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The Food and Drug Administration (FDA) needs to establish the safety and effectiveness of antibiotics used in animal feeds. The safety of several antibiotics has not been decided, and FDA has not established regulations specifying when and how most antibiotics used in animal feeds prevent animal diseases and stimulate growth. 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 purpose. Although scientists have determined that several antibiotics failed to meet one or more of the safety criteria, and although many antibiotics have not been proven effective under the approved conditions of use, FDA has permitted the continued use of subtherapeutic levels of these antibiotics in animal feeds. Only three antibiotics met all safety criteria for low-level use in one or more animal species. FDA has not yet published Federal Register notices specifying the conditions under which most antibiotics used in animal feeds are effective. The FDA Commissioner should take appropriate steps to insure that policy advisory committees are used to review only broad policy matters in accordance with FDA regulations and that their members are fully aware of their responsibilities. (SC)

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Statement of
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before the
Subcommittee on Oversight and Investigations
House Committee on Interstate and Foreign Commerce
on
Food and Drug Administration's
Regulation of Antibiotics Used in Animal Feeds

Mr. Chairman and Members of the Subcommittee, we are pleased to appear here today to discuss our report on the Food and Drug Administration's (FDA'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.

Expert advisory panels have reviewed the public health aspects of the use of antibiotics in animal feeds as well as the effectiveness of the use of antibiotics to promote growth and prevent disease in animals.

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 disease. 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:

- The feeding of certain antibiotics to animals has led to the development of antibiotic-resistant bacteria in food animals that may be transmitted to humans.
- The continuous feeding of certain antibiotics to animals has been reported to compromise the treatment of certain animal diseases.
- Limiting the types of antibiotics used in animal feeds is a step toward controlling the resistance problem.

--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, tetracyclines, 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:

- All growth promotion and feed efficiency uses of penicillin be discontinued.
- Growth promotion and feed efficiency uses of tetracyclines be discontinued where effective substitutes are available.
- Disease prevention use of penicillin be discontinued when effective substitutes are available.
- 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 sulfaquinolone 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, DA 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:

- A significant adverse effect on the relative quantity, prevalence, and shedding or excretion of salmonella organisms in animals.
- A significant increase of salmonella organisms in the animal resistant to antibiotics used therapeutically in man or animals.
- A significant increase of coliforms (intestinal bacteria) resistant to antibiotics used therapeutically in man or animals.
- A condition in which disease is more difficult to treat.
- 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 afford 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 (1) a significant increase in the percentage of salmonella organisms resistant to ampicillin, an antibiotic used in human and animal therapy, and (2) 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 (1) there was a significant increase in the percentage of salmonella resistant to tetracyclines, (2) there was an increase in salmonella shedding in medicated versus nonmedicated animals when there were high numbers of drug resistant bacteria, and (3) 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 penicillin and tetracyclines.

GAO RECOMMENDATION
AND AGENCY COMMENTS

We recommended that the Secretary of the Department of Health, Education, and Welfare (HEW) 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 antibiotics--penicillin, tetracyclines, and sulfaquinoxaline--used in animal feeds. HEW said that FDA will issue a Notice of Opportunity for Hearing proposing to:

- Withdraw approval of penicillin for growth promotion purposes.
- Discontinue use of penicillin for disease prevention when effective substitutes are available.
- Restrict the use of tetracyclines for growth promotion to certain minor animal species.
- Restrict the use of tetracyclines for disease prevention to uses for which effective substitutes are not available.

--Continue the present uses 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 sub-therapeutic uses of tetracyclines will be issued shortly.

QUESTIONABLE USE OF 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 issues. 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 pencillin, tetracyclines, and sulfæquinoxaline and seconded a motion which overturned a subcommittee's recommendation that the use of tetracyclines be restricted.

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 discussion 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 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.

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