RESIDUE PHOBIA, RESIDUE AVOIDANCE AND THE REAL WORLD

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Introduction

The public is becoming increasingly exposed to food safety issues. The print media routinely publishes articles concerning food and many of these articles question the safety of the food we eat. Several years ago the American Veterinary Medical Association and the National Milk Producers Federation met to discuss public concerns over safe food and what risks this concern held for the markets for milk products. At that point the veterinarian was seen by the milk industry as the cause of most milk adulteration through abuse of their extra-label drug use authority. This was a turning point for the profession. The choices were limited. We could continue to be viewed as the source of the problem or we could take a leadership role and be seen as a significant part of the solution.

If the consumer's needs for confidence in a safe food supply are to be met as we move into the 21st century, there must be a continued cooperation between the dairy veterinarian, the milk processing industry and the dairyman. The regulatory agencies and pharmaceutical industry must also be involved, if we are to meet both the needs of the consumer for safe dairy products and care for our patients in a humane and cost effective manner.

The goal of this paper is to deal with food safety and veterinary therapeutic issues from the consumer, veterinarian and pharmaceutical industry perspective. We start with problems the food animal veterinary practitioner faces concerning the choice of therapeutic agents. Next, safety issues concerning these agents are dealt with, in an attempt to provide background information on the approval process for therapeutic agents that are used in lactating dairy cattle. We build on the safety issues by describing how residue testing is done by the dairy industry. And finally, the Upjohn Company's injectable antibiotic, Naxcel® Sterile powder (Ceftiofur sodium), is used as example of how new generation therapeutic agents can be developed and approved under guidelines that meet the consumer's need for safe dairy products and still provide the veterinarian with efficacious treatments for their patients.

The Veterinarian's Dilemma

The veteriniarian's dilemma involves a series of commitments that, even with the best of intentions and efforts, may not be possible to resolve. We have a responsibility to our patients to provide for their welfare. This commitment is spelled out in the oath we took on graduation. In production animal medicine we have a responsibility to the animal's owner to provide care in a manner which protects their economic interests. Finally, we have a responsibility to the consumer to protect their food supply from unsafe levels of our therapeutic agents. With the drugs that are currently approved for use in food animals these three responsibilities are becoming more difficult to meet.

In spite of this dilemma, the goal of most dairy farmers and veterinarians is to provide the best care available and to do so in a manner that maintains a safe food supply. When we look at the approved injectable antibiotics available to dairy veterinarians, the magnitude of this task becomes obvious. There are only seven drugs approved for lactating dairy cows and most of these are older antibiotics that clinicians feel compelled to use at higher than label dosages to be effective. When we look at the diseases that we treat and look at the labels of the available antibiotics, there are only two or three diseases of dairy cows on those labels. The list of seven may soon be reduced to six, as the Penicillin-Dihydrostreptomycin combinations are at risk of being removed from the market because of concerns over prolonged tissue residues.

The Food, Drug and Cosmetic Act states that all drugs must be used according to label instructions. Any use of those drugs beyond the label, either in dosage, route of administration, frequency or species would then be a violation of the law. If a violation does occur, it is punishable as a criminal offense. The problem is that the practice of veterinary medicine has moved ahead more rapidly than the approvals of new animal drug products. This has led to a conflict between good veterinary practice and the law. The Center for Veterinary Medicine of the FDA has dealt with this problem by publishing Compliance Policy Guidelines which allow the veterinarian to use drugs in an extra-label manner in food animals; if,

they have a client-patient relationship and they accept full responsibility for any residues. **This does not say that what the veterinarian does is legal, only that the FDA will not prosecute them under most conditions.** Since the only penalties in the law are criminal, the offense must be very serious before FDA normally takes action.

Today, the level of public and governmental concern has shifted towards food safety. Representative Weiss from Brooklyn, New York, has pressed for tougher enforcement of the existing laws and removal of the FDA compliance policy guidelines. He has initiated Government Accounting Office (GAO) investigations of the FDA to determine if they are protecting the consumer's interests. The new head of the FDA, Dr. Kessler, has been charged with restoring public confidence in the agency.

Drug Residue Semantics

Discussions concerning what levels of a pharmaceutical compound can safely be in the meat, milk or eggs are complicated by a difficult set of definitions. The concepts of tolerance (both zero and non-zero), safe concentration, and FDA "safe levels" all have very different meanings, but these must be understood in order to deal with the concepts of food safety. Some people would say that the concept is easy; that no residue or level of drug is acceptable. Those individuals who support zero levels for all therapeutics in food don't understand that this in fact means that no drugs could be used.

The term safe concentration is used for compounds with proven safety and is used to determine meat or milk withholding times. Safe Concentration is the total level of drug allowed in milk or meat, determined by safety studies, plus a safety factor of either 100x or 1000x, depending on the tests used. For drugs with residues that do not go below the safe concentration by 12 hours after administration, a tolerance is established to determine how long the animal and products from that animal must be withheld from the market before they can be safely consumed. A tolerance can either be for the parent drug or for a metabolite of the drug which parallels the decline of the total drug. A tolerance of zero was established for the older antibiotics; Penicillin, Erythromycin, Dihydrostreptomycin and Chlortetracycline. This value of "zero" was defined by the testing methods available at the time (1950's). When these drugs were originally approved in the 1950s, the assays for these drugs could only detect them in the high parts per million. Today, we are able to detect these drugs in the low parts per billion or parts per trillion. For the drugs with zero official tolerances and for some non-food animal drugs that are commonly used in an extra-label manner, the FDA has determined through "risk analysis", a level called "FDA safe level". This is a level of drug that is used for regulatory action if the drug is found in milk or meat above this level. The "FDA safe level" does not have the force of law like a tolerance or safe concentration.

Residue Testing

The routine testing of dairy products for antibiotics was initiated to protect the bacterial cultures that are used to make cheese and yogurts. Levels of penicillin as low as 0.005 IU could cause a batch of cheese to fail. In 1960, the tests used to detect penicillin had a limit of detection of 0.05 IU and the percentage of positive samples was over 5 percent. By 1975 the assay sensitivity had increased to 0.005 IU of penicillin and from 7 - 15% of all samples tested were positive. This past year, Milk Industry Foundation data shows less than 0.1% of the milk samples tested were positive and the test limits of detection have been reduced to 0.002 - 0.005 IU. The new Pasteurized Milk Ordinance (PMO) has mandated the screening of all loads of milk for ß-lactam antibiotics as of 1 January 1992. This mandate is still only for ß-lactams antibiotics, even though the new PMO is concerned about all drugs used in lactating dairy cows.

If the dairy industry is primarily concerned about testing to protect their bacterial cultures, why is the consumer so concerned? The fact that 5 - 10% of the public is allergic to penicillin in amounts as small as 0.003 IU raises public awareness. In fact, there have been no documented cases of severe hypersensitivity reactions or deaths from food-borne antibiotic residues. The concept of resistance transfer from animals to human enteric flora is also raised as a concern. To date, this concept has not been substantiated in the world scientific literature. The real facts are that this is an emotional issue and the consumer is concerned about any potential hazards in their food and they expect zero risk to their health from consuming food derived from animals that could harbor residues of drugs.

There are many tests that are used today to screen for ß-lactam antibiotics. The creameries are using tests which are rapid to perform, relatively inexpensive to purchase and have a proven low rate of false negatives. All milk trucks are tested prior to unloading. If a positive test is found, most creameries still confirm the positive result with an official test that would include the

Bacillus Stearothermophilus Disk Assay, the Delvotest P® or the Charm II® with liquid reagents. If these are also positive, the load is considered adulterated and condemned.

Questions are raised concerning quality control within the dairy testing system and are the tests run properly? In our investigations of alleged Naxcel residues we have seen problems with some of the testing, even in states with lab validation three times a year. For the BSDA, these have included not heating the milk to 82 degrees Centigrade for two minutes to remove some of the nonspecific inhibitors, not using penicillin controls and interpreting any zone of inhibition as a positive rather then measuring 16mm. There is also an increased concern on the weekends, as normal lab personnel are not running the assays.

Increased penalties for positive loads and the 10-Point Dairy Quality Assurance Program have increased the number of individual cows that are having their milk tested prior to going back in the tank after treatment. This is particularly true with animals that have been treated with drugs used in an extra-label manner. The tests that are being used were designed for bulk tank milk and not for milk from a single cow. The farmer using one of these tests on the farm or the creamery testing individual cow samples must realize there are a high percentage of false positives. Milk samples for testing individual cows with microbiological tests must be taken from the total milking from the cow and not directly from the teat.

Veterinarians today are resisting getting involved in antibiotic testing and in general are poorly informed as to test kit limits of detection or which antibiotics the kits detect below safe levels. There appears to be a feeling that they don't want to increase their liability because of incorrect testing. If the veterinary profession continues to use drugs in an extra-label manner, testing at the clinic with excellent documentation may be the only way to decrease their liability.

Naxcel and the Dairy Industry

Consumer interest groups such as Center for Science in the Public Interest would like to see all extra-label drug use stopped. One of their solutions is to have the pharmaceutical manufacturers get more food animal drugs properly and legally approved. What they don't understand is how difficult it is to get a drug approved or even to get the label on an already approved drug changed for an additional indication or different species. These changes take years and millions of dollars to accomplish. The approval of Naxcel Sterile Powder (Ceftiofur sodium) for lactating dairy cattle gives a view from the pharmaceutical industry perspective of some of the problems and opportunities that both the dairy industry and the pharmaceutical industry face.

Naxcel is an advanced generation cephalosporin with activity against both gram positive and gram negative pathogens. It is a ß-lactam antibiotic that is detected by all of the routinely used assays for antibiotics in milk. Naxcel's greatest assets are it's very wide safety margin in humans and it's pharmacokenetic properties which results in drug concentrations below the safe concentration in all tissues and milk by 12 hours after injection. The milk safe concentration is 1000 parts per billion. This unusual safety allows Naxcel to be marketed with a zero milk discard and no pre-slaughter withhold for meat. The pre-approval safety testing for a new antibiotic includes toxicology, metabolism and residue studies. Because it is a ß-lactam, Naxcel also had to pass strict hypersensitivity guidelines to prove that it would not cause allergy problems in humans.

One of the initial questions that had to be considered was how a drug could have zero milk discard and still be effective. Naxcel has extremely low Minimum Inhibitory Concentrations (MIC) against many of the important food animal pathogens. In addition to low MIC's, the drug is rapidly metabolized in the serum to an active metabolite and covalently bound to serum proteins. With this protein binding, only a small percentage of the serum level gets into the milk. This percentage is approximately 0.15%. When the drug is used in the muscle according to the label directions, there is no parent Naxcel in the milk, only a small amount of metabolite detected. The bottom-line still comes back to the fact that FDA is solely responsible for defining both safety and efficacy for therapeutic agents and Naxcel was able to meet both criteria with no discard of milk or meat.

Prior to approval of the dairy claim, we realized that there were many things about Naxcel that the veterinarian and dairy farmer would not understand. A comprehensive educational program was designed to promote the proper label use of the drug. Two educational letters have been sent to the dairy veterinarians and our sales representatives have contacted veterinarians personally to express our concern that the drug must be used according to the label directions.

Can Naxcel cause residues and problems to the processing industry? The answer to this is yes; **if it is used in an extra-label manner in the mammary gland without a milk discard.** When used in this manner Naxcel is like any

other ß-lactam antibiotic and most dairy farmers or veterinarians would not put straight penicillin or a mastitis tube in a quarter and still use the milk at the next milking. We believe that our message has been heard and very few veterinarians or dairymen are continuing to use Naxcel in the mammary gland without discarding the milk.

Naxcel Investigations

During the last six months of 1991 and the first month of 1992, Upjohn Technical Service investigated twenty eight incidents where milk was condemned and the drug that was implicated was Naxcel. The term "implicated" is important because these farmers were using Naxcel and they really believed that Naxcel had caused their bulk tank to be adulterated. In reality, only 4 of the 28 investigations found Naxcel as the cause. The use of other antibiotics was still continuing on these farms and mistakes that dairymen have made for years continued to be made. These would include milking of cows treated with other antibiotics prior to their withdrawal time, the inclusion of dry treated cows with the milking cows and other common errors of improper animal identification. Our results are summarized below:

Results of Investigation	Incidence	Percent
No antibiotic detected	2	7%
Penicillin, Amoxicillin, Ampicillin	7	25%
Cephapirin and Cloxacillin	4	14%
Non-ß-lactam antibiotic	3	11%
Naxcel	4	14%
No retained sample	8	29%

It is important to note that no sample was retained by the creamery in 29 percent of these cases. We have suggested to National Milk Producers Federation and directly to the creameries involved, that it would be in their best interests to save at least 60 cc. of the milk in question in their freezer. Many of these situations when samples were not retained occurred on the weekends, when there seems to be more problems with poorly trained analysts and questionable results.

There were four cases in our investigations where Naxcel was shown to be the cause of the adulteration. Two of these cases were due to the farmer misreading the veterinarian's label or thinking that IM meant in the mammary gland. No further lab work was done to confirm these two incidents. A violation in Minnesota was due to a dairyman using the drug in the mammary gland for mastitis. We worked with his creamery and veterinarian to suggest that he should not continue to use the product in this manner. The final case with Naxcel in the milk occurred in Colorado. The dairy farmer said the drug had been used according to label in 5 of his 95 Holstein cows for mastitis. Our lab was able to show that there was a sufficient quantity of "parent" Naxcel in the sample and that Naxcel was put into the mammary gland or dumped directly into his bulk tank. When this was brought to the farmer's attention, he admitted that he had not personally given the drug and that the hired help might have used it in the quarter.

The bottom line is, to date, we have not had one case where the label use of Naxcel has caused the milk to be condemned. This is becoming more important as all positive screening tests for bulk tank milk are required to be reported to state authorities and one of the questions that they are asking is "what drug was implicated?". We will continue to defend the proper use of Naxcel because we know that if the drug is used according to label, it will not cause violative residues in the milk.

To prove this point to ourselves and to the industry, we treated 30 lactating Holstein cattle at the Upjohn Research Farm. The study was designed to be a "worst case" scenario, with all animals starting treatment at the same time using the highest label dosage of Naxcel. In the field, a situation like this would normally not occur. Even in a severe herd outbreak of pneumonia, the onset of the disease is staggered over a three to ten day period. The thirty cows in the herd were divided into three ten cow groups to study the effect on pooled or bulk tank milk. We used three residue tests that are commonly used by the industry. The Bacillus Stearothermophilus Disk Assay is the official test for ß-lactam antibiotics. The industry standard 16 mm zone size was used as the measure of positive. The Charm II® Assay (Charm Sciences, Inc., Malden, Mass.) was run using the two methods described in their instruction manual. For most of the dairy industry they recommend that a 0.008 IU Penicillin G standard be used to set the control point. This method approximates the results obtained with the BSDA and a 16 mm zone size, but appears to detect Naxcel at slightly lower levels. Their other method is an AOAC validated method which sets the control point at 85% of a zero reading. This method detects very small amounts of all ß-lactam antibiotics. The final test used was the Cite Probe® ß-lactam test (Idexx, Inc., Portland, Maine). This test is used as a screening test by many creameries throughout the country.

Study Results

Test	Herd	Individual Cows
BSDA (16 mm zone)	All groups negative	All cows negative
Charm II (0.008 IU Control)	One group suspect for 2 milkings after the 3rd injection -- all others negative	10% positive 10% suspect
Cite Probe	All groups positive the milking 12 hrs. after an injection, negative at 24 hrs.	45% positive at the 12 hr. milking 24% positive at the 24 hr. milking
Charm II (AOAC method)	All groups positive during treatment	most animals positive during treatment

The results of this study reinforce our conviction that Naxcel will not cause violative residues in the milk if it is used according to label instructions. It should be remembered that the level of Naxcel detected by the Disk Assay is still well below it's safe concentration of 1000 parts per billion. Recently, it has been suggested to cheese manufacturers that more sensitive tests should be used to protect dairy product manufacturing when Naxcel use is suspected. This concern came from information that we had shared with the testing industry about the effects of Naxcel on dairy cultures. The study was Upjohn sponsored at the University of Wisconsin and it found that if Naxcel was used according to label, it would not cause problems for any of the cultures. When parent Naxcel (not found in milk with label use) was put into the cultures, negative effects were seen with as little as 7 parts per billion. This is not unexpected, as penicillin has similar effects starting at 2 parts per billion. The important fact is that if the drug is used in the mammary gland without a milk discard, all of the commonly used ß-lactam tests will detect this violative use and cause the milk to be condemned. Using lower limit of detection methods will only cause more safe milk to be discarded.

Role of the Veterinarian

One of the main roles that the veterinarian can assume concerning food safety is the role of an educator. The public has a difficult time understanding the scientific issues involved in the food safety debate. As a respected community member, the veterinarian can speak to interested groups on food safety issues and on what the FDA is doing to protect the consumer's interests. We have to help consumers understand that, if we are to do our job protecting the welfare of animals, we must use antibiotics and other pharmaceutical agents. Consumers must also understand that there will be some of these compounds in the milk and meat, but the residues will be below the levels that the FDA has deemed to be safe when the drugs are used according to label or FDA guidelines.

Finally, we must be responsible for our own actions and live up to the trust that the public puts in the veterinary profession. If we choose to use drugs in an extra-label manner, we must realize that this use is under severe scrutiny and we must follow the compliance policy guidelines to the letter. This use must include extended withdrawals for both meat and milk. We must also be aware that some drugs carry a greater risk than others. Penicillin is rapidly becoming the "fallback" drug for the dairy industry. Dairy farmers are using this over-the-counter (OTC) drug in an illegal manner, copying the way their veterinarian uses the drug. Penicillin would probably not get FDA approval today, as an OTC or prescription drug, because it might not meet the criteria that new antibiotics must meet concerning hypersensitivity. It was also recently demonstrated that if penicillin is used in extra-label dosages and given subcutaneous (SQ) it will be detected in the milk for up to 12 days. Dairy veterinarians must also stop using tetracyclines in the uterus without a milk discard. The choice is ours, whether we want to be a leader or just part of the problem.

The Future

New and reliable testing methods that can be used at the farm bulk tank are needed to limit financial loss and disposal costs for both the farmer and the creamery. The discarding of truck loads or silos of milk due to a single patron's error must stop. These same tests could be used by the farmer and the veterinarian to protect the food supply from potential violative residues from extra-label drug use. The treated animal's milk could be tested until it was confirmed negative for the drug of concern and then returned to the tank. Our dealings with some of the residue testing companies suggest that tests which will meet these needs are in the final development stages and should be available in 1 - 2 years.

Changes must also be made in the Food, Drug and Cosmetic act and in the mechanisms for veterinary drug approval. In a recent interview in the FDA Veterinarian Dr. Guest, the Director of the Center for Veterinary Medicine (FDA), suggested three changes to reduce the conflict between veterinary medicine and the law. The first was to urge legislation to modify the Food, Drug and Cosmetic Act to accommodate veterinary medicine, while still protecting the public. The second would be to provide incentives to drug sponsors to increase the number of approved drugs available to the veterinarian. And finally, to make prescription drug labeling more flexible to allow for more general efficacy claims while providing strict parameters on food safety. This has been called "professional labeling". The FDA needs the profession's support through a very difficult time to help them maintain credibility with the public.

A big question that is coming out of this food safety debate is who will control the practice of veterinary medicine. In the not too distant past, the practitioner only had to worry about his patient's well-being. He compounded some of his own medicines and had little understanding or worry about what effect those medicines might have on the ultimate consumer of the meat or milk. In more recent times, the practitioner has been limited in compounding pharmaceuticals and they have been regulated by what effects their antibiotic therapies might have on the manufacturing cultures used by the dairy industry. Today, our list of acceptable drugs is narrowing. We are very limited in what compounding we can do with those available drugs. And finally, the consumer's political power is demanding that we only practice within the labels of the few drugs that are approved for food animals. We must stress the welfare of our patients to the consumer critics that want to control how we practice. We must also unite politically with the rest of the animal industry to support the changes that CVM has suggested.

The food supply in this country is the most abundant and the safest in all of the world. Being the best does not mean that there isn't room for improvement. Establishing a single governmental agency, responsible for all food safety, would help in this effort. The public must be educated to the real risk in our food supply, which is bacterial contamination. They must also understand that they play a critical role in keeping the food they eat safe and wholesome with proper food handling and preparation. The dairy industry is the model for safety in the whole food industry and dairy veterinarians can be proud of their critical role in keeping milk and dairy products free of violative residues and bacterial contaminants, while attending to the welfare of their patients in a cost effective manner.