The Future of Antibiotics and Other Additives in Livestock Feed

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It is a pleasure for me personally to speak to you this morning, and to represent the Center for Veterinary Medicine of the Food and Drug Administration, as a co-sponsor of the conference. I commend your program chairman, Dr. Hoffsis, and the organizers of this conference. It is an excellent program on an important aspect of veterinary medicine.

A number of factors or issues come to mind when one thinks of the future of antibiotics and other chemicals as additives in livestock feed. Broadly speaking, one must decide what impact the use of any particular substance in animals has on the animal's health; the impact on the efficiency of producing meat, milk or eggs; and what impact the practice may have on man's health. In addition to these very real and largely scientific considerations, we (you and I) are also very much aware of public opinion and the perceptions of the urban American consumer when one speaks of using an "additive" in livestock or poultry feeds. Often times the word additive, antibiotic, or hormone conjures up a feeling in the consumer that something bad, poisonous, or at least unnecessary is being thrust into our diet. The perception factor is one that is with us today and it should be kept in mind as you and I go about our business of practicing the very best veterinary medicine possible.

My talk this morning will focus on several current issues involving the use of drugs in animal feeds. I will discuss these issues from the FDA perspective and in each case, I will give you my views on the future. My perspective is obviously not the only one and my crystal ball is not always 100% accurate, so when we are into the question and discussion time, I will be interested in your opinions, as well.

Perhaps the feed issue that is number one these days in the minds of the livestock producer, the veterinarian, and the consumer is the issue of the long-term, subtherapeutic uses of antibiotics in animal feeds. To understand this issue, one must be familiar with just a bit of its history.

During the 1960's, scientists became concerned about the continued or long-term use of subtherapeutic antibiotics in animal feed and its potential effect on both human and animal health. This concern resulted from the fact that these drug levels are high enough to select for antibiotic-resistant strains of bacteria in an animal's gut even though the drugs are not being used to treat diseases. This phenomenon results in suppressing or killing the drug-susceptible bacteria which normally inhabit the gut and allows the drug-resistant strains to predominate. Even more alarming, it was shown that since resistant bacteria are often resistant to more than one antibiotic the use of one antibiotic could select a population of bacteria that are resistant to that antibiotic as well as to other unrelated antibiotics.

Concern over antibiotic resistance grew with the discovery that antibiotic resistance can be transferred from one bacterial cell to another. Since this transfer could occur between bacteria or different genera, the resistance in a bacterial organism that would not ordinarily cause disease could transfer to other bacteria that do cause disease. These pathogens could then survive in the presence of the antibiotic(s) to which they are resistant; effective treatment of diseases in humans and animals caused by such antibiotic-resistant pathogens would then be more difficult or impossible.

During this period, FDA supported research, held symposia, and consulted with outside experts to review the non-medical uses of antibiotics in animal feeds. Following a report issued by the British Government Joint Committee (known as the Swann Committee) "On the Use of Antibiotics in Animal Husbandry and Veterinary Medicine," the FDA in April 1970 established its own Task Force of scientists, consultants from government, universities, and industry, to review as comprehensively as possible the use of antibiotic drugs in animal feeds.

I want to pause here to mention a couple of points that often cause confusion, and I believe they are easily understood if one has the correct information.

The first point is that the public health concern associated with the low-level use of antibiotics is that populations of largely-drug resistant bacteria—both pathogenic and non-pathogenic—will be created and that these bacteria have the potential for creating diseases in man and/or animal which will be more difficult to treat. The confusion I speak of occurs because the press and the public often do not separate this concern from that of a chemical (or drug) residue in meat, milk, or eggs. In short, chemical residues are not an issue in the current antibiotics in feeds controversy. With the exception of sulfamethazine residue in swine, feed-use antibacterials have an excellent record and chemical residues from feed-use drugs are not a problem.

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The second point concerning antibiotics that I would like to mention is on the subject of the regulation of antibacterials in England and the European Economic Community. One often hears that "England banned the use of antibiotics in feeds in 1971." That information is incorrect. England did separate antibacterials into two major categories: (1) those used for therapy in man and (2) those not used for therapy in man. Those antibacterials on the so-called therapeutic list can be used in animal feeds, but only on the order/prescription of a licensed veterinarian. These drugs include the tetracyclines, penicillin, and several sulfonamides, among others. The second category, called "feed" antibacterials can be used without veterinary prescription. Examples of these products are: bacitracin, flavomycin, and virginiamycin.

I might add that the system used in England has been largely adopted by the European Economic Community (common market) countries.

Now back to the Antibiotics Task Force again, which was established in the United States in 1970. That Task Force issued its report in 1972. The report raised questions about the practice of the use of antibiotics in feeds. As a result, the Food and Drug Administration imposed requirements for testing each antibiotic product by the drug sponsor.

After a thorough review of the data submitted by the industry on marketed products the Bureau (BVM) in conjunction with the Agency's National Advisory Food and Drug Committee (NAFDC) established the Antibiotics in Animal Feeds Subcommittee (AAFS).

In September 1976, the AAFS presented preliminary recommendations to the parent NAFDC and the final report was submitted in January 1977. From these recommendations, came the eventual development of the notices of opportunity for hearing (NOOH) calling for the withdrawal of penicillin and certain uses of the tetracyclines at subtherapeutic levels from animal feeds.

The post '77 years saw the intervention of the Congress of the United States in 1979 directing FDA to contract with the National Academy of Science (NAS) to study the issues involved. Congress also mandated that FDA hold in abeyance any implementation of its proposed actions pending final results of these studies. This action by the Congress did not preclude the use of the guidelines and mandatory testing procedures established under 21 Code of Federal Regulations (CFR), Section 558.15 which require testing of new products submitted for FDA evaluation. These procedures are still in use today as part of the new animal drug approval process and a number of compounds including lincomycin, hygromycin, virginiamycin, bambermycin, bacitracin, oleandomycin, erythromycin, salinomycin, monensin and lasalocid have been approved under these procedures.

In March of 1980, NAS released its report entitled "The Effects on Human Health of Subtherapeutic Use of Antimocrobials in Animal Feeds." After reviewing the evidence available at that time, the NAS Committee (Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds) concluded that the postulated hazards to human health from the subtherapeutic use of antimicrobials in animal feed were neither proven or disproven. The lack of data linking human illness with this subtherapeutic use must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk had not, in the opinion of the Committee, been conducted. Further, the Committee suggested several areas of research which it felt would provide additional information relevant to the question of hazards to the public health.

At the FY-81 appropriations hearings for the House Appropriations Committee, the FDA was requested to initiate epidemiological studies of the antibiotics in animal feeds issue in conjunction with the NAS recommendations. Again, the Committee stated that the FDA should hold in abeyance any implementation of the proposed withdrawal pending completion of the studies and a thorough re-evaluation of FDA's concerns regarding the issue. As the result of that directive, the Center for Veterinary Medicine has funded additional research and clearly a number of important pieces of research and epidemiology have been added to the published literature since our 1977 proposals to limit the use of penicillin in animal feeds. All this information is currently undergoing review.

Recent events have included the Natural Resources Defense Council's (NRDC) petitioning the Secretary of Health and Human Services, Mrs. Heckler, to declare the subtherapeutic uses of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health. NRDC argued that, on the basis of three recently published scientific studies—two CDC studies (1984) and a paper by O'Brien et al. (1982)—FDA is likely to eventually withdraw approval of the subtherapeutic uses of penicillin and the tratracyclines in animal feeds and that based on these studies, these uses meet the criteria for imminent hazard under the law.

On November 13, 1985, Secretary Heckler rendered a decision on the imminent hazard issue. The petition concerning whether the approved use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds should be declared an "imminent hazard" under section 512(e) of the Food, Drug and Cosmetic Act was denied. The Secretary found that the immediate suspension of these approvals is not warranted.

There remains the possibility that an evidentiary hearing before an Administrative Law Judge (ALJ) could be held by the Center for Veterinary Medicine on the earlier proposals to restrict penicillin and tetracycline uses (1977). However no decision has been made at this time as to the next step in this antibiotics in feeds issue.

At the time of FDA's original proposal to ban the subtherapeutic uses of penicillin and to restrict the tetracyclines in animal feeds, the contention was advanced that there were gaps in the scientific position to support the chain of events linking the feeding of low-level antibiotics to

animals to disease in humans. Scientific data generated since 1977 have been useful in adding to our knowledge and are being used to develop an Agency position regarding the 1977 proposals.

The years of debate and the additional research which have occurred since 1970 concerning this issue have been, indeed, useful. The industry and the Agency have steadfastly pursued scientifically defensible answers to complex questions. There has been a concerted and largely successful search for feed-use products that are not used for treatment of disease in man. We have carefully guarded and sustained the position that drugs such as chloramphenicol, semi-synthetic penicillin, gentamycin, and kanamycin not be used in animal feeds. The time and the energy have not been wasted. Indeed, the world is still wrestling with this issue and there is optimism in the FDA that appropriate resolution will evolve.

There is no doubt that we are using antibiotics in feeds more wisely today than when this issue first surfaced. The numbers of available antibiotics not used for therapy, but reserved for feed use, have increased. I think that there is a future for the judicious use of antibiotics in livestock production. But, we can no longer afford a casual, routine approach to antibacterial drug use in animals. We all have had experience in the past that suggest that a livestock producer may be buying and using drug products for which he either has no knowledge that these are in the feed or he has no idea why they should be there. None of us, including the animal industry, can tolerate that approach to animal production. I think we all feel that we have a better chance of successfully treating a bacterial disease problem on a farm, if there has been some careful thought given to the routine uses of antibiotics in those animals. We don't always get careful use. Antibiotics are potent and important tools to all of us. Our understanding of the pharmacokinetics of antibiotics and the bacterial drug resistance phenomenon is increasing. I urge you to stay informed in these areas. More veterinary medical involvement is needed to help provide for the efficient and safe uses of antibiotics in our livestock. Informed use and increased veterinary medical involvement may well be the answer to the questions of the future.

I mentioned earlier in my remarks that our meat, milk, and egg supply have an excellent record from a drug residue point of view. We know this is true, because we have an excellent system in USDA and FDA for checking on drugs and chemicals (pesticides) of concern and we know with the exception of sulfamethazine residues in pork and other sulfonamide residues in meat from neonatal calves that the numbers of residues detected are extremely small indeed.

I would like to spend a few minutes on the sulfamethazine in swine issue. This is a recurring problem looking for a permanent or at least a long-term cure. As you can see from this slide (slide #1), the residue violation rate for sulfamethazine has run from a high of 9.7% in 1978 to a low of 4.2% in 1981. Results in 1985, to date, show that 5.9% of samples of swine tested show sulfamethazine levels above the 0.1 ppm level, which is the residue tolerance for this drug. The violation rate that you see here is certainly unacceptable when compared to all other drugs in all species of food animals. The typical violation rate for other drugs run below 1%.

SULFA VIOLATIVE RATES (%)

1978—1985
1978—9.7
1979—6.5
1980—4.3
1981—4.2
1982—4.9
1983—6.3
1984—5.9
1985—5.9 (9 months)

We have credited an intensified educational program for the 1980, 81, and 82 decrease, but as you can see, the levels have crept upward from that time.

FDA, USDA, and the National Pork Producers Council, beginning early in 1985, have again stepped-up the educational activity. On March 25, 1985, FDA and USDA sent a letter to 114,000 pork producers throughout the U.S., informing them of the problem and warning that further action must be taken if the residue violation rates do not improve.

Beginning in April 1985, the USDA Food Safety and Inspection Service increased the sampling program and gave priority attention to laboratory testing for sulfamethazine. The results of sampling in 1985 are broken down by months on slide #2.

1985 MONTHLY BREAKDOWN

	Samples Collected	Samples Violative	%
January	109	12	11.0
February	114	9	7.9
March	100	6	6.0
April	186	10	5.4
May	46	3	6.5
June	129	5	3.9
July	110	4	3.6
August	126	4	3.2
September	122	10	8.2
October	20	0	Limited
November	—	—	—
December	—	—	—
TOTAL	1062	63	5.9

Follow-up inspections by FDA personnel at farms where violative pigs originate, showed that sulfamethazine residues are usually due to poor animal husbandry or management practices. For example:

- Putting finishing hogs in the same pen where starters were held, without cleaning pens or removing medicated feed;

- No records at all kept, so withdrawal times could be observed;
- Non-medicated feed added on top of medicated feed;
- Mixers not cleaned or flushed prior to mixing non-medicated withdrawal feed;
- Finishing hogs breaking into starter pens just before going to slaughter;
- Hired help not knowing about medicated feed withdrawal times.

LOCATION OF SULFA VIOLATIONS
April 1—September 30, 1985

State	Number of Samples Collected	Number Violative
Virginia	27	2
Alabama	7	2
Georgia	7	1
North Carolina	23	2
Tennessee	8	3
Mississippi	5	1
Kentucky	15	2
Texas	4	2
Missouri	23	2
Iowa	160	7
Kansas	4	1
Nebraska	42	2
Ohio	8	2
Indiana	26	1
Illinois	71	5
Michigan	10	1
South Dakota	14	1
Minnesota	29	1
Wisconsin	9	1
TOTALS	492	39

* Please note that 1,062 samples were collected nationwide from January 30 to September 30 with a total of 63 being violative, for a 5.9% residue rate nationally.

This program has re-affirmed what we already knew. Specifically we know that it takes only a small amount of sulfamethazine carry-over in a feed mill or in feeding equipment to cause levels of residue in swine tissue to remain relatively high. That is to say that once a pig has been on 100 grams/ton or more of sulfamethazine, that it only takes contamination in withdrawal feed at the 1 to 3 grams per ton level to cause a residue violation. We also know that pigs kept in pens where sulfamethazine is fed routinely can pick-up enough sulfamethazine from the litter to cause a residue even if non-medicated feed is fed for the withdrawal time. This says that finisher hogs have to be moved to clean pens or that the pen they are in must be cleaned when withdrawal feed is started.

FDA is currently conducting long-term or life-time laboratory animal feeding studies to see if the tolerance levels for sulfamethazine in tissues can be modified. The present tolerance was established on short-term, (mostly 90-day) feeding studies. If the studies show that the tolerance can be raised, this may offer some relief for the problem. If the studies call for a lowering of the tolerance level, the current problems become greater. In the meantime, it is imperative that everyone involved in swine production and swine medicine do everything possible to lower the rate of residue violations for sulfamethazine. Failing this, alternatives to the present practices or uses of sulfamethazine in feeds must be explored. The drug is no doubt an important tool in swine husbandry, but continued high sulfamethazine residue rates must be corrected.

I have given you a considerable amount of detail on two important feed additive issues in the animal drug area and my general impression about the two (2) in the future.

Feed-use drugs are important today and I believe given the tendencies in animal production techniques, the use of these products will be important in the future. I do believe that an increase in the involvement of the veterinarian is indicated, although this has not been the tradition in the United States. Even our laws and regulations seem to set aside feed-use products in a system that causes the veterinary profession to look to other vehicles for drug delivery. I do not think it has to necessarily be that way. I think the veterinarian has a place in feeding, even under today's system. He or she should learn the medicated feeds rules and regulations and work within those systems with the feed industry.

I sense a recent trend and a consensus emerging among many livestock producers which says I need all the help I can get, including veterinary medical involvement in use of feed additives and other medication to ensure the integrity of animal food products and to hold consumer confidence in the safety of these foods. I think it is a healthy trend for tomorrow and it will serve to increase the quality of an already excellent food supply.