The Current Perspectives on Drug and Chemical Residue Problems from FDA's Center for Veterinary Medicine

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Good Morning. I really appreciate the opportunity to participate in this the 22nd Annual Conference of the American Association of Bovine Practitioners. It is a pleasure to be here and I am particularly looking forward to the Residue Avoidance Symposium this afternoon.

There are several points I would like to cover with you this morning. I will begin with a short discussion of what I believe is the role of the veterinarian in drug residue prevention. I will talk about residue problems as far as cattle are concerned and a little bit about what is being done about them. And I will wrap-up with a discussion of the current status of BST which although not a residue problem, is, I believe, of some interest to this group.

First, the role of the veterinarian in drug residue prevention. To begin with, in general when discussing the veterinarian's role in the prevention of drug residues, we must recognize it's not just the private food animal practitioner we are talking about. Obviously public practice veterinarians, particularly those with regulatory responsibilities, and drug and feed industry veterinarians, also are very important. However this morning I want to focus on the private food animal practitioner.

Obviously proper drug use, as it relates to drug residues prevention, starts with a thorough knowledge of the animal drug one is using. The axiom "above all else, do no harm" still applies. However, we need to recognize and appreciate that a finding of violative residues in animals at slaughter can be as harmful to a client's well being as the death of animals. Thus, it is incumbent upon practitioners to be thoroughly familiar with the pharmacology including the pharmacokinetics, of the drugs they are using and to refrain from using drugs with which one is unfamiliar or for which necessary information is lacking. This latter circumstance, of course, applies most often to those situations where the extra-label use of a drug is being contemplated.

The best source of information on the pharmacology of animal drugs is the drug label including the package insert. Of course this applies only to approved drugs being used for the indications for which they were approved. Why? because only with approved drugs are we dealing with products of proven quality, purity, and potency with labeling that has been demonstrated under strict scientific standards to assure safe and effective use.

With animal drugs, the adage that "you get what you pay for" was never more true. There is a good explanation for how those people who sell drugs that although not approved, are advertized as the same as recognized approved drugs but are sold at a substantial savings, can stay in business. They don't have to worry about anyone's standards of purity, potency and quality. They don't have to worry about Good Manufacturing practices. And they certainly don't have to worry about supporting a research and development effort that will result in new and better animal drugs for the future.

I don't have to tell you that today, comsumer perceptions are often more important to us than reality. We as a profession and particularly food animal veterinarians, must project an image of quality and professionalism. We must establish high standards of practice in food aminal medicine and we must demonstrate every day and in every way that we place adherance to those standards over personal convenience or financial gain.

That brings me to another role of veterinarians vis-a-vis prevention of drug residues in animal-derived food products. Food animal veterinarians must recognize that like it or not, they represent a very influential source of information and example of behavior for their clients and others on the farm. If one is very casual and off-hand in the use, handling and storage of drugs, that sends one message. If one is very deliberate and careful in use, handling and storage of drugs, that sends a different message. If one provides only casual, off-hand verbal comments on the use of drugs dispensed or recommended, that sends one kind of message. On the other hand if one provides specific instructions, in writing, and emphasizing the importance of strict adherence to the instructions, particularly withdrawal times, that sends a different message.

And while I'm on this point, I would like to emphasize to dairy practitioners the importance of adhering to recently adopted requirements for labeling individual containers with one's name and address when one dispenses or prescribes prescription drugs for use in lactating dairy

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cattle. For one thing, FDA has implemented a compliance program focusing on mobile peddlers and others illegally distributing prescription veterinary drugs. If we can't distinguish at the farm level between prescription drugs that have been obtained from legal sources from those that have been distributed or sold illegally, it makes accountability very difficult.

With respect to drug residues in cattle, the major concern is for residues of antibiotics in culled dairy cows and in veal calves. Among cull dairy cows, IM injection of antibiotics accounted for most of the violations while among veal calves oral administration either in feed (milk replacer) or as a bolus was most often the route of administration. The major drugs involved included streptomycin penicillin, oxytetracycline, gentamicin, sulfamethazine and neomycin.

Our investigation of violative residue reports indicate that the overwhelming majority are caused by human error. Failure to observe the drug withdrawal time is the most common cause. Failure to follow label directions, failure to segregate medicated animals, failure to adequately clean mixers and/or feeders, use of unapproved products, and failure to keep appropriate records are all common causes as well. Although in the majority of instances the animal producer has caused the illegal drug residue, I believe veterinarians can play a significant role in reducing the incidence of violative residues simply by emphasizing and insisting upon adherence to principles of proper drug use, particularly withdrawal times.

What is being done about the residue problem? As you know, responsibility for enforcing laws and regulations pertaining to residues of animal drugs in food derived from treated animals is shared jointly by FDA and USDA. The Food Safety Inspection Service (FSIS) of USDA supervises the processing of meat and poultry in all federally inspected slaughter plants. FSIS monitors animals at slaughter and reports violative drug residues to FDA for follow-up. FDA conducts investigations of FSIS-reported violations to determine the party responsible for introducing the violative article into commerce and why/how the violation occurred. This program focuses on prevention and regulatory enforcement to reduce the prevalence of illegal residues.

There is considerable focus on increasing the cooperation and communication between agencies at the Federal, State and local levels. As this becomes more of a reality it will become increasingly difficult for individuals with a history of producing animals, milk or eggs with violative residues to find markets that will accept them.

Most importantly, with respect to what is being done about the residue problem, is the revolutionary change in attitude that is going on within the veterinary profession and among livestock producers. Evidence of the change is everywhere; in expansion of the concept of verified production control and other quality assurance initiatives and program sponsored by producer organizations; in standards of practice being established by various veterinary practice specialty groups providing veterinary services to the livestock industry; and in adoption by the AVMA of the Guidelines for Supervising Use and Distribution of Veterinary Prescription Drugs.

Food animal veterinarians generally and the AABP and its leaders have taken a leadership role in this revolution. In the mid-80's the Academy of Veterinary Consultants came out with their Standards of Practice.

Keith Sterner, Tom Fuhrmann, Glenn Hoffsis and others among your colleagues have been exceptionally effective in shaping, guiding, and directing the changes that are occurring. They have taken the initiative in coming to the FDA and the Center and to the Animal Health Institute and its member pharmaceutical and animal health product companies not with a laundry list of problems but with innovative ideas about how to solve problems and with the drive and commitment to make them work.

It is always dangerous when you start naming people because you invariably leave out someone who should be mentioned. However, I do want to mention how pleased we in CVM are to have Dr. Hentschl as a member of FDA's National Veterinary Medicine Advisory Committee. Not only is he an exceptionally effective representative of the veterinary profession generally and of bovine practitioners specifically, he brings a measure of quiet strength and wisdom that is very important to the committee.

Now I would like to turn to the current status of BST. Let me begin by giving you a little background on the drug approval process generally and how BST fits into the process.

Before a new animal drug such as BST may be marketed commerically, it must be found to be safe and effective in the target animal, safe from the standpoint of human food consumption, and safe for the environment. Incidentally, they must also prove they can consistently manufacture the product to specificed standards of purity, potency and stability. FDA's Center for Veterinary Medicine (CVM) is responsible for assuring that these standards are met as a condition for approval prior to commercial marketing. The process, as outlined in the Federal Food, Drug and Cosmetic Act and in FDA's regulations is two-staged; the Investigational New Animal Drug (INAD) stage and New Animal Drug Application (NADA) stage.

During the investigational stage, the drug sponsor develops scientific data demonstrating the safety and effectiveness in target animals (the species and class of animal in which the drug is to be used), the safety of any drug residues that might occur in edible tissues or milk for human consumption, and safety for the environment. The investigational research includes both basic and applied research in the laboratory and clinical research conducted as field trials.

The law requires that investigational drugs being tested for safety and efficacy be registered with the Agency at the time they are shipped in interstate commerce, that is, prior to them being shipped across state boundaries, including to other countries. If they are intended for food-producing animals, an additional requirement must be met that any food derived from the animals be considered safe by FDA before the food is allowed for either human or other animal comsumption. (Therefore, it is not uncommon for the Center to have assessed, to some degree, the safety of drug residues even prior to the review of a new animal drug application requesting commercial marketing of the new drug product.)

For a company to be able to legally investigate the effects of a new drug, it must submit information to FDA as to the identity of the chemical, any information being supplied to the investigators, the name and address of each investigator receiving the drug, the approximate number of animals being treated and when the experiments will take place, and the dose and the route and duration of administration of the drug. As mentioned before, the company or investigator must receive FDA authorization to market any food derived from animals being administered investigational unapproved drugs. Scientific data must be supplied to achieve this authorization, the amount and extent depending on how many animals are involved and will eventually be used for food, the toxic properties of the drug, and how long the drug is proposed to be withdrawn from the animal before meat or milk are marketed for food.

Generally speaking one of three possible decisions is reached regarding requests for authorization to market food derived from animals treated during investigation stages of the drug development process.

1. Authorization to market food products derived from experimentally treated animals is denied. This occurs when information on the toxicology of potential residues resulting from the test drug or on their elimination from tissues is inadequate to support such authorization.
2. Authorization to market food products derived from expermentally treated animals is approved but based on an extended withdrawal period following treatment. This occurs when information on the toxicology of potential residues resulting from the test drug and/or on their elimination from the tissues of treated animals is adequate to assure that under the conditions specified (withdrawal period) no harmful or potentially harmful residues will be present in human food derived from the experimentally treated animals.
3. Authorization to market food products derived from experimentally treated animals is approved without a requirement for a withdrawal period. This occurs under circumstances in which the sponsor has demonstrated (a) that no residues occur following treatment; and/or (b) that such residues as may be present represent no risk to humans (are neither harmful nor potentially harmful) consuming food-products derived from experimentally treated animals.

I should also point out that apart from the review and evaluations we conduct at our headquarters in Rockville, MD, there are also FDA field officers throughout the U.S. At headquarter's direction, inspections are performed of ongoing investigations. These inspections help assure the company is complying with all the requirements for unapproved drugs being studied under an investigational status. CVM has, in fact, ordered inspections on all of the pivotal BST trials that have been conducted or are currently ongoing in this country.

Of course this has been an area of some controversy with respect to BST. I should point out here that the development of BST and its consideration by the Center for Veterinary Medicine has been unique in my experience with the Center. You see, the FD&C Act prevents the Agency from discussing or even acknowledging the existence of an investigational use registration or a New Animal Application for a particular drug unless authorized by the sponsor to do so, and drug sponsors rarely do so. So for the Center to be so involved in discussions about drugs still in the investigational state is highly unusual. BST is further unique in that for most drugs, particularly new drug entities such as BST, being investigated for use in food animals, the most significant data hurdle they have to get across is the demonstration of human food safety.

Although target animal safety and efficacy and environmental safety must be demonstrated, they tend to be less of a problem from a science point of view and certainly less expensive. However with BST, the sponsors were able to demonstrate very early in the process that there are no significant changes in the milk from lactating dairy cows treated with BST versus the milk of untreated cows. Also that such residues as might be present represent no risk to humans consuming the milk. This finding by the Center's Division of Human Food Safety is based on four facts about BST.

1. BST is a protein which when ingested is broken down or digested in the gastrointestinal tract and thus inactivated. (BST is inactive even in cows when given orally).
2. BST is species specific. That is, even if BST is injected into humans it is still inactive. The somatotropin from some species are fairly similar and when that is true there may be some cross-reactivty. However that is not the case with respect to BST in humans. A number of years ago BST was investigated as a drug for treatment of growth disorders in children and was found to be inactive in humans even when injected.
3. Data demonstrate that the milk from BST-treated cows is not different than that from untreated cows. That is, one cannot demonstrate any significant increase in the amount of BST present in milk from treated cows over that present in the milk from untreated cows. Nor is there any difference in the nutrient content of milk from

treated versus untreated cows. Thus, there is no concern for changes in nutritional value.

4. Humans consuming animal derived food products have always been exposed to small amounts of naturally produced BST in milk and meat.

Thus, the conclusion of the Center's Division of Human Food Safety is that the experimental treatment of lactating dairy cows with BST presents no risks with respect to the human consumption of milk from such cows. Accordingly, as you all know, the Food and Drug Administration has authorized the sale for human consumption of milk from cows treated experimentally with BST during the investigational stages of BST development.

Eventually, the investigational phase or stage of this development of a given drug product is completed. At that time the sponsor submits the data in the form of an NADA. The law requires that **all** data in the sponsor's possession must be submitted, not just data that support approval and they must submit the raw data - not just their data summaries, evaluations and conclusions.

Our review scientists then evaluate the data, draw their conclusions and recommend either approval, or more often generally - a finding of **incomplete.** That is, the data package as it presently exists, is **incomplete** in terms of demonstrating that the product is safe and efficacious for its intended uses. In such cases, the data deficiencies are identified and the sponsor sets about collecting the additional data.