?

Dr. Bennett. Probably so, in some circumstances. But those are circumstances divorced from growth promotion. There may indeed be circumstances where disease occurs in animals where it does make sense to use therapeutic doses for a short period of time in an effort to control a disease problem that may wipe out or ultimately cause serious economic consequences to the farmer.

There may be other circumstances where the use of antibiotics may, in fact, make good sense from that standpoint. I have mainly addressed "growth promotant" effects and whether it is different from the so-called therapeutic uses or true prophylactic uses. There may be value to feedlot owners from true prophylactic or therapeutic uses.

I am not convinced that the data is available on which to make a clear judgment that growth promotion itself is a phenomenon independent of disease prevention. Nor am I convinced that the so-

called "subtherapeutic" levels are levels that the microbes distinguish as different from "therapeutic" uses. I think it is rather arbitrary as to what is "subtherapeutic." In terms of the development of resistance among strains, I do not think the microbes know the difference. In fact, what we call "low dose" seems to produce the same kinds of effects in terms of the frequency of resistance and multiple resistance as higher doses.

"Subtherapeutic" may be a convenient term, but I doubt that it has a great deal of relevance in the real world. I would have to be shown that it was truly subtherapeutic as established by demonstrating that those doses were not successful in treating the disease.

ASP 250 was previously considered to contain "subtherapeutic" levels and to be a growth promotant compound. Yet, as you look at it, it is preventing disease in animals that are treated with it which appears to contradict the premise that it contains "subtherapeutic" levels. As you look at the combination of drugs in ASP 250 and figure out on a miligram per kilogram basis what the dosage is, we are not talking about "subtherapeutic" levels. I also sincerely doubt that we are talking about "subtherapeutic" levels with a tetracycline level of 50 grams per ton which is now considered "subtherapeutic." It would have to be looked at very carefully. I doubt that the microbes really make these distinctions in accord with present human classifications of "therapeutic" and "subtherapeutic" doses.

Mr. McLain. Thank you, Dr. Bennett.

Trank you, Mr. Chairman.

Mr. Moss. Mr. Wunder?

Mr. Wunder. Thank you, Mr. Chairman.

Dr. Bennett, would not the farmer and the animal handler have the highest degree of exposure to these antibiotics of any group?

Dr. Bennett. Yes; in terms of aerosols that may be created from the feed on the farm. Yes; in terms of the most direct contact with the animals who may be excreting the antibiotics in urine and feces and creating aerosols that are breathed by humans.

From the standpoint, however, of exposure to antibiotics that may derive through the food chain, it depends on whether they consume their own meat or whether they market it elsewhere. All of those avenues of exposure to antibiotics used in animals are possible.

Mr. Wunder. In effect, they would be getting it twice: when they handle it and as it comes through the food chain.

Dr. Bennett. The farmer?

Mr. Wunder. Yes.

Dr. Bennett. Yes; I think the farmers definitely would be exposed to more antibiotic.

Mr. Wunder. Do you have any health records comparing the differences between farmers and nonfarmers?

Dr. Bennett. I am sure that data must exist someplace, but do not personally know of any such data. I believe, though, what you are asking for is something that would be very interesting to obtain in a prospective study.

There have been studies, of course, that have looked at the frequency of resistance bacterial studies among farmers.

Mr. Wunder. What do they show?

Dr. BENNETT. As one might hypothesize, the frequency of resistance is much greater among those farmers who have contact with animals that are medicated.

It is not too far from that observation to a conclusion that those resistances may be important for humans because so much of the infections that occur in humans occur by strains that they themselves carry, the so-called endogenous strains. We all have a flora within our gastrointestinal tract. Most of the urinary tract infections that occur in man, for example, are caused by strains that we carry in our gut. They gain access to the bladder, either at the time of catheterization or gain access through other mechanisms, and cause an infection.

So, if the frequency of multiple resistance is greater among farmers, then one must surely predict that, when they develop infections of that type, that their likelihood of having a resistant strain would be greater than those who do not carry as high a frequency of resistant strains.

So, I think the available studies do support the notion that farmers, either through contact with the flora of the animals and/or through contact with the antibiotics which get aerosolized in a variety of different ways do, in fact, have a higher frequency of carriage of resistant strains than farmers who do not contact animals that are medicated.

Mr. WUNDER. We have had some difficulty through the course of these hearings in identifying the villain. Dr. Falkow said it may be the overuse of antibiotics in hospital therapy. Dr. Kennedy said the same thing.

If you had the resources, could you in fact identify the villain? Is that possible?

Dr. BENNETT. Yes; I think so; although, I think what we are going to identify is the villains because there probably will be more than one in this.

Based on the salmonella data that I have mentioned to you, it is pretty clear that prior exposure to antibiotics is more important than hospitalization in terms of resistances. If you separately compare the resistances of strains from persons with community-acquired and nosocomial infections, there is a 2 to 3 times greater frequency of multiply resistant strains for both types of infection among persons who received antibiotics prior to the isolation of the salmonella.

The impact of hospitalization on the frequency of resistance is not as strong, though it is still clearly there. You can see an increase from about 18-percent resistance of the community-acquired strains, without exposure of those humans to antibiotics before culture, on up to about 24 percent of hospitalized persons who did not receive antibiotics before culture; that is, they acquired the organism after hospitalization but were not treated with antibiotics before the strain was isolated.

There is clearly an impact there of hospitalization. But, quantitatively, I think we already have the data to conclude that hospitalization is not as important as the antibiotic exposure of the humans in terms of the multiple resistance.

Mr. WUNDER. Thank you, Mr. Chairman.

Mr. MOSS. Doctor, I want to thank you. I think you have been an excellent witness. I have thoroughly enjoyed what you have had to say.

Dr. BENNETT. Thank you.

Mr. MOSS. Thank you.

The statement of Congressman Rose will be included in the record at this point.

[Congressman Rose's prepared statement follows:]

STATEMENT OF HON. CHARLES ROSE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NORTH CAROLINA

Mr. Chairman, I wish to compliment you on calling for a review of the Food and Drug Administration's actions in the area of antibiotic use in animal feeds. Last May, from the 23rd through the 25th, my subcommittee held hearings into the drug and chemical impact on the dairy, poultry and honey industries, whose welfare is within my jurisdiction. We also reviewed the regulatory process. Twenty-six out of twenty-nine witnesses responded with information concerning antibiotics, six of whom were scientists. Except for Commissioner Kennedy and our honey people, they unanimously rejected FDA's basis and reasoning for attempting to eliminate at this time the use of antibiotics in animals and feed.

In cattle, antibiotics improve their weight gain by eliminating digestive tract disorders, reduce liver abscesses, aid in controlling subclinical infections and controls anaplasmosis. In poultry, their use increases breeder production, weight gain, feed efficiency and prevents intensive rearing-associative diseases. Their main uses are metabolic, nutrient-sharing and disease control.[1]

The main issues here in conflict with FDA's announced intentions concern the shedding of Salmonella, the transfer of resistant pathogens, the prevalence of bacteria resistance, sources of resistance, and cross-specie contamination. While FDA Commissioner Kennedy conceded in my hearings that his reasoning for his actions were based on speculation that his something negative might happen in the future, all my other witnesses produced testimony that the scientific and practical data does not support his premise. Rather, they have 27 years of known competent field trials and data collected to support the continued low-level and therapeutic use of these drugs in animals and food.

It is well known that the 1969 Swann Report from Great Britain was the precoursor for today's FDA proposals. That report recommended that antibiotics and nitrofurans were to be made available only on prescription, "feed" antibiotics could continue to be given swine without prescription, and therapeutic antibiotics were to be given only upon prescription.

Testimony before our subcommittee reflected little new supporting scientific documentation into the problems of alleged resistance and transference. Indeed, supporting scientific data used by the Department of Agriculture confirms that "there is no evidence of any obvious effect on human health resulting from reductions in drug resistant bacteria" and that "the statistics clearly point to no relationship between the usage of antibiotics in animals, as well as between total use of antibiotics in human medicine, and the incidence of food poisoning from Salmonella infections or any other causes." [2]

Your GAO report of June 27, 1977 mentions the Swann Report, but not the data that illustrates NAFDC's problems with their scientific basis for these changes. The existence of the Braude study refuting Swann is a good example. While you are concerned at the apparent lengthy delay by FDA at not issuing the final regulations governing antibiotics, I must reiterate that the very basis for the change is still not settled in the minds of the scientific community and at my hearings they stated their side well for the need for clear resolution of that issue before proceeding. The Canadian Department of National Health and Welfare now claims "the lack of even a gross measure of the potential risk . . . does not appear to justify a ban in Canada." [3] And we know how highly FDA values their judgment on saccharine. Also, the AVMA now concludes the subtherapeutic use of antibiotics should be permitted without order of the veterinarian * * *" [4] In one sense, FDA has acted prudently in attempting to collect all the data necessary to form a legitimate basis for these changes. On the other hand, I got

[1] "Briefing Paper; Food and Drug Administration Proposal to Restrict the Use of Selected Antibiotics at Subtherapeutic Levels in Animal Feeds," U.S. Department of Agriculture, Economic Research Service, ERS–662, September 1977, p. 2.

[2] "Little Effect of British Antibiotic Restrictions," National Hog Farmers, March 1977, pp. 142, 145.

[3] "Canada Won't Follow U.S. in Banning Certain Antibiotics," Feedstuffs Magazine, September 1977.

[4] "AVMA Reacts to FDA Antibiotic Proposal," Journal American Veterinary Medicine Association, September 1, 1977.

the distinct impression from my witnesses that FDA was refusing to listen to data from them if it reflected information contrary to their theoretical premise, a premise based on scant fact.

At our hearings, we did not get any sense that the scientific community agreed on the resistance and transfer problems, rather they stated in the majority what they did know was not being accepted or heard by FDA. We were shown instead that the regulatory process in this case was to be enforced according to the following maxim: "Although we can point to no specific instance in which human disease is more difficult to treat because drug resistance has arisen from an animal source, it is likely that such problems could have gone unnoticed. The theoretical possibility that drug-resistant pathogens can be produced by antibiotic selection has become a real threat with the emergency of human diseases.[5] Also "The question is whether, in the past, it is possible to say that the use of antibiotics in animal feeds has contributed to human disease problems. That's iffy . . . We can't say that it has not happened.[6]

Testimony before our subcommittee by producers and drug manufacturers directly responsible for the continued health of animals, indicated that scientific and practical evidence, not future speculations, species regarding R-plasmids and E-coli bacteria, that the basic reason for FDA's current dilemma with antibiotics is the result of public fears backlashing from the issue of DES and the more harmful chemical additives or substances finding their way into the food chain. Even USDA observes only partial support for resistance transmissibility between people and animals, no evidence of residue impacts, and "still a lack of evidence that these new antibiotic-resistant organisms have in any way contributed to an increase in infectious diseases of people or animals." [7]

Aside from other legitimate concerns of FDA, we feel the continued low-level use of antibiotics is acceptable for better herd and flock production and we advocate the preventive medicine approach as a way of production, rather than crisis-oriented therapy. This, by the way, is the way our national health policy for humans is heeded and producers should be applauded for their attempts to give consumers healthy "super" chickens and beef, rather than the scrawny "road-runners" of the past. To us, 27 years of practical experience without sick animals or people speak louder than a theoretical supposition engendered by collective anxiety and helped along by our ever-popular press.

We also believe that FDA's actions here are creating a heavy burden by the affected parties. While FDA by law must have reasonable grounds before issuing such changes, the testimony brought before me indicates such extreme conflict as to the scientific basis that it appears unreasonable at this time to determine any basis for change. As it is, we have Senator Talmadge from the Senate Agriculture Committee to address our concerns in their study on the "Implications of Using Drugs and Chemicals in Animal Feeds" and are monitoring another study being done by 24 scientists. Our OTA Assessment will involve an evaluation of benefits to producers and consumers; an appraisal of drug usage risks, an analysis of alternative acceptable risks, and a listing of congressional options. These are questions FDA should have answered before today and then the consumer, for whose sole benefit FDA must consider changes, would have been able to respond properly. As it stands now, they lose again as the costs involved in securing the missing links are obtained by those fighting this rear-guard action and passed on through to them.

During our hearings, witnesses objected to FDA's ignoring their scientific contributions, their potential economic distress and the lack of cooperation in ensuring effective substitutes. Commissioner Kennedy himself has admitted to others in the past that, on this issue, he has more homework to do.[8] FDA has also failed to prove a relationship between human resistance and increased animal resistance. If humans are requiring larger doses due to built-up resistance over the years, would this same problem occur in animals? Yet figures show the same doses are still being given with the same beneficial effects over the past 20 years.

In conclusion, I worry more about the unknown "effective substitutes" of the future which FDA is forcing upon producers, rather than about the continued

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[5] Remarks by Commissioner Donald Kennedy of the Food and Drug Administration before the National Advisory Food and Drug Committee, April 15, 1977, Rockville, Md., pp. 4–5; see also "Transcript of Proceedings," same meeting, p. 270.

[6] Ibid., pp. 274–275.

[7] "Briefing Paper: Food and Drug Administration Proposal to Restrict the Use of Selected Antibiotics at Subtherapeutic Levels in Animal Feeds," U.S. Department of Agriculture, Economic Research Service, ERS–662. September 1977, p. 3.

[8] "Transcript of Proceedings," NAFDC meeting, Rockville, Md., April 15, 1977, p. 269.

proper use of drugs that maintain preventive health measures and ensure healthier animals for human consumption. I am surprised to find, however, that past statements of the commissioner lead me to believe his agency wants to operate by surprise and secrecy while we in the Congress are entering a new era of "sunshine" in our administrative deliberations.[9] I for one, as a strong advocate of the producers right to feed the world with healthy products and also earn a living as nonproducers do, believe the producer and consumer must not be shut out from any part of the regulatory process if they are to be so drastically affected by any changes. That is only fair. I also do not foster attitudes that because food producers are under my legislative jurisdiction that somehow an illegitimate end is served and consumers ignored, nor that my testimony here today would not be welcomed if it ran counter to predetermined ends.

One last word on the economics of these proposed changes; while your GAO report identified a possible conflict of interest problem with one of the NAFDC members, I contend that if this particular regulatory process is finalized too quickly and without recognition of opposing views, then the estimated $2 billion consumer cost impact will smart indeed. In the field of turkeys and broilers, consumers stand to pay some $200 million more for their food.[10] It is my hope that your hearings will encourage FDA to carefully consider all sides of this issue. We do not feel the verdict is in from the scientific community and they deserve to be heard. Thank you. If you have any questions about our hearings, I shall be happy to answer them. A copy of our hearings will be submitted for your record.

Mr. Moss. With that, and with our thanks to the witnesses, the committee is adjourned.

[Whereupon, at 1:05 p.m., the hearing was adjourned.]

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[9] Ibid., p. 278.

[10] "Briefing Paper: Food and Drug Administration Proposal to Restrict the Use of Selected Antibiotics at Subtherapeutic Levels in Animal Feeds," U.S. Department of Agriculture, Economic Research Service, ERS–662, September 1977, pp. 7–9.

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