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The Food and Drug Administration (FDA) has permitted the continued use of low levels of several antibiotics in animal feeds. Findings/Conclusions: The safety and effectiveness of the continued use in animal feeds of several antibiotics, particularly penicillin, tetracyclines, and sulfaquinoxaline, has not been established. The possibility exists that antibiotic-resistant bacteria may develop, and that this resistance may be transferred from animal to man. On April 15, 1977 the FDA decided to restrict the use of these drugs in animal feeds. Questions are raised concerning the use of the National Advisory Food and Drug Committee by the FDA, including insufficient expertise, conflict of interest, and improper involvement in regulatory matters instead of policy only. Recommendations: FDA should determine the safety and effectiveness of antibiotics used in animal feeds based on available data, and withdraw approval of any not shown to be safe and effective. Policy advisory committees should be used only to review broad policy questions in accordance with FDA regulations, and their members made aware of their responsibilities with regard to and the restrictions of conflict-of-interest laws and regulations. (Author/DJE)

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9/19/77

REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES

Need To Establish Safety And Effectiveness Of Antibiotics Used In Animal Feeds

Food and Drug Administration
Department of
Health, Education, and Welfare

Antibiotics are used at low levels in the feed of most food-producing animals to promote growth and prevent disease. Because many of these antibiotics are also used to treat disease in humans or animals, the development of antibiotic-resistant bacteria due to the use of antibiotics in animal feeds may lessen the effectiveness of antibiotics in treating human and animal diseases.

The Food and Drug Administration has permitted the continued use of low levels of a number of antibiotics in animal feed even though the safety and effectiveness of such use has not been established. On April 15, 1977, the agency's Commissioner announced the decision to restrict the use of penicillin, tetracyclines, and sulfaquinoxaline used in animal feeds.



COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

The Honorable John E. Moss, Chairman
Subcommittee on Oversight and
Investigations
Committee on Interstate and Foreign
Commerce
House of Representatives

Dear Mr. Chairman:

In response to a December 10, 1976, request from your office, this is our report on the Food and Drug Administration's regulation of the use of antibiotics in animal feeds. The Food and Drug Administration is part of the Department of Health, Education, and Welfare.

We invite your attention to the fact that this report contains recommendations to the Secretary of Health, Education, and Welfare. As you know, section 236 of the Legislative Reorganization Act of 1970 requires the head of a Federal agency to submit a written statement on actions taken on our recommendations to the House Committee on Government Operations and the Senate Committee on Governmental Affairs not later than 60 days after the date of the report, and the House and Senate Committees on Appropriations with the agency's first request for appropriations made more than 60 days after the date of the report.

We will be in touch with your office in the near future to arrange for copies of this report to be sent to the Secretary and to the four Committees to set in motion the requirements of section 236.

Sincerely yours,

A handwritten signature in black ink, reading "James B. Starks".

Comptroller General
of the United States

REPORT OF THE COMPTROLLER
GENERAL OF THE UNITED STATES

NEED TO ESTABLISH SAFETY AND
EFFECTIVENESS OF ANTIBIOTICS
USED IN ANIMAL FEEDS
Food and Drug Administration
Department of Health, Educa-
tion, and Welfare

D I G E S T

The Food and Drug Administration has permitted the continued use of low levels of several antibiotics, including penicillin, tetracyclines, and sulfaquinoxaline, in animal feeds even though the safety and effectiveness of such use has not been established.

In addition, the agency has made questionable use of its National Advisory Food and Drug Committee to help review the benefits and risks of using antibiotics in animal feeds.

Antibiotics are used at low levels in the feed of food-producing animals to promote growth and prevent or control disease in the animals.

In 1970 about 60 percent of the cattle, almost 100 percent of the chickens and turkeys, and about 90 percent of the swine and veal calves raised in the U.S. were given feed containing antibiotics. This was about 43 percent of the antibiotics used for all purposes.

EARLY CONCERN ABOUT SAFETY

Since about 1960 scientists have worried that low levels of antibiotics in animal feed may lead to the development of antibiotic-resistant bacteria and that this resistance may be transferred between animals and humans.

This is important because many of the antibiotics used in animal feeds are also used to treat disease in people or animals. If resistance developed, antibiotics might not be effective in treating disease.

In 1971 the United Kingdom restricted to veterinarian's prescription the low-level use of certain antibiotics, including

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penicillin and tetracyclines in animal feeds. Antibiotics seldom or never used in treating diseases in humans or animals and which will not lead to the development of resistance to other antibiotics used to treat disease remained available without prescription.

In 1973 Food and Drug Administration regulations provided that approval of current low-level uses of antibiotics in animal feeds would be revoked as of April 20, 1975, unless manufacturers or other interested parties proved the antibiotics were safe and effective according to the agency's criteria. (See ch. 2.)

ANTIBIOTICS FAIL TO MEET SAFETY AND EFFECTIVENESS CRITERIA

The safety of several antibiotics has not been decided. As of April 1, 1977, only bacitracin, flavomycin, and oleandomycin had met all safety criteria. Several antibiotics, including penicillin and tetracyclines, failed to meet one or more of the criteria. They could create a hazard to humans and animals when used at low levels in animal feed.

The Food and Drug Administration had not established regulations specifying when and how most antibiotics used in animal feeds prevent animal diseases and stimulate growth. In the case of penicillin, no data has been submitted to the agency to support its effectiveness in preventing disease.

The claims and dosages for use of tetracyclines and sulfaquinoxaline in animal feeds determined acceptable by agency scientists, but not yet adopted by the agency, do not include most of the current low-level uses for disease prevention and control. (See ch. 3.)

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

The agency must 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.

The Secretary of the Department of Health, Education, and Welfare (HEW) should direct the Commissioner of the Food and Drug Administration to promptly determine the safety and effectiveness of antibiotics used in animal feed and withdraw approval of any antibiotic not shown to be safe and effective as approved. (See p. 34.)

HEW agreed and said that the Commissioner announced on April 15, 1977, the agency's decision to restrict the use of penicillin, tetracyclines, and sulfaquinoxaline used in animal feeds. (See p. 34.)

QUESTIONABLE USE OF ADVISORY COMMITTEE

The Food and Drug Administration's 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 agency regulations, such policy advisory committees deal with broad policy issues and should not get involved in specific regulatory matters.

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

Members of policy advisory committees are to represent diverse interests, education, training, and experience and are not required to have technical expertise in the subjects to be considered. As a result, the committee members did not have sufficient expertise to adequately review the complex regulatory issue. (See pp. 36 and 37.)

One committee member, the president of an animal feedlot, voted on the continued use of antibiotics in animal feed although he had a definite interest in such use. This raised a conflict-of-interest question. (See pp.38-41.)

The feedlot president said the Food and Drug Administration did not discuss conflict-of-interest laws and regulations with him either at the time of his appointment or afterward. He said that had he been informed, he would not have participated in the committee's deliberations on antibiotics. (See p. 40.)

GAO proposed that the Secretary of HEW direct the Commissioner of the Food and Drug Administration to resolve the question of whether the feedlot president, or any other committee member, was involved in a conflict of interest.

HEW said that the agency reviewed the case and found no conflict of interest. HEW said the agency believes all committee members properly participated in the discussion. (See pp. 42 and 43.)

Concerning the use of the National Advisory Food and Drug Committee to review the use of antibiotics in animal feed, HEW said the agency believes the committee was addressing a broad policy issue--one not involving a "particular matter." HEW believes that GAO assumed the committee was addressing a particular matter in the context of Federal statutes relating to conflict of interest.

In GAO's view, the appropriateness of subjects reviewed by Food and Drug Administration advisory committees is determined not by the agency's conflict-of-interest regulations, but by its regulations concerning the use of advisory committees (although review of purely regulatory matters would also involve application of the conflict-of-interest regulations).

GAO believes the agency's regulations on policy and technical advisory committees are based not on whether the issue discussed is a

particular matter in the context of conflict-of-interest regulations, but on whether the issue is a policy or a regulatory issue. (See pp. 43-45.)

The Secretary of HEW should direct the Commissioner of the Food and Drug Administration to guarantee that (1) policy advisory committees are used to review only broad policy matters in accordance with agency regulations and (2) their members are fully aware of their responsibilities with regard to, and the restrictions of, conflict-of-interest laws and regulations. (See p. 46.)

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ABBREVIATIONS

BVM	Bureau of Veterinary Medicine
DESI	Drug Efficacy Study Implementation
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
NADA	new animal drug application
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

On December 10, 1976, we were asked to provide to the Chairman of the House Subcommittee on Oversight and Investigations, House Committee on Interstate and Foreign Commerce, information on the Food and Drug Administration's (FDA's) regulation of antibiotics used in animal feeds. In later discussions with the Chairman's office, we were asked to prepare a chronological summary of information on various panel reviews of antibiotics used in feeds and to review the use of the National Advisory Food and Drug Committee to assist FDA in its current review of antibiotics used in animal feeds.

REGULATION OF ANTIBIOTICS USED IN ANIMAL FEEDS

Basic legal authority for regulating antibiotics in animal feeds is contained in the Federal Food, Drug, and Cosmetic Act, (FD&C Act), as amended (21 U.S.C. 301 et seq.). FDA, part of the Department of Health, Education, and Welfare (HEW), administers the act.

The FD&C Act requires that a sponsor (a manufacturer or other individual or group seeking to ship a new animal drug in interstate commerce) file a new animal drug application (NADA) with FDA and obtain its approval of the drug's safety and effectiveness before introducing such product into interstate commerce. If the new animal drug is to be used in food-producing animals, FDA must also approve the safety of any drug-related residues in food.

The FD&C Act (21 U.S.C. 321(w)) defines a new animal drug as any drug intended for use in animals other than humans:

"(1) the composition of which is such that such drug is not generally recognized * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * * or

"(2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which had not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions; or

"(3) which drug is composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative thereof, except when there is in effect a published order of the Secretary declaring such drug not to be a new animal drug * * *."

FDA's regulatory authority over new animal drugs was broadened by the Food Additive Amendments of 1958 (Public Law 85-929) and the Drug Amendments of 1962 (Public Law 87-781) to the FD&C Act. The 1958 amendments authorized FDA to issue regulations prescribing the conditions under which an animal drug may be safely used in food-producing animals. The 1962 amendments required drug sponsors to demonstrate the effectiveness of animal drugs.

FDA regulations (21 CFR 514.1 et seq.) require that any animal drug residue in meat, milk, or eggs be proven safe and that FDA set a limit, or tolerance, on the amount of the drug allowable in food. FDA may establish a withdrawal period before slaughtering an animal or taking any food yielded by or derived from the animal during which time the animal drug may not be administered (21 U.S.C. 360(i)).

If experience or new scientific data shows an animal drug to be unsafe or ineffective under its approved conditions of use, the FDA Commissioner is required, after notifying the NADA holder of the findings and affording him an opportunity for a hearing, to issue an order withdrawing approval of the NADA (21 U.S.C. 360b(e)(1)).

A Notice of Opportunity for Hearing, which is published in the "Federal Register," affords the NADA holder and other interested parties 30 days to file objections to FDA's proposed actions and to request a hearing to discuss their objections. FDA can either grant a hearing if it determines that the request raises issues of fact or deny a hearing if it finds that the request raises no valid issues (21 CFR 514.200).

Under the FD&C Act (21 U.S.C. 360b(e)(1)) and FDA regulations (21 CFR 514.115), the Secretary, HEW, can suspend approval of a NADA upon determining that use of the animal drug as intended creates an imminent hazard to human health. The holder of the NADA must receive prompt notification of this action and an opportunity for an expedited hearing on the suspension.

FDA's Bureau of Veterinary Medicine (BVM) has primary responsibility for reviewing NADAs which are submitted to

demonstrate the safety and effectiveness of new animal drugs. FDA's Bureau of Foods assists BVM by reviewing data submitted to demonstrate the safety of any drug-related residues in food. 1/

HOW ARE ANTIBIOTICS USED IN ANIMAL FEEDS?

Antibiotics are chemical substances produced wholly or partially by a microorganism which has the capacity to inhibit the growth of, or to destroy, bacteria and other microorganisms. In addition to the true antibiotics such as penicillin and the tetracyclines, other antibacterials such as the sulfonamides and nitrofurans, have been developed. For the purposes of this report, the term "antibiotics" will refer to true antibiotics and the sulfonamides and nitrofurans.

Antibiotics are used in veterinary medicine not only at therapeutic levels to treat animal diseases, but also at subtherapeutic levels to prevent disease, promote growth, and increase feed efficiency (i.e., increase the amount of weight gained per pound of feed consumed). Subtherapeutic levels of antibiotics are administered to food-producing animals, including swine, poultry, and beef cattle, through the use of medicated feeds.

The ability of antibiotics to increase the growth rate of animals (often accompanied by a decrease in the total feed consumption) was discovered in the early 1950s. Since then, the practice of adding antibiotics to animal feed has steadily increased. 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 virtually 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.

1/Up until Jan. 1, 1966, when BVM was established, the Bureau of Medicine was responsible for regulating both human and animal drugs.

The Bureaus of Foods and Drugs were established on Feb. 1, 1970. Before then, the functions of the Bureaus of Foods and Drugs were divided among the former Bureaus of Medicine, Science, and Compliance.

The amount of antibiotic included in animal feeds depends upon its intended function. Up to 50 grams of an antibiotic are added per ton of feed to promote growth and/or increase feed efficiency and 50 to 200 grams are added per ton of feed to prevent disease. Concentrations of antibiotics exceeding 200 grams per ton are considered therapeutic dosages.

Antibiotics used in animal feeds include procaine penicillin, tetracyclines (oxytetracycline and chlortetracycline), tylosin, bacitracin, neomycin sulfate, streptomycin, erythromycin, sulfamethazine, oleandomycin, novobiocin, lincomycin, virginiamycin, furazolidone, nitrofurazone, sulfadimethoxine, sulfaquinoxaline, monensin, sulfathiazole, and flavomycin.

Many of these antibiotics are also used in human therapy.

WHAT IS ANTIBIOTIC RESISTANCE?

A bacterial strain is considered resistant when a genetic change allows it to tolerate a significant increase of an antibiotic concentration. Bacteria may become antibiotic resistant by spontaneous chromosomal mutation (an inheritable change of an individual gene which may alter its functions) or by transfer of a small independent genetic element known as a resistance factor, or R-factor (also known as a resistance plasmid), from a resistant microorganism to a sensitive one. Two other kinds of resistance are phage mediated 1/ and inductive 2/.

A strain of an organism which has developed resistance to one antibiotic may exhibit resistance to other antibiotics to which it has not been exposed, especially if the antibiotics are chemically similar or act in similar ways. In addition, some resistant organisms may transfer antibiotic resistance to other organisms through contact with them. This phenomenon is known as transferable drug resistance.

Although only one or two organisms in a large population of bacteria may initially exhibit a degree of antibiotic resistance, a large population of resistant organisms may quickly develop in the presence of the antibiotic.

1/A phage, or bacteriophage, is a virus of a bacterium that may transfer bacterial resistance.

2/In inductive resistance the antibiotic directly influences the bacterial cell to produce a new chemical within the bacterium that now renders it resistant to the antibiotic.

Although only one or two organisms in a large population of bacteria may initially exhibit antibiotic resistance, a large population of resistant organisms may quickly develop in the presence of the antibiotic. Although the antibiotic is effective against the sensitive microorganisms, its effectiveness against the resistant organisms is limited. Thus, the resistant organisms are able to flourish and develop an antibiotic resistant strain.

CHAPTER 2

ADVISORY PANELS QUESTION

THE SAFETY AND EFFECTIVENESS

OF ANTIBIOTIC USE IN ANIMAL FEEDS

Because of the concern about the increased incidence of bacteria resistant to antibiotics, several expert advisory panels have been established since 1960 to review the public health aspects of antibiotics in animal feeds. These panels also considered the effectiveness of antibiotics to promote growth and prevent disease in animals.

Advisory panels, such as England's Joint Commission on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (referred to as the Swann Commission) and FDA's Task Force on the Use of Antibiotics in Animal Feeds, have recommended restrictions on the use of antibiotics in animal feeds because of the potential human health hazard.

In April 1973, FDA required drug sponsors to initiate and complete within 2 years studies to determine whether human and/or animal health hazards result from the use of antibiotics in animal feeds and whether the antibiotics were effective for their intended purposes. As of April 1, 1977, many such studies had been completed, but FDA had not made a determination about the safety and effectiveness of many antibiotics used in animal feeds. (ch. 3 discusses the status of antibiotics used in animal feeds.)

NETHERTHORPE COMMITTEE EXPRESSES CONCERN

Because of concern about the reported increased incidence of bacteria resistant to antibiotics, in March 1960 England's Agricultural and Medical Research Councils established a joint committee, called the Netherthorpe Committee, to review the use of antibiotics in animal feeds. The Netherthorpe Committee reported in January 1962 that it saw no reason to discontinue the use of antibiotics in animal feeds, but it recommended that such use of antibiotics continue to be monitored. The committee also recommended that if a new antibiotic were developed that had little or no therapeutic application but had growth promotion potential equal to penicillin, chlortetracycline, and oxytetracycline (antibiotics that were being used in medicated feeds in England), the continued use of these three antibiotics be reconsidered.

Subsequently, the Scientific Subcommittee of the Netherthorpe Committee reviewed available data on the transfer of antibiotic resistance from a resistant microorganism to one that was not exposed to the antibiotic concerned.

The subcommittee reported in 1966 that the data on transferrable drug resistance and the growing incidence of antibiotic resistance among strains of Salmonella were grounds for concern but that there was no evidence to suggest that penicillin and tetracyclines in animal feeds had played a part in bringing about the resistance problems. The Swann Commission was established in 1968 following a subcommittee recommendation that a panel with a broader background be established. (See p. 9 for a discussion of the Swann Commission findings.)

EARLY RECOMMENDATIONS OF WORLD HEALTH ORGANIZATION

In a report based on its December 1962 meeting, the World Health Organization's (WHO's) Expert Committee on the Public Health Aspects of the Use of Antibiotics in Food and Feedstuffs concluded that the concentration of antibiotics needed for growth promotion purposes should not exceed 20 grams per ton of the animal's total feed intake. The committee also concluded that antibiotics are effective only in the animal's early growing period and recommended that the addition of antibiotics to animal feed for growth promotion purposes be confined to specific age periods for the various animal species.

At a July 1968 meeting, a joint Food and Agricultural Organization of the United Nations/WHO Expert Committee on Food Additives recommended that effective controls be established over the use of antibiotics in animal feeds. The committee concluded that the addition of growth promotion levels of antibiotics to animal feeds would be unlikely to cause serious problems, but that the addition of disease prevention levels might result in residues in food and in the development of antibiotic-resistant organisms. It suggested that a distinction be made between antibiotics for growth promotion and feed-efficiency and antibiotics for disease prevention, and recommended that antibiotics be available for disease prevention only with a veterinarian's prescription.

EARLY FDA CONCERN

In May 1966, an eight-member FDA Committee on the Veterinary Medical and the Non-Medical Uses of Antibiotics reported its findings about the safety and effectiveness of the use of antibiotics in veterinary medicine to the FDA Commissioner.

The committee, composed of university and hospital affiliated doctors and scientists, reported that they were particularly concerned about the long-term use of antibiotics in animal feeds and the possibility of microorganisms in animals becoming resistant to antibiotics.

The committee recommended that FDA begin studies to monitor the use of antibiotics in food-producing animals to determine if ecologic changes may be occurring under such conditions of use. It further recommended that there be continuous evaluation and surveillance of the safety and effectiveness of the use of antibiotics in food-producing animals.

NATIONAL ACADEMY OF SCIENCES RECOMMENDS RIGID CONTROL

A June 1969 report entitled "An Evaluation of the Salmonella Problem" prepared by the National Academy of Sciences' Committee on Salmonella, at the joint request of FDA and the Department of Agriculture, stated that:

"A review of the literature on antibiotics in animal feeds and on R factors indicates that, as currently practiced, the additives are causing undesirable changes in the balance between host and pathogen.

"Additional research is often of value, of course, and * * * surveillance and other studies * * * should be done, but there are ample data now in the literature to support more rigid control of antibiotics in animal feeds and water."

The committee found the available data adequate to support the following recommendations.

"Only truly low levels of various antibiotics should be used in feeds, in water, and in feed ingredients--those minimal amounts sufficient to promote growth.

"Antibiotics should not be used routinely for prophylaxis [disease prevention] of animals."

SWANN COMMISSION RECOMMENDS
BROAD RESTRICTIONS

England's Swann Commission concluded in a November 1969 report to the Parliament that use of antibiotics in farm animals, particularly at subtherapeutic levels, posed certain hazards to human and animal health, and recommended broad restrictions on their use.

The Swann Commission concluded that:

- Use of antibiotics for growth promotion and other purposes in farm animals has led to a dramatic increase over the years in the numbers of strains of enteric bacteria (bacteria present in the intestines) of animal origin which show resistance to one or more antibiotics.
- Resistant strains of bacteria are able to transmit their resistance to other bacteria.
- There is ample and incontrovertible evidence that humans may commonly ingest enteric bacteria of animal origin, usually through the consumption of food of animal origin.
- There has been an increased tendency for some enteric organisms capable of causing disease in both humans and animals to give rise to generalized infection in humans. If the strain or organism of animal origin shows multiple resistance to antibiotics, treatment of the disease in humans with antibiotics may not be possible.
- Although some organisms such as Escherichia coli (a species of organisms constituting the greater part of the bacteria normally present in the intestines of humans and other animals) may be incapable of causing disease in adult humans, they may be resistant to antibiotics and may transfer that resistance in the human intestine to highly dangerous organisms.
- The use of antibiotics, particularly tetracyclines, for growth promotion purposes has been of major importance in the development of antibiotic resistance in bacteria and the resulting hazards to the human population.

--Although obvious economic benefits have accrued to the livestock industry from the use of penicillin and tetracyclines for growth promotion, similar benefits could be obtained by using antibiotics which have little or no therapeutic application in humans.

The Swann Commission recommended that:

- Permission to supply and use drugs without prescription in animal feed be restricted to antibiotics which (1) are of economic value to livestock production, (2) have little or no use as therapeutic agents in humans or animals, and (3) will not impair the effectiveness of a prescribed therapeutic drug through the development of resistant strains of organisms.
- Therapeutic antibiotics be available for use in animals only if prescribed by a veterinarian who has the animals under his care.

With regard to specific antibiotics, the commission recommended that:

- Legislation permitting the supply and use of chlor-tetracycline, oxytetracycline, and penicillin without prescription be revoked.
- Tylosin and sulfonamides not be available as feed additives without prescription.
- Nitrofurans be available only on prescription, except when they are shown to be devoid of any antimicrobial activity and shown not to cause resistance to their own actions nor to cause cross resistance to any therapeutically useful antibiotic.

England implemented the recommendations of the Swann Commission in March 1971 by issuing its Therapeutic Substances Regulations of 1971 which:

- Restricted the availability of penicillin, chlor-tetracycline, oxytetracycline, tylosin, nitrofurans and most sulfonamides so that they can be obtained only on prescription or written veterinary authority.
- Made available without prescription or written authority two new growth-promoting feed antibiotics (flavomycin and virginiamycin).

--Made available without prescription or written authority two sulfonamides (sulfaquinoxaline and sulfanitran) as coccidiostats (drugs used to treat or prevent coccidiosis, a disease of the intestines).

NATIONAL ACADEMY OF SCIENCES
REVIEWS DRUG EFFECTIVENESS

Pursuant to a contract awarded by FDA, the National Academy of Sciences reported in 1968 on the results of its reviews of the effectiveness of animal drugs originally marketed between passage of the FD&C Act in 1938 and the Drug Amendments of 1962. The Academy's review included penicillin, tetracyclines, sulfaquinoxaline and other antibiotics used in animal feeds.

None of the antibiotics used in animal feeds reviewed by the Academy were found to be "effective" for all labeling claims. While most were classified "probably effective," some were classified "probably not effective" or "not effective." Placement of a drug in any classification other than "effective" required drug sponsors to submit to FDA additional documentation to justify continued marketing of the drug.

The Academy concluded that:

"Claims made regarding 'for prevention of' or 'to prevent' should be replaced with the following: 'as an aid in the control of * * *' or 'to aid in the control of * * *.'

"Data is needed to support revised claims for the control of animal diseases. Control differs from treatment in providing for antibiotic administration to a group of animals containing some with overt signs of disease."

The chairman of the Academy's panel reviewing antibiotics told a BVM official that the Academy panel had found no data to show that the use of antibiotics would prevent disease. He noted that antibiotics can help keep an infection under control, but cannot prevent an infection.

FDA OFFICIALS RECOMMEND
STRONGER CONTROLS OVER
USE OF ANTIBIOTICS

FDA established a Drug Efficacy Study Implementation (DESI) task force to implement the Academy's recommendations.

As a member of the DESI task force, a BVM veterinarian prepared a report in March 1970 on the use of antibiotics in animal feeds. He noted that implementation of the Academy's recommendations would preclude the use of antibiotics in animal feed during periods of stress (such as during shipment or other times when there are no overt signs of disease) and for prevention of animal diseases.

The BVM veterinarian also recommended that action to implement the restrictions on veterinary uses of antibiotics proposed by the Swann Commission not be delayed until it was necessary to react to a hazardous public health problem. As an alternative to immediate implementation of the Swann Commission proposals, the report recommended that the continued use of antibiotics for growth promotion be limited to those species of animals and for that phase of the growth cycle for which available data indicates that antibiotics are useful.

Specifically, the report proposed prohibiting the use of antibiotics for growth promotion in cattle more than 3 months of age, sheep including lambs, swine weighing more than 75 pounds, rabbits, mink, and horses until additional data were submitted to establish their safety and effectiveness in these animals. The report further recommended limiting the maximum dosage level for growth promotion to 20 grams of antibiotic per ton of feed and prohibiting use of antibiotics for preventing animal diseases.

Also, early in 1970, FDA's Acting Director, Division of Veterinary Research, recommended to FDA's Director, BVM, that FDA consider regulating the use of antibiotics in animal feeds based on the importance of the antibiotics for therapy in human and veterinary medicine. He further recommended that FDA curtail the use of antibiotics in animal feeds at disease prevention levels unless adequate data are available to justify their use.

The Acting Director said that FDA had ample evidence that an animal's greatest growth response to antibiotics occurs in the very early phase of its growth cycle. He recommended that FDA require studies to determine the optimal dosages and time periods for which antibiotics should be administered for growth promotion purposes.

FDA TASK FORCE REVIEWS ANTIBIOTICS

In April 1970, FDA established an 11-member Task Force on the Use of Antibiotics in Animal Feeds chaired by the BVM

Director, and composed of experts from FDA, the Center for Disease Control, the National Institutes of Health, and the Department of Agriculture. Four consultants were appointed to assist the task force in reviewing the economic benefits and long-term effects of antibiotics in animal feed. Later, a fifth consultant was added and all consultants became members of the task force, increasing the membership to 16.

In December 1971 the chairman of FDA's task force submitted a copy of its draft report to each member. Seven members were dissatisfied with the report's analysis of the economic impact of banning antibiotics in animal feeds and did not sign the report. Two of them noted that the economic analysis section of the report had not been subjected to the same degree of scrutiny as the sections concerning human and animal health hazards resulting from the use of antibiotics in animal feeds.

In January 1972, the task force chairman transmitted to the FDA Commissioner the task force's final report together with appendixes on human and animal health hazards and economic value and reports on minority opinions. In transmitting the report, the chairman noted the dissatisfaction of some task force members with the data developed on the economic value of antibiotic usage and stated that the appendixes were being included with the report with the understanding that they had not been approved by the task force. The chairman said that he decided against holding another task force meeting to discuss the data on economic value because of 'he need to submit the report to the Commissioner as soon as possible.

Task force report

In its report, the task force concluded that:

- Although antibiotics used in animal feeds either alone or in combination with other drugs may increase the rate of weight gain and feed efficiency, the response varies with the animal's environment, species, age and the amount and type of antibiotic used.
- The safety and efficacy of long-term subtherapeutic feeding of antibiotics for disease control and prevention have not been adequately demonstrated.
- 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.

--Continuous feeding of certain antibiotics to animals has been reported to compromise the treatment of certain animal diseases.

--Limiting the types of antibiotics in animal feeds is a step toward controlling the resistance problem.

The task force established guidelines for evaluating the human health hazard, the animal health hazard, and the efficacy and resultant benefits from the use of antibiotics in animal feeds.

The task force recommended additional research and restrictions on the use of antibiotics in animal feeds. The restrictions recommended by the task force included:

--Prohibiting the growth promotion and disease prevention use in animals of antibiotics that are also used in human medicine and fail to meet the task force's safety and efficacy guidelines by the following dates:

1. January 1, 1973, for tetracyclines, streptomycin, dihydrostreptomycin, sulfonamides, and penicillins used in poultry.
2. July 1, 1973, for tetracyclines, streptomycin, dihydrostreptomycin, sulfonamides, and penicillins used in swine, cattle, and sheep.
3. December 31, 1973, for all other approved antibiotics.

--Limiting tetracyclines, streptomycin, dihydrostreptomycin, neomycin, spectinomycin, penicillins, and sulfonamides to short-term therapeutic use by a veterinarian or with a veterinarian's prescription unless they meet the safety and efficacy guidelines for growth promotion or disease prevention use.

--Prohibiting the use in animal feeds of the antibiotics most critically needed for therapy in humans and animals; i.e. chloramphenicol, semisynthetic penicillins, gentamicin, and kanamycin. Such antibiotics would be available only for short-term therapeutic use in animals when administered by a veterinarian or on his prescription.

Economic value appendix

A subcommittee of the task force developed estimates on (1) the number of animals reared on low levels of antibiotics in their feed, (2) improvements in the rate of weight gained, and (3) improvements in feed efficiency. Based on these estimates, the subcommittee predicted that producers of meat animals would lose about \$414 million annually if the use of antibiotics in animal feeds were banned.

The subcommittee noted, however, that it was not possible to estimate the economic impact of restricting the use of antibiotics since some antibiotics would remain available for growth promotion purposes.

Human health appendix

A subcommittee of the task force evaluated the potential effects on human health of low level uses of antibiotics in animal feed and concluded that:

"* * * the use of low level antibiotics in animal feed for growth promotion and/ or disease prophylaxis [prevention] 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'."

The subcommittee cited the following section of the FDA statement of general policy to support its conclusion.

"The definition [of imminent hazard] does not preclude the finding of an 'imminent hazard' solely because the anticipated injuries are few in number. On the contrary, it is intended to provide notice that even few anticipated injuries may result in a finding of 'imminent hazard' if the nature, severity and duration of the anticipated injury so warrants."

Animal health appendix

A subcommittee of the task force evaluated the available data on the effects on animal health of the low-level use of antibiotics in animal feeds. The subcommittee determined that the use of antibiotics in animal feeds has

- facilitated and increased R-factor transfer in animals;
- resulted in the development of drug-resistant organisms;
- made some animal diseases more difficult to treat;
- caused an increase in the percentage of animal diseases caused by resistant organisms; and
- caused an increase in incidence of resistant strains of salmonella in pigs, poultry, and cattle.

Minority reports

Two minority groups filed objections to parts of the task force report and/or the appendixes. One group of seven task force members expressed the opinion that the evidence presented in the appendix on human health hazards "does not support the statement that there is, in fact, an 'imminent hazard' to human health caused by the low-level feed use of antibiotics for food-producing animals." This group said that there is no sound evidence that the increase in resistant organisms present in animals because of antibiotic feeding has caused disease problems in humans which were not present before the development of antibiotic resistance. They suggested that additional research be conducted to generate reliable data.

A second group of six task force members said that it was not in favor of including a quantitative economic value of the use of antibiotics in animal feeds in the task force report. The group pointed out that it is impossible to balance the economic impact on the meat producing industry against the increased costs of medical care for both humans and animals which could result from the use of antibiotics in animal feeds. It also pointed out that since the task force report indicates that the effectiveness of many antibiotics used in animal feeds is questionable, any quantitative estimate of economic benefit would be based on questionable data and be misleading.

Interpretation of imminent hazard

The Deputy Director of FDA's Bureau of Foods, who also served as a member of the Human Health Hazard Subcommittee of the Task Force, advised the FDA Commissioner by memorandum of January 5, 1972, that he did not completely agree with the

minority views concerning the presence of an imminent hazard. In rebutting the minority views, the Deputy Director said:

"The phraseology 'imminent hazard' can be interpreted in a variety of ways. On the one hand, a reader of the Task Force report could get the impression from the summary statement that should immediate corrective action to remove low level antibiotics from animal feed not be taken, a widespread epidemic of human disease would result. Such in my estimation is not a valid interpretation of the facts of the matter. On the other hand, the reader could interpret the phraseology 'imminent hazard' to connote that human disease has or is likely to result from current practices of using low-level antibiotics widespread in animal feed. This latter interpretation in my estimation is the more correct one."

He further said:

"It has been my personal experience, acting as an epidemiologist and communicable disease control officer for state and local health departments, that in fact quite a few salmonella outbreaks are from food of animal origin, primarily poultry and that severe cases of salmonellosis are very difficult to treat effectively with our present anti-microbial armamentarium because of the phenomenon of bacterial resistance to these therapeutic agents."

NATIONAL ACADEMY OF SCIENCES DISAGREES WITH TASK FORCE

At its July 1972 meeting, the National Academy of Sciences/National Research Council's Ad Hoc Committee on the Use of Antibiotics in Animal Feeds reviewed a position paper prepared by the Academy's Division of Biology and Agriculture recommending that the disease prevention use of antibiotics in animal feeds continue. The position paper pointed out that antibiotics have been used since 1949 with no evidence of harm to humans from their animal uses. The Ad Hoc Committee agreed with the position paper.

The Ad Hoc Committee discussed the FDA task force report and questioned the factual basis upon which the task force's recommendations to restrict the use of antibiotics in animal feeds were made.

In an August 3, 1972, letter to the FDA Commissioner, the president of the National Academy of Sciences asked FDA to defer any action to implement the task force recommendations until after the Academy's Ad Hoc Committee on the Use of Antibiotics in Animal Feeds had completed reviewing the task force report. The Academy president also noted that statements were being developed within the Academy that might be useful in establishing a national position on the use of antibiotics in animal feeds.

On August 21, 1972, the FDA Commissioner advised the Academy president that FDA would not delay implementation of the task force recommendations. In his letter, the Commissioner advised the Academy that although FDA would be interested in the views of the Academy's Ad Hoc Committee, FDA did not believe "that another review by another scientific and medical group will eliminate the need for additional data."

In October 1972, the chairman of the Ad Hoc Committee presented his report on antibiotics to the Academy's Drug Research Board. The chairman strongly criticized the FDA task force's conclusions and recommendations concerning the presence of a public health hazard from the use of antibiotics in animal feeds. At one point he concluded that:

"* * * the classification of a hazard, and particularly of an imminent hazard is totally without justification in fact and from long (22 years) experience. Hence withdrawal of the antibiotics is certainly not warranted on that ground."

The chairman endorsed a position paper prepared by the Academy's Division of Biology and Agriculture which recommended that the disease prevention use of antibiotics in animal feeds continue because of the evidence supporting the economic benefits from such use and the scarcity of evidence that such use is hazardous to human health.

In a dissenting opinion, one member of the Ad Hoc Committee questioned whether a cursory review by the Ad Hoc Committee of the documentation and recommendations of the task force was adequate to set aside the task force's recommendations. He stated that although he did not discern any imminent disaster from the use of antibiotics in animal feed he continues to support the recommendations of the task force.

Objection to Academy
Ad Hoc Committee report

In a December 14, 1972, letter the Chief of the Center for Disease Control's Bacterial Diseases Branch, who served as a member of FDA's task force, notified the chairman of the Academy's Ad Hoc Committee that he objected to the chairman's position in his October 1972 report on antibiotics in animal feeds.

He noted that the Ad Hoc Committee had endorsed the Academy's Division of Biology and Agriculture's position paper before reviewing the documentation contained in the task force report appendixes, and that many task force members felt there was no real chance to constructively modify the Academy's position when they met earlier with the Ad Hoc Committee to discuss the task force report.

IMPLEMENTATION OF THE
TASK FORCE RECOMMENDATIONS

FDA published in the February 1, 1972, Federal Register a proposed regulation concerning FDA policy on the continued use of antibiotics in animal feeds. According to the proposed regulation, FDA would revoke the currently permitted uses of antibiotics in animal feeds for disease prevention and growth promotion. In addition, it would restrict them to short-term therapeutic use by a veterinarian or on a veterinarian's prescription when such drugs are also used in human clinical medicine unless the drugs' sponsors submitted data to demonstrate their safety and effectiveness under specific criteria based on the task force guidelines.

Under the proposed regulation, persons wishing to retain approval of tetracyclines, streptomycin, dihydrostreptomycin, sulfonamides, and penicillins for use in animal feeds after the dates established in the task force report (see p. 14) would be required to satisfy the FDA Commissioner within 30 days after the effective date of the final regulation that adequate and appropriate safety and effectiveness studies based on the prescribed criteria had been undertaken.

FDA received about 380 comments from individuals, livestock and poultry producers, producer associations, and drug and feed manufacturers on its proposed regulations. Some of the comments concerned the (1) differences of opinion within the FDA task force, (2) widespread use of the drugs for about 20 years without injury to the public, (3) practicality of restricting the drugs to prescription use, (4) increased costs of production if antibiotics were no longer available for use in animal feeds, and (5) immediacy and seriousness of the

human and animal health hazards from the current use of antibiotics in animal feeds.

After considering the comments, FDA concluded that restricting certain antibiotics to use under a prescription would insure the continued availability of a useful product while limiting the improper use of a product which has exhibited a safety hazard or failed to show efficacy at subtherapeutic levels. FDA concluded that, because some antibiotics would continue to be available for use in animal feeds, the implementation of the task force report would have a favorable long-term economic effect. FDA further noted that whenever significant questions are raised about a potential or theoretical hazard, sound scientific data must be generated to resolve the issues.

The Director, BVM, established a committee to develop specific criteria for conducting research to determine whether the use of antibiotics in animal feeds creates a hazard to human or animal health and whether such use is effective for its intended purposes. Two members of the committee were members of the task force.

Several meetings were held between the BVM criteria committee and the Animal Health Institute, an industry trade association, in an effort to reach agreement on the criteria. The criteria committee also obtained input from task force members, the Bureau of Foods, FDA's Associate Commissioner for Compliance, and Canadian health officials.

In January 1973, BVM's Special Assistant for Review of Antibiotics in Animal Feeds ^{1/} recommended, after obtaining input from BVM's criteria committee, that up to 2 years be allowed for completion of the studies outlined in the human and animal health safety and effectiveness criteria.

FDA regulations published

FDA published in the April 20, 1973, Federal Register (38 FR 9811), regulations to implement the recommendations of the task force. The regulations stated FDA's intention to withdraw approval of antibiotics for use at subtherapeutic levels in animal feeds no later than April 20, 1975, unless data were submitted by drug sponsors to establish conclusively, using criteria developed by the BVM criteria committee based on guidelines established by the task force (see pp. 27-28),

^{1/}On January 3, 1977, the Special Assistant for Review of Antibiotics in Animal Feeds was made director of BVM's Division of Drugs for Swine and Minor Species.

their safety to humans and animals and effectiveness for their intended purposes.

In the preamble to the regulations, the FDA Commissioner concluded that:

"* * * there is sufficient proof of the safety and effectiveness of the drugs involved to justify continued approval conditioned upon the immediate undertaking of additional tests to confirm safety and effectiveness."

The Commissioner further stated, however, that:

"* * * No additional evidence or data were submitted [since issuance of the task force report] which would justify a conclusion other than that arrived at by the task force regarding the questions of health hazard."

The Commissioner cited two reasons for not adopting the target dates recommended by the task force (see p. 14); (1) the establishment of testing requirements was more complex than the task force realized and (2) there was no legal basis for arbitrarily withdrawing the drugs from the market because the task force did not conclude that there was a lack of proof of safety of the drugs.

On August 6, 1974, FDA published in the Federal Register (39 FR 28382) a listing of 136 antibiotic products for which 17 manufacturers, in response to the April 1973 regulations, agreed to make tests to establish safety and efficacy under BVM criteria. FDA proposed to remove from the market several hundred antibiotic products for which no commitments were made for submission of additional safety and effectiveness data.

On February 25, 1976, FDA published in the Federal Register (41 FR 8282) a revised listing of manufacturers and antibiotic products which had complied with the requirements for continued marketing established in FDA's April 1973 regulations (i.e., filed commitments to make studies).

WORLD HEALTH ORGANIZATION RECOMMENDS RESTRICTIONS

In October 1973, WHO convened a Working Group on the Public Health Aspects of Antibiotics in Feedstuffs in Bremen, Germany, to consider the effects of antibiotics in animal feeds on public health. The Working Group concluded, among other things, that:

"Widespread resistance among bacteria already poses difficulties in human and veterinary therapy and may, if the present trend continues, render antibiotics far less effective than at present, thus depriving mankind of a most valuable weapon against many diseases."

* * * * *

"All uses of antibiotics for human and veterinary purposes, including low-level additions to animal feed for growth promotion, are responsible for the selection of antibiotic-resistant strains in bacteria."

* * * * *

"Certain antibiotics which are not generally used in medical or veterinary therapy are as effective and economic for growth promotion as those which are now commonly used in therapy."

The Working Group recommended that only antibiotics other than those of therapeutic value be used for growth promotion in animals. Specifically, the Working Group recommended that penicillins, tetracyclines, sulfonamides, and antibiotics of the aminoglycoside group, such as streptomycin and neomycin, not be used for growth promotion purposes.

IMPACT OF RESTRICTIONS IN ENGLAND

Officials from BVM, the Department of Agriculture, and Canada's Health Protection Branch visited England in May 1974 and met with several government and professional groups to assess the impact of the restrictions placed on use of antibiotics in animal feeds as a result of the Swann Commission report. (See pp. 10 and 11.) These groups generally felt that the general philosophy of the restrictions was sound and that the availability of alternative antibiotics had made the changes less of a hardship to the farmers.

The Association of British Pharmaceutical Industry reported that decreased sales of the antibiotics which were restricted to therapeutic use had been partially offset by increased sales of the antibiotics still available for feed use. The Royal College of Veterinary Surgeons and the British Veterinary Association felt that the restrictions had had a very positive effect by decreasing the indiscriminate use of antibiotics, improving animal husbandry practices, and creating

a closer relationship between the veterinarian and the animal producer without increasing production costs.

ESTABLISHMENT OF ANTIBIOTICS
IN ANIMAL FEEDS SUBCOMMITTEE

In November 1974, the Secretary of HEW established a National Advisory Food and Drug Committee. The committee's charter stated that the committee would review and evaluate FDA programs and provide advice and guidance to HEW and FDA on policy matters of national significance relating to FDA's statutory responsibility for foods, human and animal drugs, and other FDA-regulated products. The charter further stated that the committee would provide advice and recommendations on many issues of national concern, including the safety of food taken from animals that have been treated with drugs or fed drugs or other additives. The committee, chaired by the FDA Commissioner, consists of 18 members representing the biomedical sciences, industrial technology, education, economics, and public affairs.

In a February 28, 1975, memorandum, the BVM Director recommended to the FDA Commissioner that a joint U.S.-Canadian committee of experts be established to review the adequacy of the safety evidence developed in response to FDA's April 1973 regulations. (See pp. 20 and 21.) At a meeting with FDA's Chief Counsel, the BVM Director expressed concern about the amount of time required to establish such an advisory committee under the formal rules of the advisory committee procedures and the resulting delay in resolving the antibiotic issues. FDA's Chief Counsel suggested that as an alternative, FDA might appoint a subcommittee of a standing advisory committee, such as the National Advisory Food and Drug Committee.

On June 16, 1975, FDA notified the Canadian Government of its intent to establish a subcommittee of the National Advisory Food and Drug Committee and invited Canadian participation as ad hoc consultants. It was proposed that presentations to the subcommittee be made by both U.S. and Canadian Government officials.

The National Advisory Food and Drug Committee, at its June 25, 1975, meeting, voted to create a three-member subcommittee to review antibiotics in animal feeds. The subcommittee, whose members were to be named by the FDA Commissioner, was to be assisted by three consultants and three representatives from the Canadian Government.

By letter dated August 26, 1975, the Canadian Government notified FDA that it would not actively participate on the Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee, but would be willing to help FDA prepare and review the data to be presented to the subcommittee and to appoint a liaison to the subcommittee. The Assistant Deputy Minister of Canada's Health Protection Branch advised FDA that he believed it was premature in establishing the subcommittee because the available information was inadequate as a base on which to make recommendations or take actions. He suggested that any action on antibiotics be deferred until more advanced and impartial research had been completed on the transfer of resistance between humans and animals.

In September 1975 the FDA Commissioner, on the recommendation of the BVM Director, approved the appointment of four consultants representing human medicine, agriculture, bacterial genetics, and veterinary medicine, to the Antibiotics in Animal Feeds Subcommittee. The U.S. Department of Agriculture appointed a liaison to the subcommittee.

ANTIBIOTICS IN ANIMAL FEEDS SUBCOMMITTEE REVIEW

The subcommittee held its first meeting on January 29 and 30, 1976, to discuss data on penicillin and sulfaquinoxaline obtained from drug company submissions, published literature, and FDA research. The charge to the subcommittee was to consider the risks and benefits involved with the use of a number of antibiotics and sulfonamides in animal feeds and to judge whether or not the use of those drugs was worthwhile.

In April 1976 BVM submitted to the Antibiotics in Animal Feeds Subcommittee a summary of the data presented to the subcommittee at its January 1976 meeting together with BVM's conclusions and recommendations concerning continued use of penicillin and sulfaquinoxaline in animal feeds.

BVM recommended that the subtherapeutic uses of penicillin in animal feeds be discontinued, but that no change be made in the present use of sulfaquinoxaline in animal feeds on the condition that the drug manufacturer furnish additional information on the antibacterial activity of the drug, hypersensitivity reactions, and drug metabolism. BVM noted that sulfaquinoxaline is used subtherapeutically only in chickens and turkeys to prevent and control coccidiosis and that the total amount of the drug used for those purposes is very small.

In addition BVM noted that sulfaquinoxaline is not used at all in humans.

During April 26-28, 1976, the Antibiotics in Animal Feeds Subcommittee held its second meeting to consider BVM's conclusions and recommendations on penicillin and sulfaquinoxaline and to discuss data on tetracyclines.

In June 1976, BVM submitted to the subcommittee a summary of the data presented at the subcommittee's April 1976 meeting together with BVM's conclusions and recommendations concerning continued use of tetracyclines. BVM recommended that the subtherapeutic uses of tetracyclines be discontinued.

After additional meetings in July and August 1976, the subcommittee prepared its report on the three antibiotics and submitted it to the National Advisory Food and Drug Committee on January 3, 1977. In its report, the subcommittee concluded that an immediate ban on the use of tetracyclines and penicillin for prevention and control of animal diseases would cause undue disruption of the producing industries, significant increases in livestock and poultry diseases, and a lesser supply of quality animal protein at higher consumer costs.

The subcommittee recommended that all growth promotion and feed efficiency uses of penicillin be discontinued and that growth promotion and feed efficiency uses of tetracyclines be discontinued when effective substitutes are available. There are currently no approved growth promotion or feed efficiency uses of sulfaquinoxaline.

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

The subcommittee also made several general recommendations concerning availability of the drugs and additional reviews and research. It recommended that animal feeds containing penicillin and tetracyclines be limited to sale by approved feed mills and producers or sale upon the order of a licensed veterinarian.

At its meeting 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 both growth promotion and disease prevention uses. The committee also adopted with some modification the general recommendations of the subcommittee.

As of April 1, 1977, FDA had not acted on the National Advisory Food and Drug Committee's recommendations or completed implementation of the National Academy of Sciences' drug efficacy study.

CHAPTER 3

ANTIBIOTICS NOT MEETING

SAFETY AND EFFECTIVENESS

CRITERIA REMAIN ON THE MARKET

The FD&C Act requires FDA to withdraw its approval to market an animal drug if scientific data shows the drug to be unsafe or ineffective under the conditions of use approved in the NADA.

In January 1972, the FDA Task Force on the Use of Antibiotics in Animal Feeds recommended that FDA prohibit the growth promotion and disease prevention use in animals of antibiotics that are also used in human medicine if they failed to meet safety and effectiveness guidelines established by the task force.

FDA's April 20, 1973, regulation implementing the task force's recommendations provided that approval of current subtherapeutic uses of antibiotics in animal feeds would be revoked as of April 20, 1975, unless drug sponsors submitted data which resolved conclusively their safety and effectiveness under specific criteria established by FDA based on the task force guidelines.

Although BVM has concluded on the basis of studies completed on a number of currently marketed antibiotics used in animal feeds, including penicillin, tetracyclines, and sulfaquinoxaline, that they create a human or animal health hazard or 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.

As of April 1, 1977, FDA had determined that only three antibiotics--bacitracin, flavomycin, and oleandomycin--have met all human and animal health safety criteria for subtherapeutic use in one or more animal species. FDA had not established regulations specifying the conditions under which most antibiotics used in animal feeds are effective.

SAFETY AND EFFECTIVENESS CRITERIA

FDA established specific 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 the intended purposes. The criteria

were developed in consultation with industry representatives, members of the Task Force on the Use of Antibiotics in Animal Feeds, FDA's Bureau of Foods, and Canadian health officials.

FDA's April 1973 regulations required all antibiotic sponsors to submit studies demonstrating the safety of their products under the human and animal health hazard criteria. Only those drug sponsors whose antibiotics were not previously reviewed for effectiveness under the National Academy of Science's drug efficacy study (see p. 11) were required to submit data on the effectiveness of their products. The effectiveness of antibiotics reviewed by the Academy was being determined under the Drug Efficacy Study Implementation program.

Safety criteria

FDA's safety criteria describe controlled studies drug sponsors are required to make to demonstrate that their products meet the human and animal health safety criteria.

Under the FDA human health safety criteria, the use of subtherapeutic levels of an antibiotic in animal feeds can be considered a human health hazard if such use creates:

- A significant adverse effect on the relative quantity, prevalence, and shedding (excretion) of salmonella organisms in animals.
- A significant increase of salmonella organisms in animals resistant to antibiotics used therapeutically in humans.
- A significant increase of coliforms (bacteria resembling Escherichia coli) resistant to antibiotics used therapeutically in humans and capable of transferring this resistance to bacteria in humans.
- Residues of the antibiotic, its metabolites (compounds a substance breaks down to in the body), or its degradation products in food which are capable of causing an increase in the prevalence of disease-causing bacteria or an increase in the resistance of disease-causing bacteria to antibiotics used in human therapy.

According to FDA's animal health safety criteria, the use of subtherapeutic levels of an antibiotic in animal feed is a health hazard if such use creates:

- A significant adverse effect on the relative quantity, prevalence, and shedding of salmonella organisms in the animal.
- A significant increase of salmonella organisms resistant to antibiotics used therapeutically in animals.
- An adverse effect on animals due to a significant increase in the resistance of coliforms to antibiotics used therapeutically in animals.
- A continuing increase in the amount of antibiotics necessary to achieve the desired response.
- A condition in which disease is more difficult to treat.

In addition, both human and animal health safety criteria provide that a human and animal health hazard exists if an antibiotic enhances the capability of bacteria to cause disease. Drug sponsors were not required to complete studies addressing this criterion within the 2-year period established by the April 1973 regulation. However, continued marketing of an antibiotic was contingent upon the initiation of such studies within the 2-year period.

Effectiveness criteria

FDA's Task Force on the Use of Antibiotics in Animal Feeds concluded that:

"Data indicate that antibiotics in feed are effective for the control of clinical illness for animal diseases when the proper antibiotic is used selectively at therapeutic levels for short periods of time. The efficacy and safety of long-term feeding of subtherapeutic levels of antibiotics for animal disease control and prophylaxis [prevention] has not been adequately demonstrated."

FDA's criteria for evaluating the effectiveness of antibiotics for disease prevention require that labels of antibiotics for which disease control or prevention

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

Drug sponsors of combinations of two or more antibiotics are required to show that the combination meets the criteria for single antibiotics and that each antibiotic in the combination contributes to the total effect of the product.

ANTIBIOTICS FAIL TO MEET SAFETY AND EFFECTIVENESS CRITERIA

A number of the antibiotics subject to FDA's April 1973 regulations, including penicillin, sulfaquinoxaline, and tetracyclines, have been determined by BVM scientists to have failed to meet one or more of the safety or effectiveness criteria.

Penicillin

In April 1976, BVM submitted its conclusions concerning the continued use of subtherapeutic levels of penicillin in animal feeds to the Antibiotics in Animal Feeds Subcommittee. BVM concluded that several of the human and animal health safety criteria had not been met. BVM found that there had been a significant increase in the percentage of salmonella organisms resistant to ampicillin, an antibiotic used in human and animal therapy, and that penicillin promoted an increase in the percentage of intestinal bacteria resistant to more than one antibiotic and capable of transferring resistance to humans.

As of April 1, 1977, the effectiveness of subtherapeutic levels of penicillin for disease prevention had not been established. FDA regulations (21 CFR 558.460), however, permit the use of penicillin at subtherapeutic levels in the feed of chickens and turkeys for the prevention of several diseases. BVM's Acting Director, Division of Drugs for Avian Species, did not know whether these claims were reviewed under the National Academy of Sciences' drug effectiveness study (see p. 11). He said that no data had been submitted to FDA to support the effectiveness of penicillin for disease prevention in chickens and turkeys.

The Academy reviewed the use of penicillin in animal feeds for bloat (a disturbance of the digestive system) protection in cattle. It found that penicillin was "probably effective" for this purpose but recommended that its use be limited to a 1- to 2-week period. FDA, however, has not issued a Federal Register notice limiting the use of penicillin for bloat protection to a 1- to 2-week period, or specifying other acceptable conditions of use.

Sulfaquinoxaline

Also in April 1976 BVM submitted its conclusions concerning the continued use of subtherapeutic levels of sulfaquinoxaline in animal feeds to the Antibiotics in Animal Feeds Subcommittee. BVM found no reason for concern about the safety of sulfaquinoxaline based on the limited data available, but concluded that additional data were needed before a final determination could be made. It was noted that sulfaquinoxaline is not used for therapy in humans.

FDA regulations (21 CFR 558.15) permit the continuous use of subtherapeutic levels of sulfaquinoxaline in the feed of chickens, turkeys, and rabbits for the prevention of coccidiosis. According to data BVM submitted to the Antibiotics in Animal Feeds Subcommittee, sulfaquinoxaline is generally used for treatment rather than prevention of disease outbreaks. BVM told the subcommittee that sulfaquinoxaline is an excellent drug for treatment of disease outbreaks, but that other drugs are available that are as good or better at preventing disease. BVM also noted that growers do not want to cause resistance to sulfaquinoxaline by using it for disease prevention because they may later need it to treat disease outbreaks.

Accordingly, BVM advised the Antibiotics in Animal Feeds Subcommittee that the subtherapeutic use of sulfaquinoxaline in poultry feed was "not really practical." BVM's Acting Associate Director, Division of Drugs for Swine and Minor Species, recommended in a January 26, 1977, memorandum to BVM's Acting Director for Surveillance and Compliance, that a Federal Register notice be issued specifying the acceptable claims and dosages for sulfaquinoxaline in animal feeds. The memorandum recommended acceptance of sulfaquinoxaline claims for control and treatment of coccidiosis in chickens and turkeys when used at therapeutic dosages for short periods, and for control and treatment of coccidiosis in rabbits when used in feeds for up to 20 days. The notice would not

include a claim for continuous use of sulfaquinoxaline at subtherapeutic levels for disease prevention and control in chickens and turkeys; any claims not included would be disallowed for the product.

As of April 1, 1977, the Federal Register notice had not been issued and sulfaquinoxaline remained available for continuous subtherapeutic use in animal feeds.

Tetracyclines

BVM submitted its conclusions concerning the continued use of subtherapeutic levels of tetracyclines in animal feeds to the Antibiotics in Animal Feeds Subcommittee in June 1976. BVM indicated that some of the animal and human health safety criteria had not been met. BVM found that (1) there was a significant increase in the percentage of salmonellae resistant to tetracyclines based on studies submitted to FDA and reports from diagnostic laboratories and hospitals, (2) there was an increase in salmonella shedding in medicated versus nonmedicated animals when there were high numbers of drug resistant bacteria, (3) there was a large reservoir of tetracycline-resistant Escherichia coli and data were available to support the spread of Escherichia coli between animals and humans, and (4) data were available indicating a trend toward compromise of subsequent therapy of salmonellosis (a form of food poisoning caused by salmonella).

The effectiveness of subtherapeutic levels of tetracyclines in animal feeds for disease prevention and control has not been established. FDA regulations (21 CFR 558.15, 21 CFR 558.128, and 21 CFR 558.450) permit the continuous use of subtherapeutic levels of tetracyclines in the feed of chickens, turkeys, swine, calves, and cattle to prevent or control a number of disease conditions.

In the National Academy of Sciences' drug efficacy study, tetracycline products for use in animal feeds were classified either "probably effective" or "probably not effective." The Academy recommended that claims made "for prevention of" or "to prevent" a disease be replaced by claims to "aid in the control of" the disease and that product labels should warn that to be effective for disease control, treated animals must consume a therapeutic dosage.

As in the case of sulfaquinoxaline, BVM's Acting Director, Division of Drugs for Swine and Minor Species,

recommended to BVM's Acting Associate Director for Surveillance and Compliance in December 1976 that a Federal Register notice be issued setting forth the acceptable claims and dosages for tetracyclines in animal feeds determined under the DESI program. Claims not specifically covered in the notice would be disallowed. The notice would not include most of the current claims for disease prevention and control. In some cases the notice would also change the dosage for disease control from continuous feeding of subtherapeutic levels to short-term therapeutic use.

As of April 1, 1977, FDA had not issued the notice and tetracyclines remained available for continuous subtherapeutic use in animal feeds.

Status of other antibiotics

FDA has determined that three antibiotics--bacitracin, flavomycin, and oleandomycin--have met all human and animal health safety criteria for subtherapeutic use in one or more animal species. According to BVM's Special Assistant for Review of Antibiotics in Animal Feeds, most of the antibiotics not reviewed for safety by the Antibiotics in Animal Feeds Subcommittee are not used as human drugs and were not designated as priority items by the FDA task force and thus were not given the same priority for review as penicillin and tetracyclines. He stated that based on its review of the safety studies submitted on the other antibiotics, BVM has required additional data or clarification on many of the studies. He expects the safety determinations to be completed on all of the drugs by the end of 1977.

BVM's Special Assistant said that two of the antibiotics not reviewed by the subcommittee--streptomycin and neomycin--are used in human therapy and pose some of the same hazards as penicillin. He said that they are used in animal feeds only in combination with other drugs and will be removed from the market because of a lack of effectiveness of the drug combinations in which they are used rather than lack of safety because the justification for the removal process is more clearcut.

In 1971, FDA identified approximately 2,500 combination products for use in animal feeds which contained an antibiotic. Since that time FDA has withdrawn sanction of approximately 2,300 of this number either because available information failed to provide substantial evidence of effectiveness of the drugs or because the drug's sponsor

informed FDA that (1) the drug combination was no longer being marketed, or (2) there was no interest in its continued marketing. According to BVM's Special Assistant for Review of Antibiotics in Animal Feeds, BVM plans to remove many of the remaining combination products from the market on the grounds of lack of effectiveness but has not yet taken final action to withdraw any of the drugs.

BVM's DESI Coordinator for the Division of Drugs for Swine and Minor Species said that FDA has not established the effectiveness of any of the antibiotics used in animal feeds which were found less than effective by the National Academy of Sciences.

CONCLUSIONS

The FD&C Act requires that FDA withdraw its approval to market an animal drug if scientific data shows the drug to be unsafe or the drug is not shown to be effective under approved conditions of use.

BVM has concluded that a number of the antibiotics currently marketed for subtherapeutic use in animal feeds, including penicillin, tetracyclines, and sulfaquinoxaline, have been shown to either create a hazard to human or animal health or have not been shown to be effective for some of their disease prevention uses. FDA, however, has permitted the continued use of the products. A determination with regard to the safety and effectiveness of many other antibiotics has not been made.

RECOMMENDATION TO THE SECRETARY, HEW

We recommend that the Secretary, HEW, direct the Commissioner, FDA, 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.

AGENCY COMMENTS

HEW agreed with our recommendation and advised us that the FDA Commissioner, on April 15, 1977, announced the agency's decision to restrict the use of three antibiotics--penicillin, tetracyclines, and sulfaquinoxaline--used in animal feeds. FDA, according to HEW, considered the

recommendations of the National Advisory Food and Drug Committee, its Antibiotics in Animal Feeds Subcommittee, and the BVM in reaching its decision on the three antibiotics.

HEW said that FDA will issue a Notice of Opportunity for Hearing and a proposal to withdraw approval for the use of penicillin for purposes of growth promotion or feed efficiency for all species of food-producing animals and to discontinue the use of penicillin for disease prevention when effective substitutes are available. According to HEW, FDA will also propose to restrict the use of tetracyclines to growth promotion in certain minor animal species and to disease control claims for which effective substitutes are unavailable. HEW further stated that FDA will propose that penicillin and tetracyclines be available for use only upon the written order of a licensed veterinarian.

HEW advised us that FDA will propose to continue the present uses for sulfaquinoxaline, which is approved only for disease prevention in chickens, turkeys, and rabbits, but limit its use to those periods of time for which its use is necessary because of the threat of disease.

CHAPTER 4
QUESTIONABLE USE OF
POLICY ADVISORY COMMITTEE

The National Advisory Food and Drug Committee was established to review and evaluate FDA's programs, and provide advice on policy matters of national significance. The committee consists of members with diverse interests, education, training, and experience. 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 use of antibiotics in animal feeds which, we believe, 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. Also, one committee member voted on the continued use of antibiotics in animal feeds, although he had a definite interest in such use. We referred the matter to FDA who decided that such action did not constitute a conflict of interest.

LACK OF TECHNICAL
EXPERTISE

FDA regulations (21 CFR 2.330) 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 policy advisory committees are to represent diverse interests, education, training, and experience, and are not required to have technical expertise in the subject matter to be considered by the committee. By contrast, members of technical advisory committees are required to possess expertise in the particular subject matter to be addressed.

FDA advises prospective members of the National Advisory Food and Drug Committee that they should be knowledgeable in one or more of the following fields: biomedical sciences, industrial technology, education, economics, and public affairs. Membership of the Committee included physicians, veterinarians, executives from FDA-regulated industries, and public affairs specialists.

FDA established the Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee to weigh the benefits and risks involved in the use of a number of antibiotics in animal feeds. The subcommittee reviewed and made recommendations on three antibiotics--penicillin, tetracyclines, and sulfaquinoxaline. According to BVM's Special Assistant for Review of Antibiotics in Animal Feeds, the subcommittee included a physician and a veterinarian who had limited training in antibiotic resistance, which was given in the medical school curriculum, but had no members with expertise in the subject. He said that the subcommittee had the help of four consultants with expertise. The consultants were not, however, voting members of the subcommittee. One of the consultants noted in an April 8, 1976, letter to FDA that

"* * * it is clear to me that the members of the advisory committee [Antibiotics in Animal Feeds Subcommittee] and several of the consultants are not fully versed in the R. plasmid field."

BVM's Special Assistant for Review of Antibiotics in Animal Feeds said that although the National Advisory Food and Drug Committee also had several physicians who would have had some training in antibiotic resistance, only one committee member, a microbiologist, might be considered an expert in antibiotic resistance. After attending the January 1977 meeting of the National Advisory Food and Drug Committee, a research microbiologist from BVM's Division of Veterinary Medical Research noted in a February 7, 1977, memorandum to the Acting FDA Commissioner that:

"It was apparent, and by their own admission, that most committee members were not familiar with the subject under discussion. Their decision was influenced by three panel members * * * whose sweeping generalities [sic] were not based on scientific fact and nevertheless went unchallenged."

REFERRAL OF POSSIBLE
CONFLICT OF INTEREST

Under FDA regulations (21 CFR 2.330), advisory committee members are special Government employees ^{1/} and are subject to the conflict-of-interest laws and regulations.

Section 208 of 18 U.S.C. prohibits a special Government employee, in the course of his official duties, from participating personally and substantially in a particular matter in which, to his knowledge, he, his spouse, minor child, partner, or a profit or nonprofit enterprise with which he is connected has a financial interest. An agency may by general rule or regulation waive certain financial interests which are considered too remote or inconsequential to affect the integrity of a special Government employee's services.

Pursuant to 18 U.S.C. 208, FDA, in November 1976, published a regulation granting policy advisory committee members a waiver from conflict-of-interest restrictions of certain financial interests (41 FR 229, Nov. 26, 1976). The regulation states that:

"The [FDA] Commissioner has determined that, because members representing particular interests, e.g., a representative of labor, industry, consumers, or agriculture, are included on [policy] advisory committees specifically for the purpose of representing such interests, any financial interest covered by 18 U.S.C. 208(a) in the class which the member represents is irrelevant to the services which the government expects from them and thus is hereby exempted pursuant

^{1/}The term "special Government employee" has been broadly defined in 18 U.S.C. 202(a) as an officer or employee of the Government who is retained, designated, appointed, or employed to perform, with or without compensation, temporary duties either on a full-time or intermittent basis for a period of not more than 130 days during any period of 365 consecutive days. In general, the term "special Government employee" is limited to those persons who have an employee-employer relationship with the agency concerned (see 5 U.S.C. 2105(a)).

to 18 U.S.C. 208(b) as too remote and inconsequential to affect the integrity of their services."

A similar waiver was not granted to voting members of technical advisory committees.

In a recent report to the Congress, "The Food and Drug Administration's Financial Disclosure System for Special Government Employees: Progress and Problems" (FPCD-76-99, January 24, 1977), we reported that:

"In cases involving members of the National Advisory Food and Drug Committee, we found that restrictions were not placed on their activities, even though they had interests with FDA-regulated industry. FDA officials stated that because members of this committee were involved with broad policy issues in a number of areas, which do not directly relate to products or firms, restrictions were not appropriate."

The apparent use of the National Advisory Food and Drug Committee as a technical advisory committee to review the use of antibiotics in animal feeds raised the question of whether the participation of one member of the Committee in the deliberations created a conflict of interest within the meaning of 18 U.S.C. 208.

The member is the president of Farr Farms, an animal feedlot. He was appointed to the committee in May 1976, 11 months after the committee was asked to assist FDA in reviewing the use in animal feeds of several antibiotics. He did not participate in the subcommittee's work.

Feedlots, such as Farr Farms, are the primary users of subtherapeutic levels of antibiotics in animal feeds. In data presented to the Antibiotics in Animal Feeds Subcommittee, FDA estimated that 75 percent of the cattle slaughtered in the United States are raised in feedlots and that 80 percent of the cattle raised in feedlots are given subtherapeutic levels of antibiotics. FDA estimated that the economic impact on feedlots of banning the use of tetracyclines (the antibiotics most widely used in animal feeds) could run as high as \$680 million a year.

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. These regulations would, of course, apply to voting members of technical advisory committees. The president of Farr Farms took an active role in committee deliberations on the three drugs. According to the transcript of the January 24, 1977, National Advisory Food and Drug Committee meeting, Mr. Farr said that:

"* * * I have been feeding them [antibiotics] ever since they have been approved, more than 25 years. I do not really believe that we have a viable alternative, for example, with bacitracin compared to the tetracyclines. First of all, it does not control the liver abscesses that are a problem. It does not control the antiplasmosis which is getting to be a larger and larger problem as the years go on. Originally we used these products and thought more of the growth possibilities, but as we have used them over the years and as our livestock operations, both cattle and hogs, have become more concentrated in larger efficient operations, but as you bring more animals together in a larger situation, then these subtherapeutic uses are much more important.
* * *

The president subsequently seconded a motion to overturn the recommendation of the Antibiotics in Animal Feeds Subcommittee that the use of tetracyclines be restricted.

The president of Farr Farms' participation occurred entirely in open session at the only meeting the committee held to discuss the subcommittee's report on antibiotics. His interest in using antibiotics was known to the other committee members and to the public observers at the meeting.

The president of Farr Farms advised us that FDA did not discuss conflict-of-interest laws and regulations with him either at or after the time of his appointment. He said that had he been advised of the potential conflict, he would not have participated in the deliberations on antibiotics. He also stated that although banning the use of tetracyclines would have an economic impact on feedlot owners, it would not result in a competitive advantage to any one owner.

Explanation of FDA's Chief Counsel

According to FDA's Chief Counsel, it appears that FDA's original rationale for referring the issue of antibiotics in animal feed to the National Advisory Food and Drug Committee was to obtain the judgments of a broad, diverse group on the overall benefit-risk issue--essentially a policy question. He said that as the Antibiotics in Animal Feeds Subcommittee worked on the subject it became involved in details of particular drugs, and, by the time its recommendations were made to the full committee, they were probably more specific than FDA had originally contemplated. This development, he said, gave a clearer regulatory focus to the committee's final recommendations, although it remains unclear whether the issue debated and resolved by the committee can be considered a particular regulatory matter within the meaning of the conflict-of-interest laws or regulations.

The Chief Counsel said that the agency's original rationale for referring the antibiotics issue to the committee also helps explain why FDA was inattentive to the conflict of interest question presented by the president of Farr Farm's participation in the committee's only discussion of the subject, for the agency had not expected that the subject would be treated as a regulatory matter. He said that the fact that the president of Farr Farms was appointed to the committee after the subject of antibiotics in animal feed had been referred to the committee may also explain FDA's failure to identify the appearance of the problem before it occurred.

Subsequently, FDA decided that the actions of the president of Farr Farms did not result in a conflict of interest. (See p. 42 .)

CONCLUSIONS

FDA regulations state that policy advisory committees will advise on only broad, general matters. Although FDA originally expected the committee to perform a broad and general function, we believe that in reviewing and making recommendations concerning specific antibiotics, the National Advisory Food and Drug Committee acted more as a technical advisory committee than as a policy advisory committee. As a result, the committee members should have possessed specific expertise in antibiotic resistance.

Also, before using a policy advisory committee for what was essentially a regulatory function, FDA should have made committee members aware of their responsibilities with regard to conflict-of-interest laws since the exemption from such laws applies only to policy advisory committees.

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 or the Antibiotics in Animal Feeds Subcommittee in the review of antibiotics used in animal feeds, contributed to conflicts of interest.

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, in fact, 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.

HEW said that a conflict of interest did not exist because the committee's discussion did not center around a "particular matter" as defined by FDA regulations, and the president of Farr Farms, who is a user of animal drugs,

- would not enjoy a unique or distinguishable competitive advantage as a result of FDA's decision to continue or discontinue the use of antibiotics in animal feeds;
- specifically referred to his background while presenting his views for consideration;
- was invited to serve on the committee in order to contribute his thoughts on issues to which his background was relevant;
- had relevant experience with disease incidence, animal husbandry, and large-scale feedlot operations to assist the committee in considering both the benefits and risks of antibiotic use in animal feeds;

--was not a member of the subcommittee of the National Advisory Food and Drug Committee established to do an indepth analysis and make recommendations to the full committee on the future of antibiotics used in animal feeds, and was not appointed to the parent committee until 11 months after the subcommittee was appointed; and

--made all of his comments in open session, subject to the scrutiny and criticism of the public.

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 believes that the committee was addressing a broad policy matter in accordance with FDA regulations.

According to HEW, we apparently assumed that in its discussion of antibiotics used in animal feeds 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 it does not believe such a position is consistent with common Government practice and that it doubts that the objective of the Office of Management and Budget's recently issued Circular No. A-63 (Transmittal Memorandum No. 5, Mar. 7, 1977) to achieve "truly balanced membership" on advisory committees could be realistically achieved if our interpretation of broad policy matters was applied throughout the Government.

HEW said that FDA's Staff Manual Guide, in stating that "Policy guidelines and procedures affecting a number of products are generally not considered particular matters by FDA," is consistent with the recent American Bar Association definition of particular matter (Formal Opinion 342) which states that "* * * the term seems to contemplate a discrete and isolatable transaction or set of transactions between identifiable parties."

FDA, according to HEW, believes that in considering antibiotics in animal feed, the National Advisory Food and Drug Committee was not discussing a particular matter as defined above. HEW noted that (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. HEW said that if such broad topics are to be considered particular matters, then the implications for all Federal advisory committees are substantial. HEW also

said that FDA has obtained on the National Advisory Food and Drug Committee the "truly balanced membership" stressed in the Office of Management and Budget circular. According to HEW, if all advisory committee members who have relationships with commercial enterprises that might in some remote way be affected by a policy issue were not permitted to participate, the value of their expertise would be lost.

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). In its comments 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 it is a policy or a regulatory issue.

According to FDA regulations, policy advisory committees, such as the National Advisory Food and Drug Committee, deal with broad policy issues and should not get involved on specific regulatory matters. (See p. 36.) HEW's comments note 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. During the course of our review, FDA's Chief Counsel acknowledged that 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.

Members of technical advisory committees are required to possess expertise, which the National Advisory Food and Drug Committee lacked, in the subject matter to be discussed. Furthermore, before members on a technical advisory committee participate in a given issue, there must be a determination that there is no conflict of interest. This is in recognition of the fact that technical advisory committees inherently consider specific technical or scientific issues (i.e., regulatory matters), any one of which

may well, in a given case, be considered a "particular matter" 1/ within the meaning of the conflict-of-interest laws.

It is because of this potential for a conflict of interest on a matter before a technical advisory committee that leads us to question use of a policy advisory committee as a technical advisory committee. We believe that the National Advisory Food and Drug Committee, in reviewing penicillin, tetracyclines, and sulfaquinoxaline, was acting as a technical committee. Since its members belong to a policy advisory committee, they may have considered themselves exempt from the conflict-of-interest rules.

As a result, FDA should have made committee members aware of their responsibilities with regard to and the restrictions of conflict-of-interest laws and regulations before they participated in the committee's discussion on antibiotics used in animal feeds rather than making such a determination afterward.

1/Although FDA's Staff Manual Guide states that "policy guidelines and procedures affecting a number of products are generally [emphasis added] not considered particular matters by FDA," the Guide goes on to state in discussing the review of over-the-counter drugs that:

"* * * some products have an ingredient or component that is product specific, i.e., unique to that product. Where a monograph or standard deals with a product specific ingredient, the Agency would consider a decision respecting the ingredient [emphasis added] to be a particular matter * * *."

It is debatable whether the committee in reviewing penicillin, tetracyclines, and sulfaquinoxaline was reviewing product specific ingredients within the meaning of the definition.

**RECOMMENDATIONS TO
THE SECRETARY, HEW**

We recommend that the Secretary, 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) their members are fully aware of their responsibilities with regard to and the restrictions of conflict-of-interest laws and regulations.

CHAPTER 5

SCOPE OF REVIEW

We examined pertinent legislation, regulations, and practices relating to FDA's regulation of animal drugs; examined FDA records relating to the past and present regulation of antibiotics used in animal feeds; and reviewed advisory panel reports on the safety and effectiveness of antibiotic use in animal feeds.

We also interviewed officials of FDA, in Rockville, Maryland, and Washington, D.C.; the Center for Disease Control in Atlanta, Georgia; and physicians and scientists from various hospitals and universities.

Our review of FDA's regulatory activities was restricted primarily to the period since January 1972, when an FDA task force recommended that restrictions be placed on the use of antibiotics in animal feeds.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

Apr 25 1977

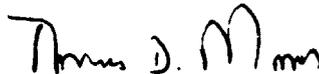
Mr. Gregory J. Ahart
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Need to Establish the Safety and Effectiveness of Antibiotics Used in Animal Feeds." The enclosed comments represent the tentative position of the Department and are subject to re-evaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,



Thomas D. Morris
Inspector General

Enclosure

DEPARTMENT COMMENTS TO GAO DRAFT REPORT ENTITLED,
"NEED TO ESTABLISH THE SAFETY AND EFFECTIVENESS OF
ANTIBIOTICS USED IN ANIMAL FEEDS"

GAO RECOMMENDATION:

That the Secretary, Department of Health, Education, and Welfare should direct the Commissioner of Food and Drugs 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 low-level use in animal feeds of any antibiotic not shown to be safe and effective under the approved conditions of use.

DEPARTMENT COMMENT:

We concur. Since the last meeting of the National Advisory Food and Drug Committee (NAFDC), the Food and Drug Administration has considered the recommendations of the NAFDC, its subcommittee, and the Bureau of Veterinary Medicine. On April 15, 1977, the Commissioner announced the Agency's decision to restrict the uses of antibiotics in animal feed. The Commissioner stated that:

"Our conclusion that the potential risks outweigh the benefits of continued unrestricted use of the tetracyclines is based upon this logic: (1) recent information indicates that human *E. coli* and those of other mammals are not separate and distinct strains, but interchangeable between man and other species; (2) the R-plasmids themselves are likely not distinguishable into 'human' and 'animal' types; (3) evidence suggests that individuals having close contact with animals or with uncooked meat have significantly elevated populations of resistant enteric bacteria; and (4) R-plasmids can be exchanged in humans between enteric bacteria and some non-enteric pathogens.

Continued unrestricted use of the tetracyclines will result in selective pressure that will continue to increase the pool of drug-resistant bacteria in our ecosystem. 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 emergence of human diseases (typhoid and childhood meningitis) caused by ampicillin- and chloramphenicol-resistant salmonella and haemophilus. The point is that known routes of transfer exist by which antibiotic use in animals can contribute to such threats.

In short, the evidence indicates that enteric microorganisms in food animals and man, their R-plasmids, and human pathogens form a linked ecosystem of their own 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 we consume it by the use of antibiotics for non-medical purposes in animals, is diminished in man. The experts on infectious disease and public health on the Task Force, the Subcommittee, and others whom I consulted in connection with this action, are overwhelmingly of this view."

The Agency is initiating the legal procedures for restricting the uses of penicillin, tetracyclines, and sulfaquinoxaline in animal feeds. A Notice of Opportunity for Hearing and a proposal to withdraw approval for the use of penicillin for purposes of growth promotion and/or efficiency for all species of food-producing animals and to discontinue the use of penicillin for disease prevention when effective substitutes are available will be issued. The Agency will also propose to restrict the use of tetracyclines to growth promotion in certain minor animal species, and to disease control claims for which effective substitutes are not available. The Agency will, further, propose that penicillin and tetracyclines be available for use only upon the written order of a licensed veterinarian. FDA will propose to continue the present uses for sulfaquinoxaline, which is approved only for disease prevention in chickens, turkeys, and rabbits; but to limit its use to those periods of time for which its use is necessary because of the threat of disease.

GAO RECOMMENDATION:

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.

DEPARTMENT COMMENT:

This recommendation is based upon GAO's opinion that the NAFDC was addressing something other than a "broad policy matter" when it reviewed the use of antibiotics in animal feeds. Apparently, the GAO report assumes that the committee was addressing a "particular matter" in the context of the Federal Statutes relating to conflict of interest. We do not concur with this assumption.

In January, 1977, the General Accounting Office published an extensive report on FDA's Financial Disclosure System for Special Government Employees. During the course of that review, FDA urged the auditors

to comment on the definitional problems and legal questions relating to the phase, "particular matter." The Agency referred the auditors to the recent American Bar Association definition of particular matter (Formal Opinion 342) which stated that "...the term seems to contemplate a discrete and isolatable transaction or set of transactions between identifiable parties." In interpreting the Statutes, FDA's Staff Manual Guide 3118.2 is consistent with the ABA opinion in stating that "Policy guidelines and procedures affecting a number of products are generally not considered particular matters by FDA." The final GAO report did not take issue with FDA's definition, and in fact, urged prompt finalization of FDA's regulation.

The Agency is of the opinion that in considering antibiotics in animal feed, the NAFDC was not discussing a particular matter as defined above. Antibiotics encompass a number of individual products; there are multiple manufacturers of these products; and the use of antibiotics in animal feeds is widespread throughout the United States. If such broad topics are to be considered "particular matters," then the implications for all Federal advisory committees are substantial. The Office of Management and Budget recently issued a circular (A-63) which stresses the need for "truly balanced membership" on advisory committees. FDA has obtained this balance on the NAFDC, but if all members who have relationships with commercial enterprises that might in some remote way be affected by a policy issue were not permitted to participate, the value of their expertise would be lost. We do not believe this is a unique problem with the NAFDC.

For example, the Pharmaceutical Reimbursement Advisory Committee was established to advise the Assistant Secretary for Health concerning the establishment of maximum costs that will be reimbursable for specific drugs purchased from pharmacies and hospitals under the MEDICARE and MEDICAID programs. If these are "particular matters," then the members who are associated with pharmacies, hospitals, or drug manufacturers would not be able to contribute their obvious expertise. Similarly, the Clearinghouse on Environmental Carcinogens, established by the National Cancer Institute which reviews the carcinogenic potential for chemical substances that are prevalent in today's environment, includes members who are employed by firms which use industrial chemicals. Their expertise would also be lost if the use of chemicals by many firms constitutes a "particular matter."

In summary, we do not believe that the GAO position is consistent with common government practice and we doubt that the objective of the Office of Management and Budget to achieve "truly balanced membership" could be realistically achieved if GAO's interpretation of broad policy matters were applied throughout the Federal Government.

GAO RECOMMENDATION

That the Secretary of HEW direct the FDA Commissioner to promptly resolve the apparent conflict of interest involving the president of Farr Farms and determine whether participation of other members of the National Advisory Food and Drug Committee and/or the Antibiotics in Animal Feeds Subcommittee in the review of antibiotics used in animal feeds created a conflict of interest.

DEPARTMENT COMMENT

FDA has reviewed the participation by the president of Farr Farms in the January 24, 1977 discussion of the use of antibiotics in animal feed and has determined that there was, in fact, no conflict of interest created by his contributions to that discussion. This individual who raises cattle for slaughter is a consumer of animal drugs. Since a majority of cattle raised in the United States are given antibiotics in their feed, he would not enjoy a unique or distinguishable competitive advantage as a result of FDA's decision to continue or discontinue the use of antibiotics in animal feeds.

Further, his background was well known to all NAFDC members and, in fact, he specifically referred to his background while presenting his views for consideration. As we pointed out in our comments on the previous recommendation, the OMB circular initiating a reevaluation of all existing advisory committees specifically calls for committees to have "truly balanced membership." The intent of the circular is obviously not only to have truly balanced memberships representing all sectors of life, but also to have full participation of all members. Indeed, the president of Farr Farms was invited to become a member of the NAFDC in order to contribute his thoughts on issues relevant to his background. In reaching a decision about the use of antibiotics in animal feed, the Food and Drug Administration had to consider the benefits of their use as well as the risks associated with that use. As president of Farr Farms, his experience with disease incidence, animal husbandry, and large-scale feed-lot operations was relevant to the decision process.

It should also be noted that he was not a member of the NAFDC subcommittee established to do an in-depth analysis and make recommendations to the full committee on the future of antibiotics used in animal feeds; and he was not appointed to the NAFDC until some eleven months after the subcommittee was established. Furthermore, all his comments were made in open session, subject to the scrutiny and criticism of the general public. This individual did not seek to influence the FDA to make a decision that would have given him an advantage over his competitors, nor was the discussion centered around a "particular matter" as defined by FDA regulations.

In conclusion, we believe the participation by the president of Farr Farms and that of all the committee members to have been proper.

PRINCIPAL HEW OFFICIALS
RESPONSIBLE FOR ADMINISTERING ACTIVITIES
DISCUSSED IN THIS REPORT

	<u>Tenure of office</u>	
	<u>From</u>	<u>To</u>
SECRETARY OF HEALTH, EDUCATION AND WELFARE:		
Joseph A. Califano, Jr.	Jan. 1977	Present
David Mathews	Aug. 1975	Jan. 1977
Caspar W. Weinberger	Feb. 1973	Aug. 1975
Frank C. Carlucci (acting)	Jan. 1973	Feb. 1973
Elliot L. Richardson	June 1970	Jan. 1973
Robert H. Finch	Jan. 1969	June 1970
Wilbur J. Cohen	Mar. 1968	Jan. 1969
John W. Gardner	Aug. 1965	Mar. 1968
Anthony J. Celebrezze	July 1962	Aug. 1968
ASSISTANT SECRETARY FOR HEALTH (note a):		
James F. Dickson (acting)	Jan. 1977	Present
Theodore Cooper (note b)	Feb. 1975	Jan. 1977
Charles C. Edwards	Mar. 1973	Jan. 1975
Richard L. Seggel (acting)	Dec. 1972	Mar. 1973
Merlin K. Duval, Jr.	July 1971	Dec. 1972
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov. 1965	Feb. 1969
COMMISSIONER, FOOD AND DRUG ADMINISTRATION:		
Donald Kennedy	Apr. 1977	Present
Sherwin Gardner (acting)	Dec. 1976	Apr. 1977
Alexander M. Schmidt	July 1973	Nov. 1976
Sherwin Gardner (acting)	Mar. 1973	July 1973
Charles C. Edwards	Feb. 1970	Mar. 1973
Herbert L. Ley, Jr.	July 1968	Dec. 1969
James L. Goddard	Jan. 1966	June 1968
Winton B. Rankin (acting)	Dec. 1965	Jan. 1966
George P. Larrick	Aug. 1954	Dec. 1965

a/Until December 1972 the title of this position was Assistant Secretary (Health and Scientific Affairs). Before March 1968, the Commissioner, Food and Drug Administration, reported directly to the Secretary of HEW. Therefore, prior incumbents of this office are not listed.

b/Acting Assistant Secretary of Health from February to May 1975.