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UNITED STATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

In re:

Petition to Suspend New Animal Drug Applications for Sub-Therapeutic Uses of Penicillin and the Tetracyclines in Animal Feed	)	Docket No. 84P-0399

DECISION OF THE SECRETARY
DENYING PETITION

I. INTRODUCTION

The issue presented to me is whether the approved use of subtherapeutic levels of penicillin and the tetracyclines (chlortetracycline and oxytetracycline) in animal feed should be declared an "imminent hazard" under section 512(e) of the Federal Food, Drug, and Cosmetic Act ("the Act"), 21 U.S.C. 360b(e), and approval of the new animal drug applications (NADAs) for that use summarily suspended before the completion of the ordinary procedures for withdrawal of approval. I conclude that immediate suspension is not warranted.

II. BACKGROUND

Penicillin and the tetracyclines are added to animal feed for food-producing animals at low -- or subtherapeutic -- levels for various purposes. These include promotion of

growth and prevention or reduction of the incidence of certain diseases. The drugs used for these purposes are generally used continuously in the feed for extended periods of time.

During the 1960's, scientists became concerned about the potential effect on the public health of the use of subtherapeutic levels of antibiotics in animal feed. The concern grew out of the discovery that the drug levels are high enough to select for antibiotic-resistant strains of bacteria in an animal's gut, and that antibiotic resistance can be transferred from one bacterial cell to another, including from "harmless" bacteria to bacteria that can cause disease (pathogens) in humans. Because such pathogens would be able to survive in the presence of antibiotics to which they were resistant, it was theorized that effective treatment of disease caused by the antibiotic-resistant pathogens would be more difficult or impossible.

In 1977, the Food and Drug Administration (FDA) initiated proceedings to withdraw approvals for the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed. In 1978, Congress directed the FDA to hold the withdrawal proceedings in abeyance until additional studies were completed.

Subsequently, the National Academy of Sciences reviewed the then-existing data and in 1980 recommended additional research initiatives to the FDA. In response to a recommendation by the House Appropriations Committee that further research be done and that regulatory action be withheld

pending completion of that research, the FDA contracted for two studies to be conducted on this issue. FDA is currently reviewing the data presented in those and other studies.

The Natural Resources Defense Council (NRDC) submitted this petition in November 1984 to declare the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed an imminent hazard, under section 512(e)(1) of the Federal Food, Drug, and Cosmetic Act. On January 25, 1985, FDA held a public hearing on this matter at which thirty-five presentations were made, representing a wide range of scientific opinion.

In its petition, at the public hearing, and in a document filed after the hearing, NRDC contended that 100 to 300 deaths (depending on which of its two estimates is used) and 270,000 non-fatal cases of salmonellosis*/ may occur each year which are attributable to the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed.

III. PROCEDURES AND CRITERIA FOR SUSPENSION OF A NEW DRUG APPLICATION

A. The Statutory Framework

As Secretary of Health and Human Services, I and my delegate, the Commissioner of Food and Drugs, are responsible for the administration of the Act. The Act requires that new animal drugs be the subject of an approved NADA before they may be shipped in interstate commerce. To

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*/ NRDC focused on Salmonella infections as a model, but pointed out that resistance also occurs in other pathogenic bacteria.

obtain approval for a NADA, a manufacturer must establish, among other things, that the drug is safe and effective. The safety of a new animal drug for use in food animals involves both the safety of the drug for the treated animals and the safety of human food products derived from the treated animals.

The Act requires the withdrawal of approval of a NADA if evidence shows that the drug is unsafe for use under the conditions for which it was approved, or if the manufacturer can no longer sustain its burden of demonstrating that the drug is safe and effective in light of new evidence. The usual administrative procedure for withdrawing approval of a NADA is a time-consuming one. It includes notice to the manufacturer of an opportunity for a hearing, a full evidentiary hearing before a hearing officer if the disputed issues warrant, and a decision by the Commissioner of Food and Drugs based on the hearing record.

The Act also provides for a special summary procedure that permits the Secretary to suspend approval of a NADA temporarily in advance of a hearing, and thereby remove the drug from the market, if the Secretary finds that the drug represents an "imminent hazard" to the health of man or of the animals for which the drug is intended. After suspending approval, the Secretary must provide the manufacturer with an expedited evidentiary hearing on whether the drug should be removed permanently from the market. This special authority is vested solely in the Secretary, and may not be delegated.

B. Criteria for Suspension

In determining whether to suspend approval of the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed because they present an imminent hazard to public health, the following criteria apply:

• The likelihood that, after the customary administrative process is completed, the drugs will be withdrawn from the general market.

• The severity of harm to humans or treated animals that could be caused by the drugs during the completion of administrative proceedings to withdraw the drugs from the market.

• The likelihood that the drugs will cause such harm to humans or treated animals while the administrative process is being completed.

• The risk to animals currently taking the drugs and to humans that might be occasioned by the immediate removal of the drugs from the market, taking into account the availability of other therapies and the steps necessary for the treated animals to adjust to these other therapies.

• The availability of other approaches to protect the public health.

Similar criteria were previously used in considering whether to suspend the approvals for phenformin, propoxyphene, and phenylbutazone and oxyphenbutazone. In re New Drug Application for Phenformin, p. 34-35 (July 15, 1977); In re Petition to Suspend New Drug Applications for Propoxyphene, p. 8-9 (Feb. 15, 1979); In re Petition to

Suspend New Drug Applications for Phenylbutazone and Oxyphenbutazone, p. 5-6 (Aug. 7, 1984). In addition, they were upheld by a Federal district court in connection with the phenformin proceeding. Forsham v. Califano, 442 F.Supp. 203 (D.D.C. 1977).

IV. EVALUATION OF THE USE OF SUBTHERAPEUTIC LEVELS OF PENICILLIN AND THE TETRACYCLINES IN ANIMAL FEED UNDER THE CRITERIA FOR SUSPENSION OF APPROVAL

Upon receiving the NRDC petition, I asked FDA Commissioner Frank E. Young, M.D., Ph.D., and his scientific colleagues to evaluate it and advise me on the proper response. After that evaluation, Dr. Young forwarded to me FDA's recommendation, including a transmittal memorandum ("Memorandum") and a detailed analysis of the specific issues raised in the petition ("Recommendation"). My decision is based on the Memorandum, the Recommendation, and the Administrative Record. My evaluation of the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed under the criteria set forth above in section III (B) follows.

A. Severity and Likelihood of Harm to the Public Health

NRDC contends that 100 to 300 human deaths and 270,000 non-fatal cases of salmonellosis could result each year from the use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds during the course of administrative proceedings to withdraw approval.

NRDC reasoned that use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds results in the development of strains of bacteria that are resistant to these and other drugs. The petitioner further contended that resistant Salmonella are responsible for a majority of deaths from Salmonella infections, and that nonfatal cases of the disease caused by resistant strains are more difficult to treat. According to one study cited by the petitioner, a large proportion of Salmonellosis outbreaks due to resistant strains are traceable to food from animals or from the animals themselves.

I agree with FDA that in this case, to justify the existence of an "imminent hazard," the petitioner must demonstrate that antibiotic resistance caused by the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed has a significant impact on the outcome of a significant number of cases of human salmonellosis. Such antibiotic resistance could adversely affect the treatment and outcome of salmonellosis if an antibiotic to which the Salmonella had developed resistance as a result of subtherapeutic animal feed use were used for treatment or if antibiotic resistance so developed were responsible for the Salmonella having greater virulence.

FDA points out that Salmonella are ubiquitous in the environment and frequently grow to infective levels in high protein foods. Consumption of food in which infective levels of Salmonella have not been eliminated by proper food preparation practices is the primary pathway of human

salmonellosis, whether due to antibiotic resistant or sensitive Salmonella. Moreover, because there is no evidence that use of subtherapeutic levels of antibiotics in animal feeds affects the total population of Salmonella organisms, there is no reason to believe that eliminating such antibiotics from animal feeds would affect the total number of cases of human infections by Salmonella.

Finally, although it is reasonable to predict that use of subtherapeutic levels of antibiotics in animal feeds will result in some increase in the number of Salmonella infections due to resistant strains of the bacteria, it is difficult to estimate reliably whether that use also results in a significant increase in the burden of disease. This difficulty is due, in part, to the existence of other sources of resistant bacteria, including use of antibiotics to treat illness in humans. Memorandum at 2-3.

FDA also points out that most Salmonella infections in people are uncomplicated diarrheal diseases which resolve in 2-14 days without antibiotic treatment. Indeed, antibiotic treatment is not helpful or recommended in those cases.

Salmonellosis can be life-threatening when it occurs in other than the intestine. This type of salmonellosis occurs in less than ten percent of people reported to have salmonellosis. Antibiotic treatment is clearly recommended in these cases. However, only a very small percentage of Salmonella are resistant to the drug of choice for treatment of that type of salmonellosis -- chloramphenicol -- and even

then, alternative therapies are available. Recommendation at 26-27. Thus, the treatment of human Salmonella infections is not significantly affected by antibiotic resistance.

The petitioners cited a study by Holmberg, Wells, and Cohen.*/ FDA has reviewed this study and although in the outbreaks of Salmonellosis examined, the death rate from resistant Salmonella infections was higher than for infections from antibiotic-sensitive Salmonella, the study did not show, and the authors did not conclude, that resistant Salmonella are quantitatively more virulent.

FDA determined that currently available data are inconclusive as to whether resistant Salmonella cause more severe disease (are more virulent) than susceptible Salmonella. Recommendation at 27-28. In fact, several medical experts testified at the public hearing that multiply resistant organisms may be less virulent than sensitive strains.

Although FDA recognizes that there are certain situations in which resistant Salmonella may account for additional cases or adverse outcomes of salmonellosis among patients who are already taking antibiotics for other infections, FDA believes relatively few persons are affected by these

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*/ S.D. Holmberg, et al., "Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S. Outbreaks," 225 Science 833-835 (1984).

situations. Recommendation at 29. FDA notes that, over the last decade, large increases in deaths from Salmonellosis have not been reported to either the Centers for Disease Control or the National Center for Health Statistics. Recommendation at 28.

FDA also points out certain weaknesses in NRDC's calculations estimating the incidence of harm. The 4.2 percent death rate from resistant Salmonella obtained from the Holmberg study is based on a very limited, nonrandom sample. Moreover, the Holmberg study does not include sufficient information to determine if Salmonella were the primary cause of the deaths, or were merely present in persons whose deaths resulted from other causes.

NRDC's estimate that 69 percent of outbreaks from resistant Salmonella are attributable to animal sources is also based on a very limited, nonrandom sample of outbreaks. NRDC further made an unsupported estimate that half of the resistant Salmonella attributable to animal sources are resistant because of the use of subtherapeutic levels of penicillin and the tetracyclines in animal feed. FDA points out that data to estimate accurately the proportions of Salmonella that are resistant for that reason are, simply, not available. Recommendation at 29-31. Because of these limitations, I agree with FDA that these data and estimates cannot be relied upon to show a significant incidence of harm.

B. Other Factors

If I had determined that the risks associated with the use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds were so high as to constitute an "imminent hazard," I would then have considered whether other factors militated against immediate suspension of approval notwithstanding the risks. As noted above, these other factors include the possible harm from immediate suspension, the likelihood that approval would be withdrawn in the subsequent administrative proceeding, and the possibility that the public health could adequately be protected by means short of suspending the drugs' approval for this use. Because I have accepted FDA's conclusion that no "imminent hazard" is presented, it is unnecessary to address these other criteria.

V. CONCLUSION

I conclude that NRDC has failed to establish that the continued use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds present an imminent hazard to public health that warrants immediate suspension of their approvals for that use.

Margaret M. Heckler
Secretary of Health and Human Services

Dated: NOV 13 1985